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Case Report

ARE YOU A ROLE MODEL??

Farid Ahmad Khan

Introduction

''Good teacher teach, while role models inspire and motivate''

In order to answer this question, first of all I should ask myself what are the qualities I want my role model to have.

First and foremost is that he is a visionary person and is able to see beyond the borders and timeline.

Second quality is he has a mission and he takes that as a passion, let it be teaching, training of his students, erecting a new institute of his specialty or building a new hospital or a medical college.

Remember that mission or passion should be beneficial not only for him but also for others to go beyond his life time.

One should remember that if one wants to build a commercial building a buy a house, it would not be a mission but a simple project, from which public at large would not be benefactors after one's demise.

Next quality of a role model is that he should be fearless.

If any obstacle frightens him he can't be a leader rather that obstacle should become a challenge in a Journey towards that bigger destination.

Next quality is to be non compromising on principals, it is the most difficult quality to have in this day and age and it doesn't mean that your role model should be stubborn and proud but he very politely and quickly persues his mission with determination and zeal .

In medicine our role model should have some additional personal qualities like punctuality, credibility, personality, empathy and competence in his field.

Last but not the least our role model or mentor should possess academic excellence as our superiority does not come with grades or ranks now let us try to find all these qualities in ourselves and see how many we possess to fulfill these stringent criteria when I looked into myself I was very empty, indeed finding the answer to my question why we have so few mentors and role models. I have tried to follow these principles, have you??

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Seizing the Moment 2020

Introduction

Like a strong social support structure cushioning for individual's growth and resilience, Good Clinical Practices (GCP) offers a framework to develop research capacity. GCP was developed by International Council of Harmonization (ICH) to standardize practices in biomedical research that has been historically marred by deception, distrust, and controversies. It has guarded to a large extent against repeating Thalidomide-like disaster(s) of twentieth century by compelling the regulators to adopt of patient safety standards and find measures to gauge it within the study. Medical research by nature breeds skepticism due to the mere consequences of any method or interpretation gone wrong. Similarly, medicine itself is a treasure trove of knowledge yet to be discovered in so many ways. The combination of human curiosity and market forces are too formidable to be left on its own hence raising the regulatory bar for ensuring the ultimate scientific value for the society at large. GCP are a set of tools that has made it possible.

Majority of earlier medical research assumed the process itself as an outcome of the greater good that practice of medicine has often been perceived as. Majority of classical diagnostic methods relied on physicians' subjective observations that they begin to document forming what could be termed as the origins of evidence-based medicine. Physician belonged to the highest pedestal of honor in a society, the fact that many have still retained. Conquests and conflicts further provided insights as early records of infectious outbreaks such as malaria, plague, smallpox, and yellow fever. The industrial age coincided with emergence of commercialization of medical treatment indicating a shift away from traditional practices and the concept of healing per se. From the claim to invention of local anesthesia used in a tooth extraction that hasn't been fully settled to date to the Flexner report of earlier twentieth century, there were indications for a vacuum that existed in the race to achieve monetary glory and copy rights. The emergence of GCP itself is credited to the evidence of deception reported in past decades. Today, it's the bulwark against subject abuse in fact empowering them to seek clarifications and exercise autonomy before deciding to participate in a study. However, despite all this evolution, several medical inventions and drug patents are daily disputed in courts around the world with financial and societal costs running in tens of billions. It comes down to a culture of both scholarly and entrepreneurial biomedical research that was not available at any time in history. In fact, low-and-middle-income countries (LMICs) could exploit it to improve their health landscape and invariably tap into positive externalities associated with such a paradigm shift.

Estimates have been equivocal in categorizing LMICs to bear the brunt of global disease burden. Its neither surprising nor new. A report from International Federation of Red Cross (IFRC) concluded each global household with at least one family member with non-communicable diseases (NCDs) that commonly includes cardiovascular disorders, diabetes, cancers, and road traffic accidents leaving victims with lifelong disabilities.That would translate into ever-increasing disease burden helped by highest population growth rate ever recorded. Even such growth rates are skewed in favor of developing nations with limited resources to spend on public health and other social development. Emergence of new infections as the ongoing pandemic (SARS-CoV-1) with corresponding lack of preparedness further compounds the grim forecasts. For LMICs, the twentieth century public health challenges like infectious disease burden never lightened owing to persistent unsanitary living conditions that high-income countries (HICs) have been able to understand and subsequently overcome mainly due to rewards of industrialization. While financial resources are often cited as the major handicap restricting development of solutions to health problems in LMICs despite record numbers graduating with

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higher degrees by research, one wonders why those researchers have been unable to contribute towards problem-solving for decades.

The state of medical research corresponding with disease burden in LMICs as summarized above raises key questions of how long the current situation is sustainable. Not for too long with emerging pandemics of zoonotic viruses every decade or two. There is no escape or "short-cut" either. Each problem comes with opportunities and set of solutions. Similarly, the abysmal state of medical research quality needs a strong promotion of GCP to encourage curious thinking for understanding local problems and possible methods to measure them. In case of Pakistan, one of the interesting development seen in international registry for registration of clinical trials (clinicaltrials.gov) is several randomized clinical trials registered since March 2020. It seems unlikely that any previous year would have that many within a short span of few months. That is a healthy trend to respond to a SARS-CoV-2 pandemic with an aim to muster whatever available resources to safeguard local population from a yet to be known scourge. Inevitably, it leads to the quality continuum been discussed here as GCP framework. More interestingly, various manuals of Drug Regulatory Authority of Pakistan cite GCP as their gold standard but was rarely practiced as now owing to local researchers trying herbal products to off-label compounds in randomized trials. The arrival of phase III, placebo-controlled vaccine trials has further boosted demand for GCP certifications. From March 2020, registered clinical trial have compelled institutions to expand their quality net around research protocols by wrapping it prominently in features that priorities subject rights such as the need for localized informed consent. It's a welcome departure from what was being observed in very recent past.

Similar to many countries with cellular-phone connectivity having skipped an entire generation of landline phones and telegraph infrastructure, LMICs have a more potent tool at disposal to promote a culture of authentic medical/health research that relies on public trust being built through demonstrable practice of GCP. Industrialized nations have probably learned it the harder way. Onus is on regulators in both academia and industry to incentivize this demonstration if sustainable health solutions are to be found.

Role of Zinc in Patients Presenting with Recurrent Hepatic Encephalopathy in Medical Unit of Tertiarycare Hospital Lahore

Asma Kamal, Asifa Kamal, Naeem Afzal, Shazia Siddique, Khadija Tahir

Abstract

Objective: To observe the effects of zinc replacement on hepatic encephaopahty. To reducce hospital admission and heath burden by reducing episodes of recurrent hepatic encephalopathy.

Methods: This study was carried out on 160 patients presenting with hepatic encephalopathy in medical ward of services hospital Lahore. The aim of the study was to assess the role of zinc in the improvement of encephalopathy.

Results: The mean age of patients in group A was 55.78 and that in group B was 56.88years.There was significant difference in mean value of hepatic encephalopathy grade in both groups A and B after 3 months of follow up (p.value 0.027) indicating zinc is beneficial in treatment of hepatic encephalopathy.

Conclusion: Our study showed that zinc replacement improved outcome in patients with Hepatic encephalopathy.

Key words: Hepatic encephalopathy, zinc supplementation, chronic liver disease.

Introduction

Cirrhosis is diffuse hepatic process characterized by inflammation and regeneration leading to fibrosis.[1-2] The complications of chirrosis include HTN, ascitis, hepato reval lynd and HE. HE is spectrum of neuro pschychiatric abnormalities in patients that is liver dysfunction.[3] The development of HE is explained by effects of neurotoxic substances which occurs in setting of chirrosis and portal hypertension.[4] The development of HE negatively impacts patient's survival. The encephalopathy leading to hospitalization is associated with survival probability of 42% at one (01) year and 25% at three (03) years.[5] Approximately 30% patients dying of end stage liver disease experience HE approaching brain edema.[6]

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The economic burden of HE is substantial. After ascitis and GI bleed hepatic encephalopathy is 2nd most common reason for hospital admission. Hepatic encephalopathy is also most common, possibly preventable cause of readmission.[7] This results in into negative impact on employment and finances of patients and their care givers.[9-11]

Overt HE occurs in 30% to 50% of chirrotic patients and tends to 10% to 50% of patients with TIPS.[24-26] The prevalence vary between 30% to 84%.[32-34] As the level of ammonia (NH3) is increased in blood, so the most common strategy is to reduce ammina production or increasing its metabolism outside the brain. To increase ammonia metabolism, one can administer L-Ornithine and L-aspatate which enhances ammonia incorporation to amino acid glutamine in skeletal muscles. An earlier approach to decrease protein intake in diet lead to decreased muscles mass, so this is no more recommended now.[12-14]

Maintaining muscles mass is important because a chemical reaction that removes ammonia by incorporating it into glutamine can occur in the skeletal muscles.[15]

Zinc deficiency is common in chirrosis and results into alter nitrogen metabolism.[3] The recommended

dietary allowance is 8 mg/day for women and 11 mg/day for men. The low serum zinc level in chirrotic patients is due to decrease intake, decrease absorption, decrease bio availability and increase loss (because of metabolism).[2]

In study of stamoulis et al in 2007, the prevalence of low serum zinc in chirrotic patients was 65.3%.[4]

Because low serum zinc level precipitate HE, so zinc supplementation is considered a potential therapeutic option. The oral zinc replacement improved performance on number connection test (NCT), but no evidence about other clinical and biochemical outcomes available.

In one randomized trial average HE grade was 1.3+ 0.9 with the placebo while 0.9+0.9 with zinc supplementation (N=39, P<0.05) and NCT was 70.6+ 29.7 seconds with the placebo while 63.6+22 with the zinc.[6]

Literature has reported that zinc supplementation is better than no zinc. There is only one local study available which showed improvement in HE by zinc supplementation.

Objective

The objective of this study is to assess the beneficial effect of zinc suppliments in the treatment of hepatic encephalopathy so the burden of recurrent admission could be reduced.

Methods

In this study 160 patients presenting with the Hepatic encephalopathy were included. Half of them (80) patients were given standard treatment for Hepatic encephalopathy i.e. Refixamin, Lactulose and branched chain amino acids were given, while the other half of patients were given standard treatment along with zinc supplements. Number connection test was carried out to assess the effect of treatment and time noted in seconds.

Inclusion Criteria: All the patients presenting with Hepatic encephalopathy were included in the study.

Exclusion Criteria:

1. Patients with organic brain disease like stroke, encephalitis, meningitis.
2. Patients with other causes of encephalopathy like uraemic encephalopathy in advanced renal failure, hypoglycaemia and severe electrolyte imbalance.

Study Design: Randomized controlled trial 160 patients with the hepatic encephalopathy were admitted through emergency and OPD over a period of 6 months. They are kept randomly in Group: A and B. Group A includes those on a standard therapy while the Group B includes standard therapy along with the zinc supplement. NCT was done during stay in the hospital at the discharge. Patients were advised to visit monthly for the follow up and NCT and recorded on the Performa.

Setting: medical unit-II of Services Hospital Lahore

Sampling Technique: Non probability consecutive sampling.

Data Analysis: SPSS 20

Results

Table 1: *Percentage Distribution of Standard Treatment Group and Zinc Supplementation Treatment Group across NCT*

NCT	Treatment Group		Total
	Standard Only	Standard +Zinc Supplementation	
<30	11 (13.8%)	15(18.8%)	26(16.3%)
31-50	19(23.8%)	32(40.0%)	51(31.9%)
51-80	34(42.5%)	21(26.3%)	55(34.4%)
81-120	13(16.3%)	11(13.8%)	24(15%)
Force End	3(3.8%)	1(1.3%)	4(2.5%)
Total	80(100%)	80(100%)	160(100%)

Figure-1 *Multiple Bar Chart showing Percentage Distribution of Standard Treatment Group and Zinc Supplementation Treatment Group across NCT*

Majority of patients (18.8%+40%=58.8%) who were given zinc supplementation along with standard treatment have low level of NCT (<50) as compared to those who were given only standard treatment.

Table 2: *Comparison of NCT Across Standard Treatment and Zinc Supplementation Treatment Using Mann – Whitney U Test.*

Treatment Type	Mean Rank of NCT	Mann-Whitney U	P-value
Standard Treatment	88.26		0.027
Zinc Supplementation	72.74	2579.5	

Table 3:

		n	Mean Rank of NCT on Standard Therapy	Mean Rank of NCT Zinc Supp. & Standard Therapy	Mann-Whitney U	P-value
Gender	Male	106	58.71	48.29	1128.5	0.069
	Female	54	30.09	24.91	294.5	0.206
Age	35-45	20	11.53	7.40	22.0	0.197
	46-55	48	28	22	210.0	0.126
	>55	92	49.50	43.63	922.5	0.273

Majority of patients (34.4%) have NCT 51-80 irrespective of treatment groups.

Average rank for zinc supplementation is lower as compared to standard that indicates that there is improvement in the NCT for adding Zinc supplementation along with standard treatment. Difference in the NCT is significant among the two groups (p-value=0.027).Table 3: Comparison of NCT across Standard Treatment and Zinc Treatment Using Mann-Whitney U Test (Stratified for Gender and Age)

Table 4:

		n	Mean Rank of NCT	Test	P-value
Gender	Male	53	41.54	Mann-Whitney U Test=660.5	0.557
	Female	27	38.46		
Age	35-45	5	35.30	Kruskal Wallis Test=3.502	0.174
	46-55	28	34.91		
	>55	47	44.38		

Effect of zinc supplementation on NCT is not significantly different among male and female (p-value= 0.557). Similarly it has not significantly different effect on NCT for three age groups (p-value=0.174).

Discussion

It has been shown that zinc which is a trace metal is deficient in patients with chronic liver disease and is involved in metabolic abnormalities primarily pertaining to ammonia which can be alleviated by zinc replacement4.Zinc is an important, cheap and readily available mineral having many effects in HCV related cirrhotic patients. HE is characterized at the neurophysiological level by disturbed corticocortical and corticomuscular coupling causing primary gliopathy.[16] Ammonia is a key pathophysiological factor in HE.[17] Zinc supplementation has shown to reduce ammonia levels in experimental animals and humans through hepatic urea synthesis stimulation and glutamine synthesis in skeletal muscles.[18] Several reports describe zinc supplementation improving psychometric performance with a reduction in blood ammonia level in HE patients.[3] In addition, combinations of zinc and conventional therapies such as a protein-restricted diet including BCAA preparation or lactitol have been reported as effective therapies for HE. Hayashi et al.[19] reported that combination treatment with BCAA and zinc supplement decreased blood ammonia level more than BCAA treatment alone in cirrhotic patients during the study period.

According to a recent meta-analysis three studies reported data on number connection test; all three showed an improvement in performance in the zinc group compared to placebo or standard therapy. This improvement suggests a beneficial effect of oral zinc in encephalopathy patients. These findings were also similar to the findings of our study as we found improved performance on the patients of encephalopathy patients with the use of zinc.[20-22] According to Takuma et al, in their study, zinc supplementation in addition to standard treatment clearly demonstrated improved liver function and HE in decompensated liver cirrhosis.[6] Although the studies show improvement in HE but in Pakistan, limited data was available. One study at Allied Hospital Faisalabad compared the HE outcome during hospital stay of one week between standard treatment and with zinc along standard treatment which showed improvement.[23-24] While another study at the same hospital showed improvement in HCV viral load when treated with zinc.[25] In our study we have given zinc for three month period and assessed the improvement via NCT. In our study 160 patients were participated including 80 in each group. Those replaced with the zinc show improvement in NCT with p value of 0.027.

In gender distribution males show more response to therapy as compared to females but the difference is not significant. This might e because of more number

of males in the study. Our females do it early according to NCT rank.

Age wise patients with the age of 46-55 years show more response followed by age 35-45 years and more than 55 years respectively. Although this difference is not significant with the p value 0.174 but it do exist.

Recommendations

As many studies show improvement with the zinc replacement along with the standard therapy, so keeping in view the health burden of decompensated liver disease one of which is HE results into repeated admissions. So zinc supplementation seems to be effective treatment for HE along with standard therapy to treat it. However more follow up studies should be conducted at other hospitals as well, so the large data could be analyzed and treatment be implemented.

List of Abbreviations

CLD: chronic liver disease

BCAA: Branched chain amino asides

HE: Hepatic encephalopathy

NCT: Number connection tests

Authors Contribution

AK: Main Author

AK: Statistical Analysis

SS: Write-up of Paper

NA: Helped in write-up

KT: Computerized write-up and editing

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Prevention of Renal Stone Recurrence: Knowledge and Practice Patterns Among Medical Officers of DHQ Hospital, Faisalabad

Muhammad Saifullah[1], Hanan Noor[2], Muhammad Waqas Iqbal[3], Nauman Khalid[4], Muhammad Sohail[5], Muhammad Akmal[6], Ghulam Mehboob Subhani[7]

Abstract

Objective: To assess the knowledge and practice patterns among medical officers of DHQ Hospital, Faisalabad in the prevention of recurrent renal stones. Cross sectional study. DHQ hospital, Faisalabad during 01-01-2019 to 30-09-2019.

Methods: In this study the medical officers of either gender and age more than 25 years and working in DHQ Hospital, Faisalabad were included. They were assessed on the basis of a designed questionnaire regarding their general practice and knowledge in order to prevent renal stone recurrence. The paper based questionnaire was circulated to medical officers in different departments of the hospital.

Results: In this study total 225 medical officers that were included. 135 (60%) of these participants were males and 90 (40%) were females. The mean age of the participants was 29.70±3.21 years. The mean working experience was 4.40±2.18 years. On assessment, 65.67% medical officers had adequate knowledge regarding recurrent renal stone prevention according to latest practice guidelines. Unfortunately 62.22% respondents were not practicing their knowledge adequately.

Conclusion: The knowledge regarding the clinical practices in light of recent guidelines was optimal, however the practice regarding the preventive strategies was below power.

Keywords; Renal stone, Recurrence, Medical officer, prevention.

Introduction

Nephrolithiasis is an ancient disease which is known to humans for centuries. It affects 5-20% of mankind at least once during their life.[1,2] It is a widespread disease affecting young males more than females.[3,4] 12% of males and 7% of females develop renal stone disease during their life.[5] It is one of the commonest urological diseases with its incidence increasing all across the globe. It has been considered a lifelong disease as it has higher chances of recurrence with poor clinical consequences.[6] These consequences include chronic renal failure, end-stage kidney disease, diabetes mellitus, hypertension and cardiovascular accidents.[1]

Stone formation is usually asymptomatic initially. However, with the passage of time as the stone size progresses, it may cause colicky flank pain, hematuria, urinary tract infection and hydronephrosis[1]. Calcium based stones are the most prevelant type of stones accounting for 70%-85% of cases.[3,7,8] Non-calcium stones include urate stones (5%-10%), magnesium ammonium phosphate stones (1%-5%), cysteine stones (1%) etc.[3] Stone analysis is valuable tool used for diagnosing underlying etiological risk factors which lead to renal stone formation, especially in rare stone varieties like urate, ammonium urate, cysteine, drug-induced and infection-induced stones.[5] Different methods used for stone analysis include infrared spectroscopy, X-ray diffraction and polarizing microscopy.

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Lifetime recurrence rate in first time stone formers is 50%. Time between recurrence episodes decreases with every passing episode.[2] Metabolic workup is compulsory for recurrent stone formers & in special circumstances for first time stone formers.[7] According to one study, advice of 24-hour urinary metabolic workup was followed only by 7% of symptomatic patients and 17% of patients with recurrent urolithiasis for prevention purpose.[9]

The significance of adopting preventive measures can be assessed by the recurrence rate of this disease. Effective utilization of the preventive strategies have reduced 5-year recurrence rate by 60%.[2] However, prevention of recurrent stone disease is always a dilemma for patients as well as health care providers. It is not possible to prevent stone recurrence without knowing the pathophysiology which leads to stone formation[1]. Sedentary life style and modern eating habits like fast foods, carbonated drinks, animal proteins, dairy products, inadequate water intake, high sodium diet, less vegetable consumption etc contribute in stone formation.[4,8]

To address this issue, we carried out a survey to evaluate the knowledge, attitudes and practice patterns among medical officers of DHQ hospital, Faisalabad regarding prevention of renal stone recurrence. The rationale of our study was to find out the knowledge of medical officers working in our hospital regarding prevention of renal stone recurrence. Furthermore, we needed to assess their attitude towards the recent guidelines and application of their knowledge in every day practice.

Objective

To assess the knowledge and practice patterns among medical officers of DHQ Hospital, Faisalabad in the prevention of renal stone recurrence.

Methods

This was a cross sectional study that was conducted at DHQ Hospital, Faisalabad during 01-01-2019 to 30-09-2019. In this study, 225 medical officers of either gender or age more than 25 years and working in DHQ Hospital, Faisalabad were included using consecutive non-probability sampling technique. After taking informed consent, medical officers were assessed on the basis of a designed questionnaire regarding their general practice and knowledge about prevention of renal stone recurrence. The questionnaire was designed according to the latest guidelines of European Association of Urology and World Health Organization regarding recurrent renal stone prevention. This included questions regarding 2 domains: knowledge and practice patterns. Demographic profile was completed. Questions regarding practice were assessed before the knowledge assessment, so that respondents may not take any leading answers. Practice and knowledge was assessed using multiple-choice questions. The paper based questionnaire was circulated to medical officers working in different departments of the hospital. SPSS-version 23.0 was used for data analysis and frequency and percentages were calculated for categorical data and mean and standard deviation for quantitative variables.

Results

In this study total 225 medical officers were included. There were 135 (60%) males and 90 (40%) females (Figure # 1). The mean age of the participants was 29.70±3.21 years. The mean working experience was 4.40±2.18 years with a range of 2 to 9 years as shown in table # 1.

Regarding knowledge, 55.56% of medical officers stated that high urine output is the most important inhibitory factor for stone formation (Figure # 2). we further noted that 68.89% medical officers were aware of the fact that high fluid intake is the single most important dietry modification which prevents recurrence of urinary stone disease (Figure # 3). 56.17% medical officers correctly identified the comorbid factors which lead to urinary stone formation. Salt intake reduction was advocated by only 39.57% (n=93) medical officers. 54.44% respondents (n= 128) were not aware about protein restriction in diet of stone formers (Figure #4). 78.89% (n=177) clinicians could not correctly identify the commonest recurring stones i.e., uric acid stones.

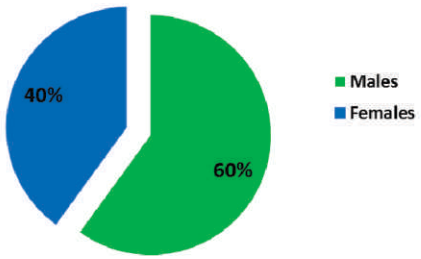
Table 1: *Demographics of Study Subjects*

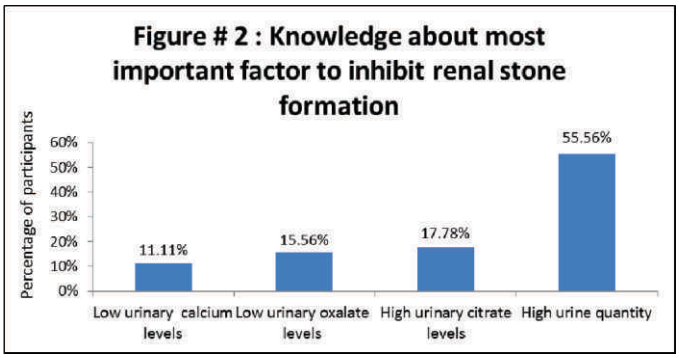
Variables	Mean ± SD	Range
Age	29.70±3.21	25-34
Working Experience	4.40±2.18	2-9

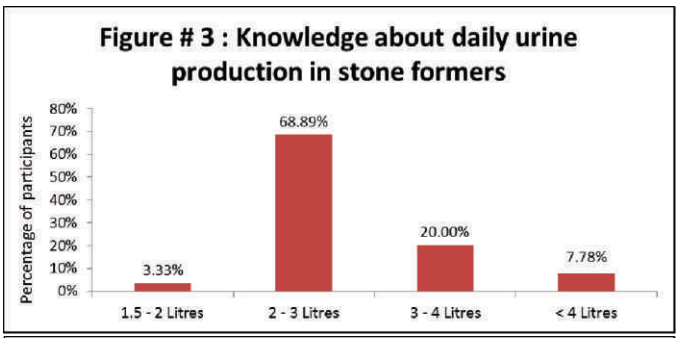
26.38% (n=62) medical officers advised stone analysis to every first time stone former who mana-

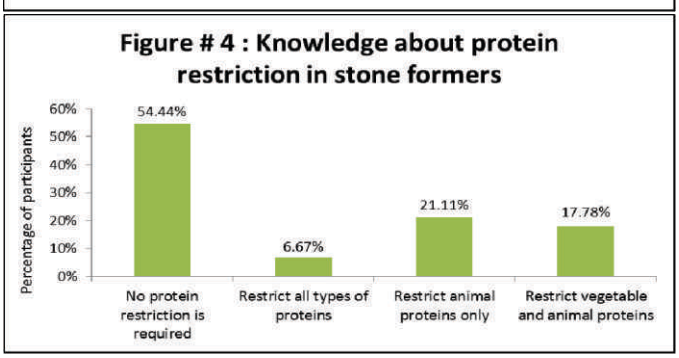
ged to retrieve the stone. Animal protein restriction was advised by only 24.44% (n=55) medical officers. Maintenance of normal calcium requirements was practiced by 45.33% (n=102) medical officers. Overall, 65.67% (n=154) medical officers had adequate knowledge regarding recurrent renal stone prevention according to latest practice guidelines. Unfortunately 62.22 % (n=146) respondents were not practicing their knowledge adequately (Figure # 5). The value of pearson correlation coefficient (R) is 0.4262. By this we conclude that there is a weak positive correlation between knowledge & practice. The p-value is < 0.00001 which is significant.

Figure # 1: Distribution of participants according to Gender



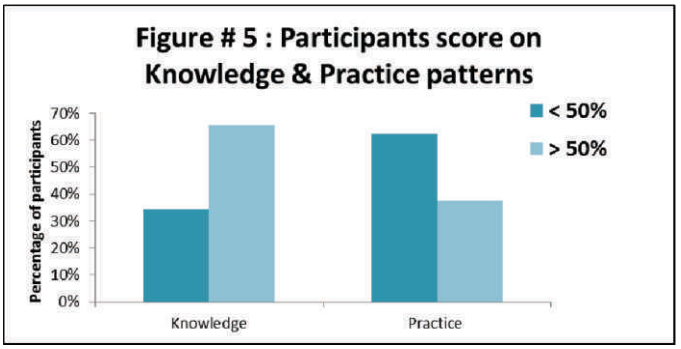






Discussion

Knowledge, Attitude and Practices (KAP) survey is a method utilized for assessment of different diseases by using predefined standardized questionnaires. There are only a few studies which address this issue. Respondents of our study did not clinically practice the preventive strategies regarding recurrent renal stones despite having adequate knowledge. Although 65.67% respondents had satisfactory knowledge regarding prevention of recurrent nephrolithiasis, only 37.78% medical officers used their knowledge productively in practice. Lack of utilization of knowledge is attributable to factors like disagreement of clinicians with guidelines and lesser outcomes than expectations.



Different studies have documented that recurrence of kidney stone disease is remarkably lower in patients who ingest high levels of fluids.[10,11] Therefore, increasing fluid consumption is the most important recommendation in prevention of urolithiasis. Current guidelines suggest maintenance of 2 to 3 L of urine volume per day. Stone formers have a very low urine output which is 1.6 L/day on average.[12,13] Decreased urinary output is due to decreased fluid intake which leads to increased concentration of solutes in urine which crystallize to form stones.[13] In our study, urine output of 2 to 3 litres per day which is required for prevention of urolithiasis was supported by 68.89% participants. However, Bos D et al noted that only 20% of participants advocated 2 – 3 litres per day of urine output. Generally, adequate fluid intake of 2.5–3 liters a day, intake of moderate amount of animal protein, dietary calcium, vitamins/mineral supplements, fruits/vegetables and weight loss are safe and reasonable dietary recommendations as per guidelines.[2]

Urate stones accounts 5–10% of all renal stones and 10-15% of all urinary stones.[11,14] High body mass index, much intake of fructose rich products, and high

protein intake has a significant association with the formation of uric acid stones.[11] Higher incidence of urate stones is commonly associated with increased urinary uric acid levels, persistent low pH of urine and decreased urine volume. Uric acid stones are notorious for their recurrence. Obesity, diabetes, environmental factors & change in dietry habits also increase risk of stone formation significantly.[14] Bos D et al concluded that more than 90% respondents were unaware of the recurrent nature of uric acid stones.[2] However, we studied that 78.89% clinicians could not identify uric acid stones as the commonest recurrent stones.

Oxalate plays an important role in formation of calcium stones. Foods rich in oxalates includes rhubarb, beets, nuts, cranberries, chocolates, wheat bran, spinach, sesame seeds, tomatoes, tea and green beans increases the risk of kidney stones.[13,15] Critical factor in formation of calcium oxalate stone is the amount of oxalate excreted in urine.[16] The concentration of calcium is considerably higher than the concentration of oxalate in urine. Therefore, change in concentration of oxalates have a more impact than change in concentration of calcium on the supersaturation of crystals of calcium oxalate. For attenuating calcium oxalate supersaturation one should take normal amount of dietry calcium and reduce the intake of high-oxalate-containing foods, thus reducing stone progression in kidney stone-forming individuals.[16] Current guidelines suggest oxalate-rich foods in moderate amount and calcium intake adjusted to 1000–1200 mg/day.[16] In stone prevention, limiting intake of sodium in diet is a key factor.[17] Recurrent calcium nephrolithiasis can be reduced by reduction in dietry sodium intake i.e., 1.8–2.3 g/day. According to the European Association of Urology guidelines, the daily intake of salt (NaCl) should limit to 4-5 grams. Volume expansion due to high sodium intake decreases sodium and calcium reabsorption in proximal tubules and thus enhances calcium excretion rendering urine more lithogenic.[12,13] Increased excretion of sodium in urine leads to increased saturation of monosodium urate. This acts as a nidus for calcium crystal formation. In our study, salt intake reduction was advised by only 39.57% (n=93) medical officers.

Cranberry juice has been reported to significantly alter key risk factors for urolithiasis as it increases urinary citrate excretion which inhibits calcium lithogenesis and decreases the excretion of phosphate and oxalates in urine. Furthermore, it has been reported that there is reduction in saturation of calcium oxalate with the use of cranberry juice.[18] Diets rich in animal proteins should be restricted in kidney stones patients. High amount of calcium and urate is excreted in urine by consuming diet rich in animal proteins from meat, fish and chicken. Purine rich products like red meat, tinned fish, meat extracts and muscles also increases the uric acid concentration, therefore intake of these products should be restricted to 1gm/kg/day.[13] An acid load is generated by consumption of animal proteins which increases excretion of urinary calcium and reduces the excretion of calcium stone inhibitor, citrate. However, in our study only 24.44% (n=55) medical officers correctly identified that animal protein restriction is mandatory for recurrent stone formers.

All renal stone patients should undergo metabolic analysis to rule out systemic disease as advocated by CUA. Stone-formers should undergo metabolic evaluation which include serum analysis (sodium, chloride, potassium, calcium, bicarbonate, albumin, creatinine, uric acid and phosphate), a urinalysis and a stone analysis. Bos D et al noted that 57% health care workers quoted multiple stones as an indication for stone analysis.[2] In our study, only 26.38% medical officers ordered stone analysis to first time stone formers.

Diet plays a very important role in urinary calcium containing stone formation. Calcium oxalate stones account for 75% of calcium containing urinary stones.[18] Diet low in calcium is discouraged as it allows more absoption of oxalates which leads to hyperoxaluria. Therefore, moderate calcium in diet (1g/day) is usually recommended for patients. Intake of supplemental calcium may increase the risk of symptomatic kidney stone while dietry calcium intake decreases the risk. Maintenance of normal calcium intake (1-1.2g/day) was practiced by 45.33% (n=102) medical officers in our study.

In this study, we noted that medical officers did not practice latest guidelines despite having adequate knowledge. Improper utilization of preventive measures is attributable to different factors which include lack of awareness, disagreement of clinicians with guidelines, lesser outcomes than expectations and

absent incentives which can improve delivery of preventive system.

In one study, it is declared knowledge of urologists in Saudi Arabia as deficient. They recommended activities to improve their knowledge. They further proposed that application of knowledge in routine practice should be enforced.[17] In another study it was noted that patients lack adequate knowledge about the dietry modifications required by the recurrent stone formers. Even educated people lacked sufficient information.[19] It was recommended in a similar study that planned educational activities offered on regular basis to the patients to improve the self care practices and knowledge.[20] Moreover, it was concluded through another study that patients having history of stone disease were more knowledgeable and careful in preventing recurrent stone formation. He advised interventions for improving preventive measures as well as correcting misconceptions.[21]

As described, many international studies have elaborated the important of preventive strategies in recurrent urolithiasis. But we have studied those healthcare professionals who are usually the first respondents to the patients. They have adequate knowledge regarding prevention of urinary stone disease. However, despite of adequate knowledge, the pattern of their clinical practices are not according to the latest guidelines.

Conclusion

The knowledge regarding the clinical practices in light of recent guidelines was optimal, however the practice regarding preventive strategies was sub-optimal.

Recommendations

We recommend more frequent awareness programs for prevention of renal stone recurrence in order to improve the knowledge of the healthcare providers. This will in turn encourage young medical officers to incorporate their knowledge in daily practice regarding recurrence of renal stone preventive strategies like dietry modifications and fluid intake etc

Conflict of Interest

There are no conflict of interest.

Author's Contribution:

MS: Principal Author & Manuscript Writer
HN: Investigator, Data Collector
MWI: Literature Review and Data Analysis
NK: Statistical Analysis
MS: Proof Reading
MA, GMS: Research Supervision

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A Morphological Study on Gross Gnatomical Variations of Embalmed Cadaveric Livers

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Abstract

Objective: To find out gross anatomical variations of embalmed cadaveric livers.

Methods: Present study was conducted in dissection halls of Anatomy departments of Allama Iqbal Medical College, Lahore, Sahiwal Medical College, Sahiwal and Fatima Jinnah Medical University, Lahore during 2016-2019. In this study, 74 livers were dissected out from embalmed cadavers and preserved in 10% formalin. Different morphological variations were observed in livers which included presence of accessory lobes, accessory sulci, notches, changes in size and shape of lobes. Liver specimens were photographed and classified according to Netter's classification of morphological variations of liver.

Results: The hepatic morphological variations observed included accessory fissures in the right, left, caudate and quadrate lobes of the liver, accessory lobes, elongated left lobe, hypoplastic left lobe, multiple deep diaphragmatic sulci, pons hepatis, Reidel's lobe, notched borders and bilobed caudate lobe.

Conclusion: The knowledge of various variations in morphology of cadaveric livers may help the radiologists to make accurate interpretation of the radiological images, thus minimizing the chances of incorrect reporting. It may also be helpful to the hepatobiliary surgeons to be aware of the morphological variations on the liver surface to avoid surgical complications.

Key Words: Embalmed cadaveric livers, accessory lobes, accessory fissures

Introduction

The liver is the largest gland in the body and occupies the right hypochondrium, epigastrium, and left hypochondrium regions of abdomen. The liver is about 2% of body weight in the adults, which amounts to approximately 1800 gms in males and 1400 gms in females. The liver has a homogenous parenchyma and is divided into four anatomical lobes by peritoneal ligaments. Externally, falciform ligament divides the liver into a larger right lobe and a smaller left lobe.[1] Caudate and quadrate lobes may be considered as the parts of the right anatomical lobe.[2]

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In 1897, Sir James Cantlie described the liver division between the right and left lobes. Later, Claude Couinaud (a French surgeon and anatomist) provided additional insight and described the segments of liver based on hepatic vasculature. According to Couinaud classification, the liver is divided into 8 functionally independent segments having their own blood inflow, outflow and biliary drainage. In the center of each segment, a branch of the portal vein, hepatic artery and bile duct is present. These fundamental studies provided a basic framework for surgical discussions of liver anatomy.[3] The peritoneum normally invaginates into the parenchyma of liver forming sulci and fissures. There are four normal fissures in human liver: fissures for the ligamentum venosum, ligamentum teres, and gallbladder and the transverse fissure.[4]

Liver development begins during 3rd week of intrauterine life. Liver parenchyma is derived from the endoderm of the foregut, whereas the stroma is derived from the mesoderm. The hepatic diverticulum is derived from the caudal part of foregut, that grows into the septum transversum, which is a splanchnic mesodermal mass which extends between the heart anlage and the mesentery. Septum transver-

sum and cardiac mesoderm have inductive influence for the development of hepatic diverticulum. Stromal tissue of the liver develops from the septum transversum and splanchnic mesoderm around gut. Septum transversum hence divides the developing organ into lobes and lobules making the connective tissue parts of the liver. Initially the development of the liver lobes is symmetric. As the development continues, the growth of the right lobe accelerates and it is difficult for the left lobe of liver to find adequate space due to progressively developing gut.[5-10]

Congenital hepatic anomalies are caused due to defective development or excessive development of the liver. Defective development of the left liver lobe may lead to gastric volvulus while defective development of the right lobe either leads to portal hypertension or remains clinically latent. Anomalies related to excessive development of the liver lead to formation of accessory lobes of liver. In most cases, the accessory liver lobe is found in the infra-hepatic position. Riedel's lobe is one of the best-known examples of a sessile accessory liver lobe.[11] Torsion is common in few cases where the accessory lobe has a pedicle. While accessory lobes can simulate tumors, there have also been some reports of hepatocellular tumor.[12] Riedel's lobe corresponds to hypertrophy of segments V and VI. It was first described by Corbin in 1830 and defined by Riedel in 1888 as a "round tumor on the anterior side of the liver, the gallbladder, to its right". The prevalence of Riedel's lobe ranges from 3.3-31%, with a higher incidence in women than in men.[13-15]

Methods

Present study was conducted in dissection halls of Anatomy departments of Allama Iqbal Medical College, Lahore, Sahiwal Medical College, Sahiwal and Fatima Jinnah Medical University, Lahore during 2016- 2019. In this study, 74 livers were dissected out from the embalmed cadavers and preserved in formalin. Morphological variations such as changes in shape and size of right, left, caudate and quadrate lobes, presence of accessory lobes, accessory sulci, abnormal processes and notches on right, superior and inferior borders of livers were noted. Porta hepatis, fossa for gall bladder, grooves for ligamentum teres & ligamentum venosum were also observed for any variation. Livers were photographed and classified according to Netter's classification of morphological variations of liver.

Results

In the present study of the 74 liver specimens, 36 livers (48.6%) were observed with normal surfaces, fissures, and borders without any additional accessory fissures or malformations. Of the remaining 38 specimens, hepatic surface variations were documented and broadly grouped as having accessory fissures, accessory lobes, presence of a pons hepatis, notching of borders.

Table 1: *Table 1. Netter's Classification of Morphological Variations of liver*[16]

Types	Description
Type 1	Normal
Type 2	Very small left lobe, deep costal impressions
Type 3	Complete atrophy of left lobe
Type 4	Transverse saddle like liver, relatively large left lobe
Type 5	Tongue like process of right lobe
Type 6	Very deep renal impression and corset constriction
Type 7	Diaphragmatic grooves

Of the superior sulci, 4 appeared to have deep multiple diaphragmatic grooves, one of liver also had hypoplastic left lobe (Fig 1). 10 livers were noted to have accessory fissures on the right, left, caudate and quadrate lobes (Figs. 2,3,4 and 5). Accessory lobes were identified on 8 specimens (10.9%). Pons hepatis were seen in 2 specimens, (Fig. 2). Notching on superior border were observed in 5 specimens (Fig 2,3)

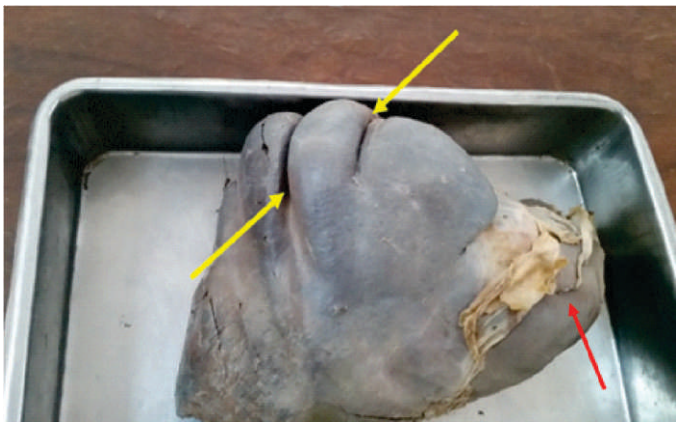

Fig.1: *Yellow Arrows (Deep Costal Sulci, Netter Type 2), Red Arrow (Hypoplastic Left Lobe)*

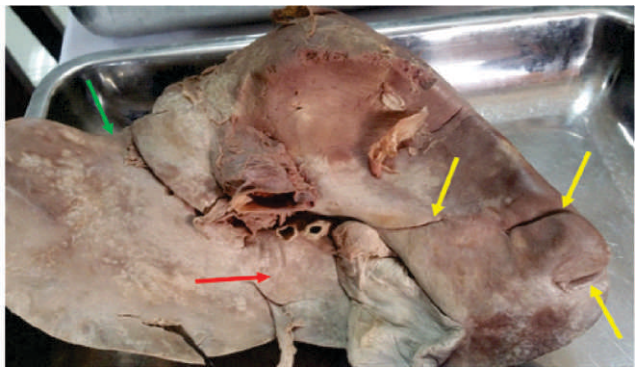

Fig.2: *Green Arrow (Deep Notch on Superior border), Yellow Arrows (Accessory Sulci on Right lobe),Red Arrow (Pons Hepatis)*

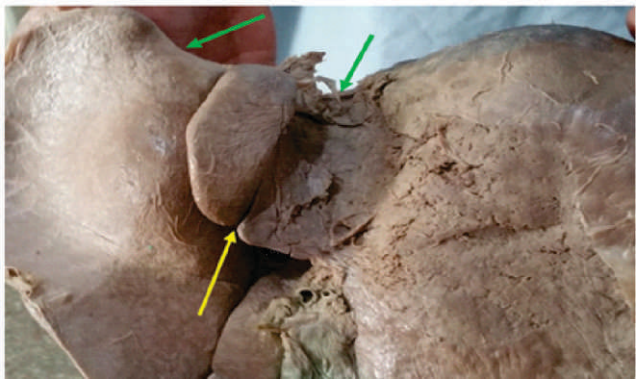

Fig.3: *Green Arrows (Deep Notches on Superior Border), Yellow Arrow (Accessory Sulcus & Bilobed Caudate Lobe)*

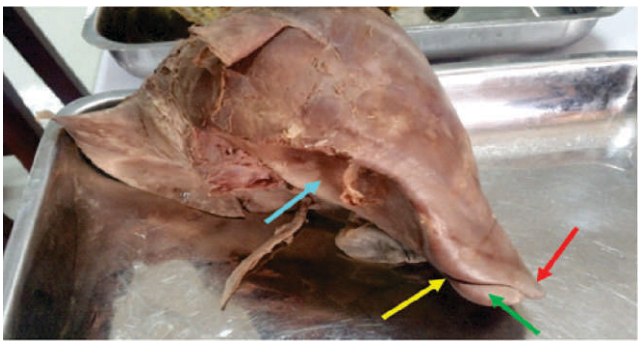

Fig.4: *Red arrow (Tongue like Process of Right Lobe, Netter Type 5), Yellow Arrow (Accessory Sulcus), Green Arrow (Small Accessory Lobe), Blue Arrow (Deep Renal Impression)*

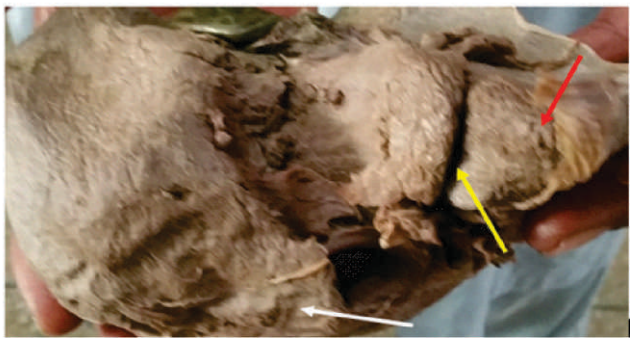

Fig.5: *White Arrow (Transverse Saddle Type Liver, Relatively Large Left Lobe, Netter Type 4), Yellow Arrow (Sulcus on Right Lobe), Red Arrow (Bilobed Small Right Lobe)*

Fig.6: *Red arrow (Lingular Process of Left Lobe)*

Table 2:

Sr No	Variations	Number of livers	Percentage
1	Accessory lobes	8	10.8%
2	Accessory fissures	10	13.5%
3	Hypoplastic left lobes	3	4%
4	Reidel's lobe	3	4%
5	Lingular process of left lobe	2	2.7%
6	Notches on superior borders	5	6.7%
7	Pons hepatis	2	2.7%
8	Deep renal impression on right lobe	3	4%
9	Prominent and deep diaphragmatic fissures on superior surface of liver	4	5.4%

Discussion:

Hepatic anomalies and variations are caused due to defective development of the liver. In present study, accessory lobes and accessory fissures were found in 10.8% and 13.5% cases respectively. Nayak carried out a similar study in South Indian population. He studied 55 formalin fixed livers for presence of abnormal lobes, impressions, sulci and position of gall bladder. In his study, 60% of liver specimens were normal. 40% specimens showed variations of lobes and fissures. Accessory lobes were found in 9.09% of cases.[17] In another study on 90 formalin fixed livers, Joshi and colleagues found abnormal shapes of the quadrate and caudate lobes. Accessory fissures were more common in the right lobe. In 18% livers, notching along the lower border of caudate lobe was observed, a longitudinal fissure was found in 30 % liver specimens, and prominent papillary process was found in 32% of liver specimens. Presence of pons hepatis, bridging the left lobe and

quadrate lobe, was observed in 30 % of the livers observed.[18] In present study, out of 74 livers studied, only 2(2.70%)livers showed pons hepatis. Pons hepatis was first identified by von Haller in 1743, as a segment of hepatic tissue connecting the quadrate lobe to the left lobe over fissure for ligamentum teres. In another study, the pons hepatis refers to hepatic tissue surrounding the inferior vena cava.[19]

Present study showed the presence of prominent diaphragmatic sulci on the superior surface of the liver in 5.4% cases. Machi et al in their study observed the diaphragmatic sulci in the superior surface of the livers in 40% of cases at autopsy. All fissures were located in the right lobe of liver and in 47% specimens, they were multiple. These findings suggest that the pressure exerted by the diaphragm as a whole may be responsible for the formation of sulci at the level of weak zones, represented by the portal grooves.[20] Another study on cadaveric livers showed variations in shape of the quadrate lobes with 40% being rectangular, 30% being pear-shaped, 20% being triangular and another 10% were square in shape. The presence of accessory fissures on the diaphragmatic surface of the liver were observed in 10%.[21] In our study, 4 (5.4 %) liver specimens showed prominent and deep diaphragmatic fissures on superior surface of liver.

Gupta and colleagues observed that the liver surfaces have 1-3 sulci distributed on all lobes in 70% liver specimens demarcating the vascular segments, which may help the surgeon during resection of liver.[22] In another study, Othman et al studied 40 liver specimens and the presence of accessory fissures were evident in only 2 specimens (5%). The accessory fissures were located in the inferior and posterior surfaces of the right lobes.[23] In our study, 13.5% liver specimens had accessory sulci.

The liver can present a number of congenital anomalies. They include irregularities of the shape, impressions on the liver surface, number of lobes, the presence of accessory lobes and accessory fissures.[24-26]

Conclusion

Study of surface variations in morphology of liver can help the surgeons to dissect in proper surgical planes to make the resection safe. Clinicians, radiologists and surgeons should be aware of such morphological variations to prevent diagnostic and surgical misadventures.

Author's Contribution

AZ: Conceived the idea, wrote the manuscript
BK: Analysis of manuscript
SM: Interpreting the results and worked on manuscript

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Frequency of Various Dermatoses Requiring Histopathological Evaluation For Definite Diagnosis; A Retrospective Analysis

Hira Tariq, Rabia Mukhtar, Abeer Fahad, Tariq Rashid, Ambereen Anwar, Ameena Ashraf

Abstract

Objective: To assess the frequency of various dermatological disorders those require histopathological analysis for definite diagnosis.

Methods: We included 669 patients of either gender and all ages in this retrospective study, carried out in the Department of Dermatology, Jinnah Hospital, Lahore for a duration of 2 years. Their clinical data and histopathological reports were analyzed. The dermatoses were categorized into (a) papulosquamous disorders, (b) bullous disorders, (c) eczemas, (d) neoplasia, (e) granulomatous disorders, (f) connective tissue diseases, (g) drug reactions, (h) vasculitides, (i) chronic ulcers and (j) miscellaneous disorders.

Results: The frequency of various dermatoses noted were as follows: papulosquamous disorders 28.25%, bullous disorders 11.5%, granulomatous disorders 11.5%, connective tissue diseases 10.61%, miscellaneous disorders 10%, eczemas 9.4%, chronic ulcers 7.17 neoplasia 6.8%, vasculitides 2.84% and drug reactions were 1.79% of total biopsies.

Conclusion: The frequency of different diagnostic groups was unique in some respects and confirmed to other studies in others. The significantly high frequency of papulosquamous disorders highlighted the importance of these disorders.

Key words: Skin biopsy, papulosquamous disorders, bullous disorders, eczemas, neoplasia, granulomatous disorders, connective tissue diseases, drug reactions, vasculitides, chronic ulcers.

Introduction

Obtaining a definite diagnosis is of utmost importance in skin disorders since management depends on it. Skin biopsy is useful tool for improving diagnostic accuracy in majority of dermatoses.[1] Interpretation of histopathology requires provision of adequate clinical information. Skin disorders constitute a major proportion of outdoor and indoor patients in developing countries.[2] Diseases of skin are a source of significant physical, social and psychological disability. No age is immune to these disorders. Clinical consequences vary from troublesome itching to death.[3] The prevalence of these diseases is often underestimated. Their distribution varies in different parts of the world and even within the same country.[4] Assessment of their frequency is important as many of these diseases are preventable.[5,6] Therefore, it is important to know the spectrum of disorders that require skin biopsy as adjunct to clinical diagnosis. In this study, we aim to analyse the pattern of dermatoses requiring skin biopsies. It will also help the concerned personnel to set their priorities.

Methods

Retrospective analysis of histopathology reports of 669 patients was conducted at the Department of Dermatology, Jinnah Hospital, Lahore. These patients underwent biopsies from 1st April 2017 to 31st March 2019. Patients of either gender and all ages were included. Based on the histopathological diagnoses biopsies were divided into following groups: (a) papulosquamous disorders, (b) bullous disorders, (c) eczemas, (d) neoplasia, (e) granulomatous disorders, (f) connective tissue diseases, (g) drug reactions, (h) vasculitides, (i) chronic ulcers and (j) miscellaneous disorders.

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Disorders like lichen planus, psoriasis and pityriasis lichenoides chronica were lumped together as papulosquamous disorders. Category of blistering diseases included pemphigus vulgaris, pemphigus foliaceous, bullous pemphigoid, linear IgA disease, dermatitis herpetiformis, phorphyria and epidermolysis bullosa. Connective tissue diseases included lupus erythematosus, dermatomyositis, morphea and mixed connective tissue disease. Granulomatous skin diseases included tuberculosis, fungal infections, leishmaniasis and sarcoidosis. Neoplastic diseases encountered were squamous cell carcinoma, basal cell carcinoma, melanoma and mycosis fungoides. Chronic ulcers included pyoderma gangrenosum, arterial and venous ulcers. Other less common diseases like hidradenitis suppurativa, keloid, sebaceous hyperplasia were put in the miscellaneous group. Results were tabulated and analyzed using percentage frequencies.

Results

Frequency of various disorders were analysed using SPSS 25. Table 1 represents the frequencies of various disease groups. The most common group of dermatoses was papulosquamous disorders with a frequency of 28.25%. Second most frequent skin disease groups were granulomatous and blistering disorders, each accounting for 11.5 % of all biopsies. Connective tissue diseases and eczemas were responsible for 10.6% and 9.4 % of biopsies respectively. Chronic ulcers were noted at a frequency of 7.17%. Neoplastic lesions constituted 6.8% of biopsies. Vasculitides constituted 2.84%, drug reactions 1.79% and miscellaneous disorders were 10% of the total biopsies.

Fig 1: Relative frequencies of various dermatoses

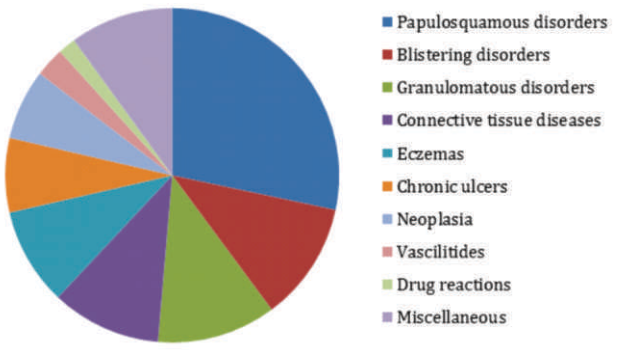

Table 1: *Frequency of Different Pathological Groups (n=669)*

Types of lesions	N (%)
Papulosquamous disorders	189 (28.25)
Blistering disorders	77 (11.5)
Granulomatous disorders	77 (11.5)
Connective tissue diseases	71 (10.61)
Eczemas	63 (9.4)
Chronic ulcers	48 (7.17)
Neoplastic lesions	46 (6.8)
Vascilitides	19 (2.84)
Drug reactions	12 (1.7)
Miscellaneous lesions	67 (10)

Discussion

Cutaneous disorders may arise from skin or may be manifestation of systemic disorders.[7] In clinical dermatology, we come across a variety of disorders that mimic each other immensely. Similarly, histopathological features of various disorders too are so nonspecific and overlapping that making a histopathological diagnosis is mostly impossible without adequate clinical data.[8]

In our study, among various categories of disorders, papulosquamous disorders formed the majority of dermatoses that underwent biopsy. This corresponds to the findings of other studies.[9,10] Papulosquamous disorders are a wide group of skin diseases and are very commonly confronted by the histopathologist. The next common groups were granulomatous and blistering disorders which occurred with equal frequency of 11.5%. This is contradictory to some other studies which reported infectious diseases to be second commonest.

This is probably because of advanced medical management of these orders which led to reduced burden and hence less requirement for them to be biopsied. Connective tissue diseases comprised the next commonest group with frequency of 10.61%, however, due to lack of advanced modalities of diagnosis like immunohistochemistry and immunofluorescence, few of the diagnoses could not be confirmed. Miscellaneous group comprised 10% of biopsies and included a multitude of disorders that couldn't be included in other groups mentioned. Eczemas constituted the next frequent group with

frequency of 9.4%. Chronic ulcers comprised 7.17% of the biopsies and were caused due to arterial, venous or mixed pathology. Pyoderma gangrenosum was another common cause. Neoplasia constituted 6.8% of biopsies which is quite alarming as our patients come from an area with a high level of exposure to sunlight.[13] This further highlights the role of sunlight in these diseases.[14]

The major limitation was lack of advanced modalities of diagnosis like immunohistochemistry and immunofluorescence to confirm histopathological diagnoses.

Author's Contribution

HT: Main Author
RM: Co-Author
AF: Collection of Cases
TR: Supervisor and HOD
AA, AA: Histopathology Analysis

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Frequency of Electrolyte Imbalance in Children of Pediatricacute Diarrhea

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Abstract

Objective: To find out the electrolyte abnomalities among children affected by pediatric acute diarrhea.

Methods: Two hundred and eighty children fulfilling the inclusion/exclusion criteria admitted in Department of Pediatrics, Services Hospital, Lahore was taken. Informed consent of the parents of children was obtained to include their data in the study. Demographic profile age, gender, was recorded. Every children with acute diarrhea was followed through 5cc venous blood test sent to the hospital laboratory with the help of pramedical staff of the hospital for evaluation of electrolyte imbalance.

Results: In our study, out of 280 cases of Pediatric acute diarrhea, 50 %(n=140) had up to 1 year of age. 64%(n=174) were male while 38 %(n=106) were females. Hyponatremia was the most common electrolyte abnormality effecting 22.5% males and 6.5% females followed by hypokalemia.Electrolyte imbalance was more common in children of age group 2-5years.

Conclusion: Electrolyte and acid base abnormalities are common in children with acute watery diarrhea affecting children of 3-12 months of age. Hyponatremia and hypokalemia are the most common abnormalities. Both abnormalities increase with an increase in duration of diarrhea, occur more frequently in patients who are severely dehydrated.

Keywords: Electrolyte imbalance, paediatric acute diarrhea, hyponatremia

Introduction

Diarrhea is defined as passage of three or more liquid stools per day or increase loss of water and electrolytes in stool leading to imbalance and later deficiency of water and electrolytes in the body.[1] Childhood diarrhea is the most common cause of morbidity and mortality, especially in the low and middle- income countries.[2] Acute diarrheal disease is the leading cause of morbidity and mortality in Pakistan.

Each year diarrhea kills around 760, 000 children under five. Globally, there are nearly 1.7 billion cases of diarrheal disease every year. It is the leading cause of malnutrition in children under five years of age.[3] Short term complications of acute diarrhea are dehydration, electrolyte imbalance, malnutrition, shock and death. [4]

Normal stool has an alkaline pH. Sodium and potassium are the primary stool solutes. The sodium plus potassium concentration in stool usually ranges between 130 and 150 mEq/L. Other cations, such as calcium and magnesium, are present at much lower concentrations.[5]

Commonly observed electrolyte disturbances are hypernatremia, hyponatremia and hypokalemia.[6] In secretory diarrhea, there is also hyperchloremic metabolic acidosis which can present as hypotension and acute renal failure. Lactic acidosis may supervene as a result of tissue hypoperfusion.[7] Hyponatremia is one of the most common electrolyte disorders, the frequency ranges from 1% to 40% in general hospital population. It can lead to cerebral edema, coma and brainstem herniation if not timely detected and properly treated.[8]

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Hypernatremia is associated with high mortality rate if sodium concentration exceeds 158mEq/l. it largely effects central nervous system.[9] Loss of bicarbonate and potassium leads to acidosis and hypokalemia which can lead to neuromuscular, gastrointestinal and cardiac symptoms.[1]

A study was done in Kathmandu University, they included 57 patients below 15 years of age who presented with diarrhea. Forty six (79%) children had some form of electrolyte abnormality while rest 11(21%) patients had normal electrolyte levels. The major electrolyte abnormalities noted were hyponatremia and hypokalaemia.[10]

As it is a common cause of morbidity and mortality in Pakistan, and limited literature is available in reference to electrolyte and acid base imbalance and there is research done on this important issue in my center. Young children die of this simple problem, so my rationale is to highlight the major electrolyte which lead to death from this simple problem.

Methods

It was a cross sectional study conducted at Department of Pediatrics, Services, Hospital, Lahore which includes 280 cases as calculated with 95% confidence level, 2% margin of error and taking expected percentage conservative of hyperkalemia i.e. 3% (least among all) different electrolytes imbalance among children with acute diarrhea.[13] sampling was done by Non probability consecutive sampling technique our inclusion criteria was children between 3 months to 5 years of age and children with acute diarrhea (Passage of loose or watery stools at least 3 times in 24 hours, for less than 14 days). Children having any chronic GI illness like celiac disease and congenital adrenal hyperplasia and children having other systemic disease like renal (urea>20mg/l, creatinine > 1.3mg/dl), gastrointestinal and metabolic diseases were excluded from the study because these cases will act as effect modifiers and if included in the study will introduce bias in the result.

Data Collection Procedure

- Children with acute diarrhea, aged between 3 months to 5 years of age were selected for the study. They were diagnosed on history (i.e. passing loose or watery stools at least 3 times in 24 hours). Source of patients will be through emergency room.
- An informed consent was taken after explaining the benefits of the study. Patients having malnutrition or any other abnormality like renal, respiratory, cardiac, gastrointestinal and metabolic diseases which can affect electrolytes will be excluded from the study. Demographic details like age and sex were noted. History of present illness was inquired for the type, severity and duration of symptoms i.e. loose motions and vomiting. The type of food intake, source of water supply, any medications taken at home and socioeconomic status of the child was noted. All the children were examined with regard to general behavior, temperature, heart rate, respiratory rate, skin turgor, anterior fontanelle and for abdominal distension.
- Under aseptic measures, about 2cc of blood was drawn by 24 G butterfly needle and non-oxalated sample was sent for serum electrolytes; sodium and potassium to the biochemistry laboratory of Services Institute of Medical Sciences, Lahore. Sodium and potassium were measured through ion specific electrode method.
- The collected data was entered and analyzed using SPSS version 16.
- Quantitative variables which includes age in months, number of episodes of diarrhea and electrolyte levels were summarized as mean± SD.
- Qualitative variables like sex used were expressed as percentages and proportions.
- The frequency and percentage of children with electrolyte imbalance i.e. hyponatremia, hypernatremia, hypokalemia or hyperkalemia in acute diarrhea was calculated.
- Data was stratified for age, electrolyte imbalance, gender, duration of diarrhea to address the effect of modifiers.
- Chi-square test was used to compare qualitative data
- $p < 0.05$ was considered as significant.

Results

In this study, two hundred and eighty patients having acute diarrhea in the age range between 3 months to 5 years were included. Among them 140(50%) were in the age range of 3-12 months as shown in Fig-1. When they were divided according to gender, 148(53%) were male and 132(47%) were females as shown in table-1.

Hyponatremia was found in 73(26%) of males and 39(14%) of females. Hypokalaemia is the second most common electrolyte abnormality. Seventy five (27%) male and 20(7%) females were found hypokalaemic. Hypernatremia is present in 38(7%) males and 18(6.5%) female whereas 12(4%) males and 5(1.5%) females were hyperkaliaemic as shown in table-2.

Ninety three patient had diarrhea from two to five days. Out of these 42(45%) had hyponatremia, 4(5.5%) hypernatremia, 28(34%) hypokalaemia, 7(8.5%) hyperkalaemia as shown in table 3. Sixty five patient had diarrhea from more than five days. Out of these 22(49%) had hyponatremia, 8(7.7%) hypernatremia, 17(38%) hypokalaemia, 7(15.5%) had hyperkalemia as shown in table 4.

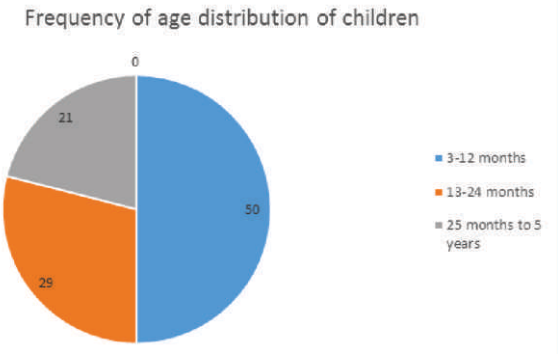

Fig. 1: *Frequency of Age Distribution of Children (n= 280)*

Discussion

In this study, we examine 280 children in the age range of 3 months to 5 years who presented to us with complain of diarrhea.

In this study, 184 patients had electrolyte abnormality and 96 were normal. Hyponatremia is the most common electrolyte abnormality in our study population. In 2016, LubabaShahrin found hyponatremia in 23.8% of subjects and 19.5% subjects were found

Table 1: *Sex Distribution of Children (n=280)*

Sex	No. of children	Percentage
Male	148	53.0
Female	132	47.0

Table 2: *Distribution of Electrolyte Imbalance (n = 280)*

Electrolyte Abnormality	Male	Female	Total	p-value
Hyponatremia	73(26%)	39 (14%)	112 (40%)	0.001
Hypernatremia	38(7.0%)	18 (6.5%)	56(20%)	0.002
Hypokalemia	75(27%)	20 (7%)	95(34%)	0.45
Hyperkalemia	12 (4%)	5(2.0%)	17 (5.0%)	0.052

Table 3: *Distribution of electrolyte and Acid Base Imbalance According to Age (n=280).*

Sodium (meq/L)	Age Range		
	3 - 12 months (n=140)	13 - 24 months (n=81)	25 months - 5 years (n=59)
Hyponatremia(<135)	62 (44.2%)	38 (47%)	12 (24%)
Hypernatremia(>145)	12(9%)	11(25.5%)	22(37.2%)
Normal	87(41%)	42(51.8 %)	33(55%)
Potassium			
Hypokalemia (<3.5)	37(26.7%)	10 (12%)	5(19.0%)
Hyperkalemia (>5.0)	6 (6.0%)	6(7%)	3(0%)
Normal (3.5-5.0)	97(67.0%)	65 (80.2%)	21 (80.0%)

Table 4: *Distribution of Electrolyte and Acid Base Imbalance According to Duration of Diarrhea (n=280).*

Sodium (meq/L)	Duration of diarrhea			p-value
	< 2 days (n=82)	2-5 days (n=93)	>5 days (n=65)	
Hyponatremia(<135)	18 (21%)	42 (45%)	22(49%)	0.005
Hypernatremia(>145)	4 (4%)	8 (7%)	8(17.7%)	0.001
Normal (135-145)	61(74%)	43 (46%)	35 (77%)	0.004
Potassium				
Hypokalemia(<3.5)	28 (34%)	26(27.7%)	15 (33%)	0.005
Hyperkalemia(>5.0)	7(8.5%)	2(2%)	7 (16%)	0.002
Normal(3.5-5.0)	57 (69%)	65 (70%)	43 (66%)	0.054

hypernatremic.[11] Our values of hyponatremia are very high than a study conducted by Sobia Naeem in 2015 where they found hyponatremia in 24.5% children only.[12] Similarly, in a study conducted in Rabwah, Pakistan reported decreased incidence of hyponatremia (10.6%) but they included diarrheal patient in the age range from 1 month to 15 years.[13]

Different factors alters the prevalence of electrolyte disorders among children with diarrhea. One of these factors is malnutrition as according to Alam and collegues malnourished children are found to be hyponatremic despite having excessive total body sodium.[14]

Hypokalemia is found in 24.5% of the patient in this

study. In a study conducted by Asma B et al, in Quetta they reported incidence of diarrhea in 55% of the study population which is very high than our study[15]. Kamberi reported diarrhea in 33.6% of the children who presented with acute diarrhea[16] and Sameen et al reported hypokalaemia in 13.6% children who presented with diarrhea.[17] There is high fecal loss of potassium in diarrhea. Normal fecal excretion of potassium is 9meq/day, and a small increase in potassium loss from body causes hypokalaemia.[18] Indiarrhea 100meq/l of potassium may be lost in the stools. Also on severe malnutrition with diarrhoea, there is a significant risk of lethal abnormalities, including hyponatraemia, hypokalaemia and metabolic acidosis.[19]

Incidence of electrolyte imbalance is higher in children who are given ORS. The reason is due to the fact that people do not have knowledge about preparation of ORS or they are not given in the proper amount at correct time. Morsiky et al, have reported in 2002 that 42% of Pakistani mothers are not administering ORS properly due to lack of awareness about its making and use.[20]

Electrolyte imbalance is also present in patients having no dehydration. The reason is that in these patients, loss of water was replaced by hypotonic solutions but the loss of electrolytes were not properly compensated. However in children with severe dehydration electrolyte imbalance is much higher. This is due to the reason that children with severe dehydration have more loss of sodium and potassium, and also these children were less properly rehydrated before coming to the hospital.

Conclusion

Electrolyte abnormalities are common in children with acute watery diarrhea. Hyponatremia, hypokalemia are the most common = electrolyte abnormalities. Children less than 2 years of age are most affected. Frequency of electrolyte abnormality increases with an increase in duration of diarrhea and occur more frequently in patients who are severely dehydrated and in those who did not receive any rehydration therapy. All children especially less than 2 years of age must be properly rehydrated. ORS should be started immediately and in proper amounts once diarrhea starts. If intravenous fluids are to be used, then give isotonic saline to avoid hyponatremia.

Author's Contribution:

MZA: Research sampling
NA: Sampling, Results
MI: Discussion
ZM: Biostatistical Analysis
BT: Sampling References
MS: Abstract, Critical Review

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Efficacy of Inhaled Salbutamol in the Management of Transient Tachypnoea of Newborn

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Abstract

Objective: To compare the outcome of salbutamol nebulization with controls (normal saline) in transient tachypnea of newborn.

Methods: In this randomized controlled trial 284 (142 in each group) neonates were included with gestational age above 35 weeks of any gender. Study was conducted in Department of Pediatrics Holy Family Hospital Rawalpindi. Sampling technique was consecutive non probability sampling. Duration of study was 6 months. Sample size had been calculated using WHO calculator; Significance level 5%, Power of test 80%, Population mean 5.4, Test value of population mean 4.8, Standard Deviation 1.8. At admission complete blood picture, C-reactive protein and chest x-ray were done. Group-1 received salbutamol nebulization at a dose of 0.15mg / kg / dose for 10 minutes in 2ml normal saline QID while Group-2 received only normal saline nebulization 2ml QID in 24 hours. Double blinding was ensured and in case of any side effects of salbutamol (tachycardia, arrhythmias and hypoglycemia) treatment was stopped immediately and managed accordingly.

Results: In this study, comparison of outcome of inhaled salbutamol with controls in transient tachypnea of newborn shows that respiratory rate per minute was 50.15+2.34 in Group-1 and 64.92+2.70 in Group-2, p value was 0.0001, heart rate per minute in Group-1 was recorded as 120.08+2.36 and 134.79+3.27 in Group-2, p value was 0.0001, oxygen saturation(%) was 97.27+0.92 in Group-1 and 83.28+1.81 in Group-2, p value was 0.0001, duration of oxygen therapy(hours) was recorded as 15.49+1.84 in Group-1 and 27.78+5.57 in Group-2, value of p was 0.0001, duration of hospitalization(days) was recorded as 2.03+0.45 in Group-1 and 5.07+0.72 in Group-2 while value of P was 0.0001

Conclusion: Salbutamol Nebulization is more effective than normal saline in TTN.

Key Words: Transient Tachypnea of newborn, management, inhaled salbutamol, outcome.

Introduction:

Most common neonatal problem after birth is respiratory distress.[1] One third of all neonates who needs admission after birth with respiratory distress are finally diagnosed as a case of transient tachypnea of newborn. Transient tachypnea of newborn results due to lung fluid collection, ultimately leading to pulmonary edema because of delay in the clearance of fluid. It usually settles down within 2-3 days after birth, but it may persist upto 5th day of life.[1,2] It is very common in dyspneic neonates, with incidence of 4 to 5.7% among term infants, while it may occur upto 10% in pre mature neonates.[3] Beta-1 receptor stimulants like catecholamines and endogenous steroids play critical role in lung fluid absorption and level of these chemicals rise during process of delivery. Neonates with lower level of these endogenous chemicals suffer with decreased rate of clearance of lung fluid, which ultimately results in fluid collection at alveolar level. Most of the time TTN is self-remitting dieses but occasionally it may complicates resulting in severe hypoxia leading to death which is labeled as Malignant TTN.[4,5] Management of TTN requires intensive supportive care unit. Aims of management is to maintain thermo-neutral environ-

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ment and provide adequate nutrition at a lower needs of oxygen supplementation.[3-5] Few previous study suggest, management of TTN medications. This data suggested various medications including inhaled adrenaline, oral, inhaled or intravenous loop diuretics, Beta-2 receptor agonists and fluid restriction. But what is the most effective treatment for this disease is still controversial.[4,5] Till date, no single effective drug option is available for this disorder except providing oxygen as a respiratory support.[5] Neonates with this disorder who are intubated and put on ventilator can develop complications like hypotension and intra-ventricular bleeds.[6-10]

A study was conducted by M Mussavi et al on effects of bronchodilator in transient tachypnea of newborn. He concluded that β2 agonist as compared to placebo causes a considerable improvement in the respiratory rate (58.5±9.2 vs 61.76±15.75), oxygen saturation (97.6 ± 1.9 vs 98 ± 1.6), oxygen therapy duration (26±29.3 vs 18.7±12.5) and treatment duration in days (5.4±2.4 vs 4.2±1.2).[11]

Mohammad Zadeh I et al observed the effect of salbutamol nebulization in TTN and result showed decreased duration of oxygen requirement, p-value 0.04, hospitalization p-value 0.006 and onset of feeding with p-value 0.03, were significantly lower in salbutamol group when compared to placebo.[12]

Literature review regarding this has been lacking in our local setups. The rationale of this study is to see the efficacy of salbutamol nebulization as a treatment in TTN through RCT. The objective of this study is to assess changes in various parameters like duration of oxygen requirement, improvement of tachypnea and shortening of hospitalization in TTN, so that better outcome could be achieved with minimum morbidity.

Methods

In this randomized controlled trial 284 neonates were included with gestational age above 35 weeks of any gender. Study was conducted in Department of Pediatrics Holy Family Hospital Rawalpindi. Sampling technique is consecutive non probability sampling. Duration of study was 6 months. Sample size has been calculated using WHO calculator; Significance level 5%, Power of test 80%, Population mean 5.4, Test value of population mean 4.8, Standard Deviation 1.8, n= 142 in each group. Informed consent was taken from the parents of all neonates. At the admission blood samples were collected for CBC, CRP, Arterial Blood Gases. And Chest X-ray was done. Enteral feeding was withheld because of tachypnea and respiratory distress. Standard fluid was administered according to day of life and gestational age. Enrolled neonates were randomly placed into 2 groups; group 1 was treatment group and group 2 placebo group. Treatment group was receiving 0.15 mg/kg/dose Salbutamol in 2 mL of normal saline, and placebo group was receiving 2 mL of normal saline in QID for 24 hours. Each group was nebulized for 10 minutes by jet nebulizer. The oxygen inhalation was given according to the oxygen saturation of neonate, in order to maintain saturation above 90%. Both drug and placebo solutions were prepared in similar shape and color coding by a health care person not involved in neonatal care in order to ensure double blinding. In case of any side effect (tachycardia or arrhythmias, hypoglycemia) treatment was stopped immediately and managed accordingly.

Results

Total 284 neonates (142 in each group) were included to compare the outcome of inhaled salbutamol with controls in transient tachypnea of newborn.

Sex distribution among participants shows that 51.41% (n=73) in Group-1 and 50.70%(n=72) in Group-2 were male and 48.59%(n=69) in Group-1 and 49.30%(n=70) in Group-2 were females. (Table No. 1).

Gestational age of the patients was calculated as 18.31%(n=26) in Group-1 and 19.72%(n=28) in Group-2 were between 35-37 weeks of gestation and 81.69%(n=116) in Group-1 and 80.28%(n=114) in Group-2 had >37 weeks of gestation, mean + SD was calculated as 38.81+1.41 weeks in Group-1 and 38.72+1.39 weeks in Group-2. (Table No. 1)

Mean birth weight was 2350.493+111.90 grams in Group-1 and 2347.88+88.09 grams in Group-2. (Table No. 1).

Comparison of outcome of inhaled salbutamol with controls in transient tachypnea of newborn shows that respiratory rate per minute was 50.15+2.34 in Group-1 and 64.92+2.70 in Group-2, p value was 0.0001, heart rate per minute in Group-1 was recorded as

120.08+2.36 and 134.79+3.27 in Group-2, p value was 0.0001, oxygen saturation(%) was 97.27+0.92 in Group-1 and 83.28+1.81 in Group-2, p value was 0.0001, duration of oxygen therapy(hours) was recorded as 15.49+1.84 in Group-1 and 27.78+5.57 in Group-2 value of P was 0.0001, duration of hospitalization(days) was recorded as 2.03+0.45 in Group-1 and 5.07+0.72 in Group-2, value of p was 0.0001. (Table No. 2).

Gestational age, sex distribution, birth weight, mode of delivery affecting final result were controlled by stratification for which independent sample t-test was applied.

Discussion

Transient tachypnea of the newborn (TTN), is a transient, self-remitting disease, that occurs due to decreased rate of lung fluid absorption in neonates. This delay in lung fluid clearance impairs the normal physiology of transition of lungs from fetal to neonatal life. Beta-1receptor stimulants enhance this rate of lung fluid absorption.

Literature review regarding this has been lacking in our local setups. The rationale of this study was to see the efficacy of salbutamol nebulization as a treatment in TTN through RCT. The objective of this study is to assess changes in various parameters like duration of oxygen requirement, improvement of tachypnea and shortening of hospitalization in TTN, so that better outcome may be achieved with minimum morbidity.

We defined TTN on the basis of following clinical criteria: 1) ≥35 weeks gestational age; 2) respiratory distress in less than 6 hours of life after birth (i.e., respiratory rate greater than 60/min, grunting, nasal flaring, subcostal or intercostal retractions); 3) typical chest X-ray findings (i.e., fluid in transverse fissure, hyperinflation, prominent vascular/perihilar markings).

Our both study groups fulfilled the criteria of TTN. We excluded our study population from Meconium aspiration syndrome, Respiratory distress syndrome and Congenital pneumonia on the basis of clinical symptoms, signs, complete blood picture, c-reactive protein and chest x-ray.

In our study, comparison of outcome of salbutamol nebulization with controls in transient tachypnea of newborn shows that respiratory rate per minute was 50.15+2.34 in Group-1 and 64.92+2.70 in Group-2, p value was 0.0001, heart rate per minute in Group-1 was recorded as 120.08+2.36 and 134.79+3.27 in Group-2, p value was 0.0001, oxygen saturation(%) was 97.27+0.92 in Group-1 and 83.28+1.81 in Group-2, p value was 0.0001, duration of oxygen therapy (hours) was recorded as 15.49+1.84 in Group-1 and 27.78+5.57 in Group-2, value of p was 0.0001, duration of hospitalization(days) was recorded as 2.03+0.45 in Group-1 and 5.07+0.72 in Group-2, p value was 0.0001.

Our data is supported by a study conducted by M Mussavi et al on effects of bronchodilator in transient tachypnea of newborn. He concluded that β2 agonist as compared to placebo cause a considerable improvement in the respiratory rate (58.5±9.2 vs 61.76± 15.75), oxygen saturation (97.6±1.9 vs 98±1.6),

Table 1: *Distribution of Study Variables (n=284)*

Demographics Variables	Group-1 (n=142)	Group-2 (n=142)
Gender:		
Male	73 (51.41%)	72 (50.70%)
Female	69 (48.59%)	70 (49.30%)
Gestational Age (Weeks):		
35-37	26 (18.31%)	28 (19.72%)
>37	116 (81.69%)	114 (80.28%)
Mean ± SD	38.81 ± 1.41	38.72 ± 1.39
Birth weight (grams):		
Mean	2350.493	2347.88
SD	111.90	88.09
Mode of delivery:		
NVD	50 (35.12%)	50 (35.12%)
C-Section	92 (64.78%)	92 (64.78%)

Table 2: *Comparison of Outcome of Inhaled Salbutamol with Controls in Transient Tachypnea of Newborn (n=284)*

Outcome	Group-1 (n=142)		Group-2 (n=142)		P Value
	Mean	SD	Mean	SD	
Respiratory rate/min	50.15	2.34	64.92	2.70	0.0001
Heart rate/min	120.08	2.36	134.79	3.27	0.0001
Oxygen saturation (%)	97.27	0.92	83.28	1.81	0.0001
Duration of oxygen therapy (hours)	15.49	1.84	27.78	5.57	0.0001
Duration of hospitalization (days)	2.03	0.45	5.07	0.72	0.0001

oxygen therapy duration (26±29.3 vs 18.7±12.5), treatment duration in days (5.4±2.4 vs 4.2±1.2).[11]

Mohammadzadeh I et al observed the effect of salbutamol nebulization in TTN and result showed decrease duration of oxygen requirement p-value 0.04, hospitalization p-value 0.006 and onset of feeding with p-value 0.03 were significantly lower in salbutamol group when compared to placebo.[12] These findings support our data. Another research evaluated the advantages and disadvantages of salbutamol nebulization in 54 pre-mature neonates with gestational age of 34-39 weeks in TTN. They observed marked reduction in need of oxygen requirement level, duration of oxygen supply and respiratory rate within 30 minutes after nebulization with salbutamol. Levels of pao2 were much better in neonates receiving salbutamol nebulization as compare to control group.[13] Findings of this research were also in accordance with our study.

However few limitations are here in our study because it is single centre and first study in our setup and effect modifiers like gestational age, sex, birth weight are present.

Based on the above data with support of other studies, we concluded that the outcome of inhaled salbutamol is significantly better when compared with controls in transient tachypnea of newborn.

Author's Contribution

SH: Data Collection
MAF: Data Collection, Introduction
MT: Abstract writing, Reviewed
IYK: Reference adjustment

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Demographic Profile of Endocrine Disorders in Patients Admitted in Endocrinology Ward, Services Hospital Lahore

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Abstract

Objective: To find out frequency and demographic profile of endocrine disorders in patients admitted in endocrinology ward at Services Hospital Lahore.

Methods: The cross-sectional study was conducted at Services Hospital Lahore in Punjab, Pakistan. The study included 105 patients admitted in Endocrinology Ward. Data used was secondary and it was collected via medical record from June, 2018 to January, 2019. All information pertaining to patients was kept confidential. Ethical Review Committee permission was undertaken with final approval from Head of Department.

Results: Demographic characteristics of patients included age, gender, and showed majority to be middle-aged females. The number of female cases were 65.71% (n = 69), while male cases were 34.29% (n = 36). The average age of all the patients was 40.62 ± 16.52. Majority of the patients with 76.19% (n = 80) cases were reported with having glucose homeostasis disorders with 65.71% (n = 69) cases having diabetes mellitus and 10.48% (n = 11) with hypoglycemia. Pituitary gland disorders comprised 8.57% (n = 9) of the cases with 5.71% (n = 6) diagnosed as pituitary tumors and 2.86% (n = 3) as hypopituitarism. Pituitary tumors further included Cushing syndrome with 4.76% (n = 5) cases and acromegaly with 0.95% (n = 1). Hypopituitarism comprised of hypocortisolism with 1.90% (n = 2) cases and Sheehan's syndrome with 0.95% (n = 1). 7.62% (n = 8) cases were reported with having thyroid disorders, with 4.76% (n = 5) having hyperthyroidism and 2.86% (n = 3) with hypothyroidism. 4.76% (n = 5) cases were diagnosed as sex hormone disorders comprising puberty disorders with 1.90% (n = 2) cases, fertility disorders with 1.90% (n = 2) and turner syndrome (inherited disorder) with 0.95% (n = 1). Calcium homeostasis disorders with 1.90% (n = 2) included one case each of parathyroid adenoma (parathyroid gland disorder) and osteoporosis (metabolic bone disease).

Conclusion: The research indicated that glucose homeostasis disorders constituted highest in frequency, followed by pituitary gland disorders, thyroid disorders, sex hormone disorders and calcium homeostasis disorders. The current study urges us to act collectively in order to prevent endocrine disorders which can be done by promoting public education programs, proper counseling about its preventive measures and undergoing periodic medical examination.

Key Words: Demography, Endocrine disorders.

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Introduction

Endocrine system is a system of specialized glands called endocrine glands that secrete hormones into the blood and via blood travel to tissues and organs all over the body.[1,2] The endocrine glands consist of pineal, pituitary, thyroid, parathyroids, thymus, adrenals, pancreas, ovaries and testes.[3] Endocrine system, together with the nervous system, acts as the body's communication network. The functions of endocrine system include growth and development, metabolism, sexual development, sleep, hunger, and electrolyte balance.[4,5]

Endocrine disorders result due to dysfunction of

endocrine glands, leading to either lack or excess of hormone synthesis, secretion and transport. Excessive action may be due to tumors secreting excess hormone, resetting of normal feedback loop, antibody mediated stimulation or excess hormone ingestion. A lack of hormone effect may result from a lack of hormone, caused by genetic deletions, damage to the endocrine gland or lack of a synthetic enzyme. Additionally, the hormone receptor may be structurally abnormal and inactive leading to hormone resistance.[6,7]

Physiologically, endocrine disorders can be broadly classified into five main types, i.e. glucose homeostasis disorders, pituitary gland disorders, thyroid disorders, sex hormone disorders and calcium homeostasis disorders.[8,9] Glucose homeostasis disorders include diabetes mellitus and hypogly-cemia. Diabetes mellitus can be classified into three main types, which are Type-I diabetes mellitus, Type-II diabetes mellitus and gestational diabetes melli-tus.[6] Pituitary gland disorders consist of diabetes insipidus, pituitary tumors, hypopituitarism and Cushing syndrome.[10] Thyroid/parathyroid disorders are classified into hyperthyroidism, hypothyroidism, thyroiditis, thyroid carcinoma, hyperparathyroidism and hypoparathyroidism.[11,12] Sex hormone disorders include inherited genetic disorders like turner syndrome and kleinfelter syndrome, disorders of sex development, hermaphroditism, delayed maturation, amenorrhea, hypogonadism and multiple endocrine neoplasia.[13]

According to Golden SH (2009), prevalence estimates in the United States revealed that endocrine disorders account for at least 5% of the total adult population. The most prevalent conditions in adult patients were osteopenia (47%) in men and (39.6%) in women, metabolic syndrome (34 - 39%), low HDL-cholesterol (37%), obesity (19 - 32%), hypertriglyceridemia (30%),impaired fasting glucose (7 - 26%), diabetes mellitus (6 - 22%), erectile dysfunction in males (18.5%),impaired glucose tolerance (17%), hypercholesterolemia (17%), osteoporosis (7.2%) in women and (6%) in men and thyroiditis (5%).[14] According to a study carried out by Anyanwu AC et al. (2013), at a tertiary care hospital in Nigeria, endocrine disorders comprised of 174 (10.2%) out of 1703 medical cases. The most common endocrine disorders were hyperglycemic crises with 75 (43.1%) cases, followed by diabetes mellitus foot syndrome with 33 (19.0%), hypoglycemia with 23 (13.2%) and diabetes mellitus related co-morbidities with 33 (19.0%) cases.[15]

In Pakistan, adequate knowledge regarding frequency and causes of common endocrine disorders is lacking. According to Raza SA (2011), there still hasnot been enough data collected on this subject to provide our doctors with appropriate guidelines to manage common endocrine disorders.[16] More researches are required to provide physicians with adequate knowledge, guidelines and estimates about endocrine disorders. In current scenario, this study is carried out to explore about the frequency and demographic characteristics of patients admitted in Endocrinology Ward at a tertiary care hospital in Lahore, Pakistan.

Methods

The cross-sectional study was conducted at Services Hospital Lahore in Punjab, Pakistan. The study included 105 patients admitted in Endocrinology Ward. Data used was secondary and it was collected via medical record from June, 2018 to January, 2019. Non-probability, convenient sampling method technique was used. Patients admitted in male, female and high dependency unit (HDU) wards were included in the research, whereas those patients who were admitted only for testing of oral glucose tolerance test (OGTT) in pregnancy were excluded from the study. All information pertaining to patients was kept confidential. Ethical Review Committee permission was undertaken with final approval from Head of Department.

The demographic characteristics included age and gender. Gender was divided into two groups (males and females), while age was divided into four intervals. The endocrine disorders were divided into glucose homeostasis disorders, pituitary gland disorders, thyroid disorders, sex hormone disorders, calcium homeostasis disorders and others. Data was entered and analyzed using SPSS software. Frequencies and percentages were used for qualitative variables like gender, whereas means and standard deviation were used for quantitative variables like age.

Results

The demographic characteristics of patients included their age and gender with majority of patients being middle-aged females. The number of female cases were 65.71% (n = 69), while male cases were 34.29% (n = 36). The average age of all the patients was 40.62with a standard deviation of ± 16.52(Table 1). Concerning frequency of endocrine disorders, majority of the patients, 76.19% cases (n = 80), were reported with having glucose homeostasis disorders, with 65.71% cases (n = 69) having diabetes mellitus and 10.48% cases (n = 11) with hypoglycemia. About 48.57% cases (n = 51) had Type-II diabetes mellitus, 10.48% (n = 11) with type-I diabetes mellitus and 6.67% (n = 7) with gestational diabetes mellitus.

7.69% (n = 8) of the cases were reported with having thyroid disorders with 4.81% (n=5) having hyperthyroidism and 2.86% (n = 3) with hypothyroidism. Pituitary gland disorders comprised 8.57% (n = 9) of the cases with 5.71% (n = 6) diagnosed as pituitary tumors and 2.88 % (n = 3) as hypopituitarism. Pituitary tumors further included Cushing syndrome with 4.81% (n = 5) cases and acromegaly with 0.95% (n=1). Hypopituitarism comprised of hypocortisolism with 1.90% (n=2) cases and Sheehan's syndrome with 0.95% (n=1). Thyroid disorders constituted 7.62% (n = 8) of the cases with 4.76% (n = 5) having hyperthyroidism and 2.86% (n=3) with hypothyroidism. Sex hormone disorders comprised of puberty disorders with 1.90% (n = 2) cases, fertility disorders with 1.90% (n = 2) and turner syndrome (inherited disorder) with 0.95% (n = 1). Calcium homeostasis disorders with 1.90% (n = 2) included one case each of parathyroid adenoma (parathyroid gland disorder) and osteoporosis (metabolic bone disease)(Fig 1 and Table 2).

Table 1: *Demographic Profile of Endocrine Disorders*

Characteristics	Age Intervals	Frequency	Percentage
Age in years	0 – 20	18	17.14 %
	21- 40	33	31.43 %
	41- 60	47	44.76 %
	> 60	7	6.67 %
Average Age		**40.62±16.52**	
Gender	Male	36	34.29 %
	Female	69	65.71 %

Table 2: *Frequency (n) of Endocrine disorders*

Endocrine Disease	Types and Subtypes		Frequency (n)	Percentage (%)
Glucose Homeostasis Disorders (n = 80)	Diabetes Mellitus	Diabetes Mellitus Type-I	11	10.48 %
		Diabetes Mellitus Type-II	51	48.57 %
		Gestational Diabetes Mellitus	7	6.67 %
	Hypoglycemia		11	10.48 %
Pituitary Gland Disorders (n = 9)	Pituitary Tumors	Cushing Syndrome	5	4.76 %
		Acromegaly	1	0.95 %
	Hypopituitarism	Hypocortisolism	2	1.90 %
		Sheehan's Syndrome	1	0.95 %
Thyroid Disorders (n = 8)	Hyperthyroidism		5	4.76 %
	Hypothyroidism		3	2.86 %
Sex Hormone Disorders (n = 5)	Puberty Disorders	Premature Puberty	1	0.95 %
		Delayed Puberty	1	0.95 %
	Fertility Disorders	Amenorrhea	1	0.95 %
		Polycystic Ovarian Syndrome	1	0.95 %
	Inherited Disorders	Turner Syndrome	1	0.95 %
Calcium homeostasis disorders (n = 2)	Parathyroid Gland Disorder	Parathyroid adenoma	1	0.95 %
	Metabolic Bone Disease	Osteoporosis	1	0.95 %
Others (n = 1)	Carcinoid Syndrome		1	0.95 %
Total (n)			**105**	**100 %**

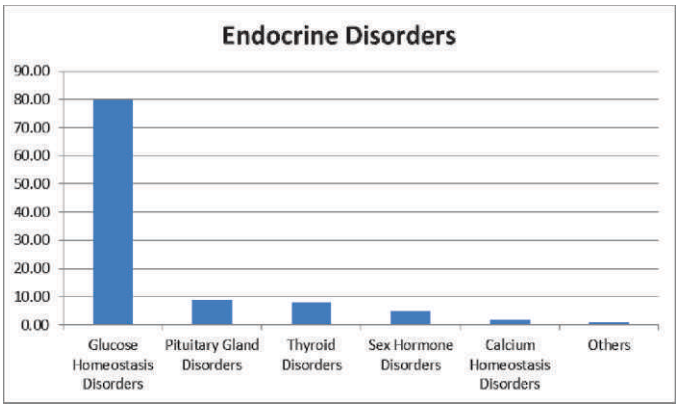

Fig-1: *Bar Chart Showing Frequency of Endocrine Disorders in Participants*

Discussion

Endocrinology is a field that needs adequate attention in Pakistan. The prevalence of diabetes and metabolic syndromes are on the rise. Early detection is vital in effective controlling of diabetes. The commonest approach for testing diabetes is via screening which is a semi-quantitative test for glucose in a urine sample followed by oral glucose tolerance test.[17] For pitui-tary disorders, important measures include continuous monitoring for anthropometric indicators associated with metabolic and cardiovascular comorbidities as well as body satisfaction.[18] For thyroid disorders, primary preventive measures include proper iodine nutrition, smoking recession and preventing alcohol intake.[19] Calcium and Vitamin-D deficiency is also becoming an irritating problem in the masses leading to many calcium homeostasis disorders. Calcium balance should be maintained in the body by proper intake of calcium nutrients met with Vitamin-D supplements and exposure to sunlight. Protein intake has shown to enhance calcium absorption. Sodium and potassium in the diet also effects calcium nutri-ture. High sodium intake increases urinary calcium excretion whereas high potassium intake helps in decreasing calcium excretion, especially in postmeno-pausal women.[20] More researches are needed about different endocrine disorders to adequately manage these public health problems.[21,22]

The current study indicates that there is a high preva-lence of glucose homeostasis disorders, among which diabetes mellitus constituted the majority, similar to studies reported by Golden SH(2009) and Sarfo-kantanka O (2017). It also showed similarity with respect to frequency of thyroid disorders and pituitary disorders.[14,23]

As far as gender ratio is concerned, the present study showed a lower male to female ratio of 36:69 (34.29 % males), showing disparity compared to studies done by Sarfo-kantanka O (2017 Ghana) and Feldman AL (2017, Sweden), but similarity on comparison with study done by Ale AO (2019, Nigeria).[23,24,25] Research study indicated dissimilarity as far as ratio of thyroid disorders is concerned with hyperthyroidism cases more frequent than hypothyroidism (4.76% to 2.86%) as compared to 1.6% to 1.8% in a study done by Stone MB (2003).[26]

Conclusion

This research indicated that glucose homeostasis disorders constitute as highest in recurrence, follo-wed by pituitary gland disorders, thyroid disorders, sex hormone disorders and calcium homeostasis disorders. The frequency and demographic results of this study can be applied for future studies as a support for ongoing further research based on endocrine disorders. The current study also urges us to act collectively in order to prevent endocrine disorders, which can be done by promoting public education programs, proper counseling about its preventive measures and undergoing periodic medical examination. This specialization area needs to be tackled with scientific evidence and guidelines for control of modifiable factors of these disorders.

Author's Contribution:

MMA: Conceptualization, Methodology, Investi-gation, Analysis, Resources, Validation, Writing, Review & Editing

ND: Conceptualization, Project Administration, Supervision, Investigation, Analysis, Review & Editing

AAR, NM, NR: Supervision, Investigation, Analysis, Review & Editing

TZ: Supervision, Investigation, Resources, Analysis, Validation, Review & Editing

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Short Term Effectiveness of Intraatricular Injection of Methylprednisolone Acetate in Subacromial Impingement Syndrome in a tertiary care hospital.

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Abstract

Objective: To determine mean decrease in VAS pain score of intraarticular injection of methyl prednisolone acetate in patients of subacromial impingement syndrome.

Methods: Its Descriptive Case Series/ Quasi experimental study. Study was conducted in department of Orthopedics Unit- I, Jinnah hospital Lahore. Study completed in Six months i.e. from June 2014 to December 2014.After taking an informed consent, 70 newly diagnosed cases of Subacromial impingement syndrome by history and examination (described by the patient as pain in subacromial space when the humerus was elevated or internally rotated and tested by having the patient place his hand on the unaffected shoulder and gradually forward flexing the shoulder (positive impingement sign)which have not received any kind of treatment were included.

Results: Effectiveness of intraarticular injection of methyl prednisolone acetate was measured on visual analogue scale (VAS) from 0 to 10 by VAS score after 6 weeks. 70 patients with mean age of 36.2 ± 10.6 years were included. 61 patients (75.7%) were male, 10 patients (14.3%) had gout and 20% were diabetic. Mean pretreatment VAS score was 5.03 ± 1.58 while mean post-treatment VAS score was 3.86 ± 0.839. Mean reduction was 1.17 ± 1.57 ranged from 2 to 6. There was non-significant association of age and diabetes with mean reduction in VAS score while female gender and gout were significantly and negatively associated with treatment outcome. It is concluded that mean reduction in VAS score after 6 weeks of treatment of subacromial impingement syndrome after intra articular methylprednisolone injection is 1.17 ± 1.57 and acceptable.

Conclusion: It is concluded that intraatricular injection of methyl prednisolone injection is efficacious and effective for treatment of Subacromial impingement syndrome in Pakistani population.

Keyword: subacromial impingement syndrome, intra articular methylprednisolone injection, visual analogue scale, effectiveness.

Introduction

Subacromial impingement syndrome (SIS) represents a spectrum of pathology ranging from subacromial bursitis to rotator cuff tendinopathy and full-thickness rotator cuff tears.[1] It accounts for 44–65 % of all complaints of shoulder pain.2the Causes of Subacromial impingement syndrome includes anatomical causes which means abnormal contact between coracoacromial arch and the rotator cuff tear[3,4] Multiple treatment options are there for the treatment of Subacromial impingement syndrome. Thses includes physiotherapy, shock wave therapy, intra-articular injection and Surgery. Some studies show that physiotherapy should be considered as first line management for Subacromial impingement syndrome.[5] Shock wave therapy alone are in combination with isokinetic exercises is also recommended for treatment of Subacromial impingement syndrome.[6] Many Surgical procedures including sub acromial decompression using acromioplasty and bursectomy are recommended.[7] Although some studies show no big difference between the surgical and non-surgical

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treatment[8]. The gold standard for the treatment of Subacromial impingement syndrome is consider to be the intra articular injection of steroid in combination with anti-inflammatory drugs and isokinetic exercises Triamcinolone and methyl prednisolone in addition with local anesthetic have been tried for intra-articular injection9.In one study, fifty patients with SIS were randomized to three treatment groups. All patients received an injection of 10 ml 0.5% bupivacaine, in group 1 without corticosteroid, in group 2 with crystalline corticosteroid and in group 3 with lipoid corticosteroid. Treatment in group 1 had to be stopped because of inefficacy. In groups 2 and 3 favorable results were achieved in 19 out of 40 patients.[10]

McInerney et al, in randomized controlled trial of single subacromial steroid injection in patients of post traumatic persistent rototar cuff impingement studied pain on VAS and shoulder abduction in two groups of patients. group Creceived only local anaesthetic injection and group S received corticosteroid injection in steroid group mean pain score on VAS was 6±2 on start of study and at 6 weeks 70% patients has pain score at VAS less than 2. So there was mean difference of 4 on VAS.[11]

JiYeon Hong, in his Comparison of High- and Low-Dose Corticosteroid in Sub acromial Injection for Periarticular Shoulder Disorder: A Randomized, Triple-Blind, Placebo-Controlled Trial showed a improvement in VAS (5.5±1.8 to 1.9±2.3) mean 3.6 after 4 weeks in group 1 which was injected 40 mg corticosteroids.[12] Temporal outcomes of 100 consecutive patients treated for SIS were prospectively evaluated. Data was collected at 6 weeks, 3 months, 6 months, 1 year and final follow up at 2 years.In that group, the average decrease in the pain score from 4.8 to 0.6. Improvement in patient VAS pain scores occurred between the initial and 6-week evaluations (4.8±1.9 to 2.7±2.1, P<.0001), between the 6-week and 6-month evaluations (2.7±2.1 to 2.0±2.1, P =.02), and between the 6-month and 1-year evaluations (2.0±2.1 to 0.9±1.5, P=.0002).[5] Because of difference in mean decrease in VAS in three international studies. Current study aimed to determine short term effectiveness in terms of mean decrease in pain on VAS in Pakistani population regarding intraarticular Injection of Methylprednisolone Acetate in Subacromial Impingement Syndrome.

Methods

Study was conducted in department of Orthopedics Unit-II, Jinnah hospital Lahore and completed in six months i.e. from June 2014 to December 2014. It was Descriptive Case Series/Quasi experimental study. It was estimated as 70 cases using 95% confidence level, d=0.05 with an expected mean decrease in VAS after 6 weeks as 2.1±0.2 in patients with SIS. Sampling technique was Non-probability consecutive/ purposive sampling. Inclusion criteria include patient from either gender between the age from 21 – 60 years , newly diagnose cases of subacromialimpingment by history and examination (a positive impingment sign) as per operational definition who have not receive any kind of treatment. X-ray of the effected shoulder including AP , lateral and exial view are done to rule out other possibilities like fracture around proximal humerus. Exclusion criteria include advanced osteoporosis as diagnosed by x-ray, H/O connective tissue disorder, previous H/O fracture around shoulder, rheumatoid arthritis and osteoarthritis of shoulder. Patient having previous surgery or intervene impigment syndrome. After an informed consent 70 patients coming to Out Patient Department of Jinnah Hospital Lahore and fulfilling the inclusion criteria were included in the study. Using consecutive non probability sampling, questionnaire containing background information i.e. age, gender and initial pain score on visual analogue scale was recorded. Time of start of symptoms and history of diabetes, gout was recorded as effect modifiers and confounders. Injection of 2ml methyl prednisolone (40mg/ml) along with 8ml of bupivicain was administered with 21G needle in orthopedic operation theatre. The included patients were evaluated 6 weeks after intraarticular methylprednisolone injection for pain score on VAS. Data collected was entered and analyzed in the SPSS version 17. Results were projected using descriptive statistics e.g. mean with standard deviation in case of continuous variables like age, pre-treatment and post-treatment VAS, decrease in VAS, frequency and percentages in case of categorical variables like gender. Pretreatment and post treatment VAS score was recorded and mean decrease in VAS was obtained by subtracting post treatment VAS score from pretreatment VAS score. Data was stratified for age, gender, duration of symptoms, diabetes and gout.

Results

A visual analogue scale (VAS) is a measurement instrument that tries to measure a characteristic or attitude that is believed to rang across a continuum of values and can not easily be directly be measured[13]. The results derived in this study were based on the patient's own evaluation and assessment of pain 70 individuals were included in our study sample with mean age distribution 36.21 ± 10.689 ranging from 21 to 60 years. Mean pretreatment VAS score was 5.03 ± 1.579 ranging from 3 to 9. Mean post treatment VAS score was 3.86 ± 0.839 ranged from 3 to 5 while mean reduction was 1.17 ± 1.57 ranged from 2 to 6 (Table-I). Study sample (n=70) consisted of 17 females (24.3%) while 53 males (75.7%) 14 individuals (20%) among study sample (n=70) were diabetic while remaining 56 (80%) were non-diabetic. Among study population 10 patients (14.3%) had gout. Sample was distributed into two groups, i.e. more (Group I) and less than (Group II) 40 years. Group 1 had 49 individuals (70%) while rest of 21 were included in group II (30%). Mean pretreatment VAS score was 5.03±1.58 while mean post-treatment VAS score was 3.86±0.839. 17 female patients were having mean decrease in VAS score 0.0588±1.02899 while 53 male patients were having 1.5283±1.55172 and independent samples T test showed non-significant results Table-II. Mean reduction in VAS score in 14 diabetic patients was 1.6429±1.905751 while in 56 non-diabetics patients Score was 1.0536 ± 1.46994.[10] patients with gout had mean reduction VAS score 0.1000±0.99443 while rest of 60 non-gout patients were having score 1.3500±1.58194. Age group 1 had mean reduction in VAS score 1.3878± 1.60489 while group II had VAS score 0.6667± 1.39044 (Table III).

DISCUSSION

Table 1: *Descriptive Statistics for Age Visual Analogue Scale Score*

	n	Mini	Maxi	Mean	Std. Deviation
Age	70	21	60	36.21	10.689
Pre Treatment VAS Score	70	3	9	5.03	1.579
Post Treatment VAS Score	70	3	5	3.86	.839
Difference of VAS Score	70	-2.00	6.00	1.1714	1.56938

Table 2: *Mean Distribution of Reduction in VAS Score Among Male and Female*

	Sex	N	Mean	Std. Deviation
Difference in VAS Score	Female	17	.0588	1.02899
	Male	53	1.5283	1.55172
Using Independent Samples t Test, p value< 0.001 (Highly significant)				

Table 3: *Mean Distribution of Reduction in VAS Score Among in different Age Groups*

	Age Groups	N	Mean	Std. Deviation
Difference VAS -Score	More than 40 years	49	1.3878	1.60489
	Less than 40 years	21	.6667	1.39044
Using Independent Samples t Test, p value= 0.078 (Non - significant)				

Subacromial impingement syndrome has been defined by the American Academy of Orthopedic Surgeons as described by the patient as pain in subacromial space when the humerus was elevated or internally rotated and tested by having the patient place his hand on the unaffected shoulder and gradually forward flexing the shoulder (positive impingement sign). The condition is also characterized by severe shoulder pain. Frozen shoulder is a common cause of shoulder disability.

Mean age of 36 years shows that a relatively young population is affected. Involvement of young age patients in this morbidity of reduced activity of shoulder. Subacromial impingement syndrome shows loss of man power and working ability. It also point out to sedentary life style of our young and middle aged population.Pain relief was scored on visual analogue scale from 0 to 10 six weeks after intraarticular injection of methyl prednisolone acetate, effectiveness of intervention was measured by mean reduction in VAS score using paired sample t test. Mean reduction was 1.17 ± 1.57 showing effectiveness of our intervention (highly significant p value < 0.001).

Intraarticular steroid injections were found safe in all of our study population. We applied independent sample t test to find whether age is associated with positive outcome or not. We found that it is non-significantly associated with treatment outcome. Gender was associated with effectiveness of intraarticular steroid. Male patients had better results as compared to female patients.

Diabetes is on rise in our population as it affected 20%

of study population high as compared to reported prevalence of diabetes in other surveys. Diabetes and gout are known to be associated with Subacromial impingement syndrome. In our study gout was associated with effectiveness butdiabetes doesn't affect the outcome of intraarticular steroid in our study population.

Conclusion

It is concluded that intraatricular injection of methyl prednisolone injection is efficacious and effective for treatment of Subacromial impingement syndrome in Pakistani population. Mean reduction in VAS score after 6 weeks of treatment of subacromial impingement syndrome after intra articular methylprednisolone injection is 1.17 ± 1.57 and acceptable. It is hereby recommended that intraarticular steroid injection is advisable in male patients with Subacromial impingement syndrome without concomitant gout.

Author's Contribution

MAS: StudyDesign, Manuscript writing
NA: Finalization write up collect of results
ZZAC: Literature Search, Write up of Results
SRA: Analysis of results and patient case
AM: Write up of disscussion,table and bars
SW: Overall supervision of Project

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Myoinositol In Restoring Spontaneous Ovarian Activity in Patients with Polycystic Ovarian Syndrome (PCOS)

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Abstract

Objective: To assess the efficacy of myoinositol in the management of patients with Polycystic ovarian syndrome (PCOS)

Methods: It was quasi experimental study conducted inDepartment of Obstetrics and Gynecology Services institute of Medical Sciences, Services Hospital, Lahore from 30-6-2018 to 31-12-2018. 140 sub fertile patients with PCOS were selected through random sampling. Patients were given 2gram of myoinositol/day. The effect was assessed after 3 and 6 months of treatment by monthly menstrual cycle regularity and ovulation. All this information was recorded in proforma.

Results: The mean age of patients was 26.90±5.52years. The mean BMI of patients was 37.38±4.08kg/m2. After 3 months of treatment, menstrual cycle become regular in 34 (24.3%) patients and ovulation occurred in 54 (38.6%) cases. After 6 months of treatment, menstrual cycle become regular in 75 (53.6%) patients and ovulation occurred in 101 (72.1%) cases.

Conclusion: The myoinositol is an effective treatment in terms of regularity of menstrual cycle and ovulation induction in subfertile women with PCOS.

Keywords: Myoinositol, Polycystic ovarian syndrome, Menstrual irregularity, Ovulation

Introduction

Polycystic ovarian syndrome (PCOS) is a multifactorial disorder. The worldwide incidence of polycystic ovarian syndrome (PCOS) is 5-10% of women of reproductive age.[1]

The clinical feature of PCOS varies from oligomonorrhea, signs of hyperadrogenism such as acne, hirsutism, alopecia, infertility and seborrhea, along with sonographic picture of polycystic ovaries.[2] It is associated with long term metabolic abnormalities such as obesity, insulin resistance, acanthosisnigricans, type II diabetes mellitus, hypertension and dyslipidemia.[3] Almost 50-70% of patients have insulin resistance and hyperinsulinemia.[4] As a result of insulin resistance, hyperinsulinemia alters the FSH to LH shift, insulin increase the production of androgens from the ovary by stimulating cytochrome P450c17alph, and this increased production of androgens leads to anovulatory infertility. There is increase production of testosterone because ovarian theca cells in PCOS affected women are more capable to convert androgens precursors to testosterone.[5] The insulin sensitizing agent can solve the hyperinsulinemia induced dysfunction of ovarian response to endogenous gonadotrophins, leading to reestablishment of menstrual cyclist, ovulation and increasing pregnancy rates.

Inositol is a chemical compound and nutrient discovered in 1936 and is commonly found in such foods as legumes, meat, citrus fruit, and whole grains in the most common form of Myo-inositol. Myoinositol (a part of vitamin B complex) has a role in both nuclear and cytoplasmic oocyte development, so higher myoinositol level in follicular fluid is an indicator of good oocyte quality.[6] Inositol phosphate can has a role in activating enzymes that control glucose metabo-

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lism. The altered metabolism of inositol phosphate can mediators in PCOS women contribute to insulin resistance. Insulin sensitizing agent such as Myoinositol reduces production of androgens from theca cells and also reducing testosterone concentration[7]. Myo-inositol is one stereoisomer of a C6 sugar alcohol that belongs to the inositol family. It is the precursor of inositol triphosphate, acting as an intracellular second messenger and regulating a number of hormones such as thyroid-stimulating hormone, FSH and insulin.[8]

Systematic review of randomized trials have shown its efficacy in improving insulin sensitivity of target tissues, restores ovulation and hormonal functions, reduces clinical and biochemical hyperandrogenism and dyslipidemia through reduction of plasma insulin level with success in achieving pregnancy.[9,10]

The rationale of my study is to observe the effect of myoinositol in improving metabolic, hormonal and clinical features in patients with PCOS. Although literature is available in studies conducted in other population but there is no local study available in this topic in Pakistan and there are genetic differences from one population to another so the effect of my drug may also vary accordingly and the study results may not be consistent with already existent literature. It may help in improvement of clinical features such as acne, hirsutism and obesity in patients with PCOS, also help in increasing conception rate by restoring spontaneous ovarian activity.

Operational Definitions

Polycystic ovarian syndrome: in 2003, the European society of human reproduction and Embyology (ESHRE) and American society of reproductive medicine (ASRM) recommends at least 2 of the 3 following features are to be present to diagnose PCOS

1. oligo-ovulation or anovulation manifested my oligomonorrhea or amonorrhea for 6-9 cycles/yr
2. Hyperandrogenism assessed clinically by acne, obesity, hirsutism or hyperandrogenemia assessed biochemically by raised level of testosterone i.e.; >70ng/dl.
3. Polycystic ovaries (peripheral arrangement of >8 follicles of size <10mm in one or both ovaries) assessed by ultrasound.

Efficacy

It was assessed on 3rd and 6th months post treatment in terms of:

Restoration of normal menstrual cycle: Normal menstrual cycle ranges from 3-7/21-35 days for 3-6 months assessed by history of the patient

Ovulation: It was the event of de-Graaf's follicle rupturing and releasing secondary oocytes. The normal ovulation day in mostly 14th day of 28 day menstrual cycle. Ovulation was assessed by day 21 progesterone level ranging from 16-28nmol/l.

Methods

It was quasi experimental study conducted in Department of Obstetrics and Gynecology Services institute of Medical Sciences, Services Hospital, Lahorefrom 30-6-2018 to 31-12-2018. After getting permission from IRB, 140 sub fertile patients with PCOS were selected through Non- probability consecutive sampling. Inclusion criteria was 18 to 35years of age, married women.

Sub-fertile women assessed by history i.e. not able to conceive after at least one year of regular, unprotected sex.

Patients selected with PCOS according to Rotterdam criteria as per operational definition. Patients known allergic myoinositol and non-complaint patients were excluded. A detailed history was taken regarding menstrual cycle, infertility, weight gain, acne, hirsutism, clinical examination including weight, height, blood pressure were noted and investigation such as transvaginal ultrasound was performed assessment of ovulation was done by measuring day 21 progesterone level ranges from 16 to 28nmol/l.

Patients were given 2gram of myoinositol/day. The effect was assessed after 3 and 6 months of treatment by monthly menstrual cycle regularity and ovulation. All this information was recorded in proforma.

Data Analysis

SPSS version 21.0 was used for data analysis. Quantitate variables like patient's age, hormonal profile were presented by mean and standard deviation. Qualitative variables like ovulation, mens-

trual cycle regularity were presented by calculating frequency and percentages. Data was stratified for age, duration of PCOS and BMI. Post-stratification, chi-square test was used taking P-value ≤ 0.05 as significant.

Results

The mean age of patients was 26.90±5.52years. The mean BMI of patients was 37.38±4.08kg/m2. Table 1

After 3 months of treatment, menstrual cycle become regular in 34 (24.3%) patients while irregular in 106 (75.7%) patients and ovulation occurred in 54 (38.6%) cases while did not occurred in 86 (61.4%) cases. After 6 months of treatment, menstrual cycle become regular in 75 (53.6%) patients and ovulation occurred in 101 (72.1%) cases. Table 2

Table 1: *Descriptive Statistics of Patients*

	140
Age (years)	26.90±5.52
BMI	37.38±4.08

Data was stratified for age of patients. After 3 months, in patients aged 18-25years, menstrual cycle become regular in 16 (26.2%) cases and ovulation occurred in 20 (32.8%). After 3 months, in patients aged 26-35 years, menstrual cycle become regular in 18 (22.8%) cases and ovulation occurred in 34 (43.0%). The difference was insignificant in both age strata

Table 2: *Distribution of outcome at 6th Month*

		Frequency	Percent
Menstrual cycle	Regular	75	53.6
	Irregular	65	46.4
Ovulation	Yes	101	72.1
	No	39	27.9

(p>0.05).

Data was stratified for age of patients. After 6 months, in patients aged 18-25years, menstrual cycle become regular in 34 (55.7%) cases and ovulation occurred in 44 (72.1%). After 6 months, in patients aged 26-35years, menstrual cycle become regular in 41 (51.9%) cases and ovulation occurred in 57 (72.2%). The difference was insignificant in both age strata (p>0.05). Table 3

Data was stratified for BMI of patients. After 3 months, in normal BMI patients, menstrual cycle become regular in 15 (32.6%) cases and ovulation occurred in 19 (41.3%). After 3 months, in overweight patients, menstrual cycle become regular in 17 (33.3%) cases and ovulation occurred in 27

Table 3: *Comparison of Outcome in Age Strata at 6th Month*

		Age (years)		Total	P-value
		18-25	26-35		
Menstrual cycle	Regular	34	41	75	0.652
		55.7%	51.9%	53.6%	
	Irregular	27	38	65	
		44.3%	48.1%	46.4%	
Ovulation	Yes	44	57	101	0.998
		72.1%	72.2%	72.1%	
	No	17	22	39	
		27.9%	27.8%	27.9%	

(52.9%).After 3 months, in obese patients, menstrual cycle become regular in 2 (4.7%) cases and ovulation occurred in 8 (18.6%). The difference was significant in all BMI strata (p<0.05). Table 4

Data was stratified for BMI of patients. After 6 months, in normal BMI patients, menstrual cycle become regular in 33 (71.7%) cases and ovulation occurred in 38 (82.6%). After 6 months, in overweight patients, menstrual cycle become regular in 25

Table 4: *Comparison of Outcome in BMI Strata at 3rd Month*

		BMI			Total	P-value
		Normal	Over-weight	Obese		
Menstrual cycle	Regular	15	17	2	34	0.001
		32.6%	33.3%	4.7%	24.3%	
	Irregular	31	34	41	106	
		67.4%	66.7%	95.3%	75.7%	
Ovulation	Yes	19	27	8	54	
		41.3%	52.9%	18.6%	38.6%	0.003
	No	27	24	35	86	
		58.7%	47.1%	81.4%	61.4%	

(49.0%) cases and ovulation occurred in 37 (72.5%). After 6 months, in obese patients, menstrual cycle become regular in 17 (39.5%) cases and ovulation occurred in 26 (60.5%). The difference was significant in all BMI strata (p<0.05) for menstrual regularity while insignificant for ovulation (p>0.05). Table 5

Discussion

PCOS is a metabolic disorder that is associated with wide range of hormonal and biochemical dysfunc-

tion. It has a high prevalence among Pakistani women

Table 5: *Comparison of Outcome in BMI Strata at 6th Month*

		BMI			Total	P-value
		Normal	Over-weight	Obese		
Menstrual cycle	Regular	33	25	17	75	0.007
		71.7%	49.0%	39.5%	53.6%	
	Irregular	13	26	26	65	
		28.3%	51.0%	60.5%	46.4%	
Ovulation	Yes	38	37	26	101	0.066
		82.6%	72.5%	60.5%	72.1%	
	No	8	14	17	39	
		17.4%	27.5%	39.5%	27.9%	

(52%) as compared to Caucasians(20-25%)[11]. The main reason for associated infertility is that the eggs in the ovaries are unable to mature efficiently and cannot be released, resulting in small cyst formations and ovarian inflammation. In fact, the presence of PCOS puts an individual at a significantly higher risk of developing type II diabetes, hypertension, gynecologic carcinomas, certain psychological conditions and low quality of life.[12]

In our study, the mean age of patients was 26.90± 5.52 years. Data was stratified for age of patients. After 6 months, in patients aged 18-25years, menstrual cycle become regular in 34 (55.7%) cases and ovulation occurred in 44 (72.1%). In patients aged 26-35years, menstrual cycle become regular in 41 (51.9%) cases and ovulation occurred in 57 (72.2%). The difference was insignificant in both age strata ($p>0.05$). The patients with subfertility belong to reproductive age group. Myoinositol was effective in older age group as well. Myoinositol has shown to improve metabolic dysfunction in postmenopausal women as well.[13]

In our study, myoinositol was found effective in inducing menstrual cycle regularity in in 75 (53.6%) patients and ovulation occurred in 101 (72.1%) cases after 6 months of treatment. Similar results have been shown in other studies where 61.7% to 65.5% female had ovulation.[8,14,15] It is a very important finding for subfertile women with PCOS. Subfertility is a curse for women of Sub continent. They are subject to all sorts of emotional harassment and stigmatized but also face threats of divorce and physical violence.[16]

Improved pregnancy rates have been reported in various studies as well but we did not follow patients for pregnancy. No moderate to severe side effects were observed when myo-inositol was used at a dosage of 2000 mg per day in our study.

The use of 2000 mg myo-inositol per day is well tolerated by patients in other studies as well.[16,17] PCOS is also associated with the failure of in vitro fertilization as these patients suffer from poor quality oocytes. Myoinositol has been found to improve quality of oocytes as it improves insulin sensitivity and decrease hyperandogenism.[18]

In our study, the mean BMI of patients was 37.38± 4.08kg/m^2. Increased BMI is itself associated with insulin resistance and decreased chances of fertility. Data was stratified for BMI of patients. After 6 months, in normal BMI patients, menstrual cycle become regular in 33(71.7%) cases and ovulation occurred in 38 (82.6%). In overweight patients, menstrual cycle become regular in 25 (49.0%) cases and ovulation occurred in 37(72.5%). In obese patients, menstrual cycle become regular in 17(39.5 %) cases and ovulation occurred in 26 (60.5%). The difference was significant in all BMI strata ($p<0.05$) for menstrual regularity while insignificant for ovulation ($p>0.05$). Myoinositol has been found to facilitate weight loss in PCOS patients in addition to improving biochemical and endocrine parameters[19,20]. Inositols have emerged as important component of endocrine modulation especially linked to insulin signalling[21]. More research is needed to generate local data so that national guidelines can be formulated.

Conclusion

The myoinositol is found to be effective in inducing ovulation and menstrual cycle regularity in sub fertile PCOS patients.

Author's Contribution

IU: Conceptalized and design the study.
NS: Data Maintenance
QJ, SZ: Data entry, Statistical Analysis
TW: Approved the final version and Data review
Data
AK: Data Collection

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Frequency of Patients Passing an Impacted Esophageal Meat Bolus by Conservative Method Alone

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Abstract

Objectives: To determine the frequency of patients passing the impacted esophageal meat bolus by conservative management

Methods: After obtaining permission from ethical committee of Hospital,a total of 62 patients meeting the study criteria were recruited in the study which was conducted in Department of Otorhinolaryn-gology, Services Hospital, Lahore. Demographic information (name, age, gender, contact) was also obtained. Patients with clinical suspicion of impacted esophageal food bolus of age 20-50 years of either gender were included. Patients with known esophageal abnormalities like stricture, web or growth on either barium swallow or esophagogastroduodenoscopy, peptic ulcer and GERD were excluded. After taking informed written consent from each patient, single intravenous dose of buscopan 20mg was given to each patient. Each patient was followed by the researcher himself for 24 hours to assess the passage of food bolus.

Results: 20-50 years was the age range in our study, with mean age being 34.10± .63 years. Majority of the patients 32 (51.61%) were between 20 to 35 years of age. Out of 62 subjects, 37 (59.68%) were male, 25 (40.32%) were females with male to female ratio 1.5:1. In our study, Frequency of patients passing the impacted esophageal meat bolus by conservative management was found in 51 (82.26%) patients.

Conclusion: This study concluded that there is a high frequency of patients passing the impacted esophageal meat bolus by conservative management.

Keywords: Esophagus, foreign body, conservative management.

Introduction

The accidental impaction of a meatbolus in the esophagus is a common occurrence especially in an under-developed society.[1] Afterear and nose, the esophagus is the third commonest site for foreign body impaction.[2] up to eighty percent of impacted foreign bodies are held up just above the cricopharyngeus.[3] 13 episodes per 100,000 population of foreign body impaction are reported annually.[4] In a study by Damghani M et al[5], foreign bodies were detected in 77% of the esophagoscopies and in the rest, inflammation, ulcer, and stricture formation was found. In another study, 77.8% were detected to have foreign bodies and in the remaining, soft tissue mass, bleeding, ulcer, edema, and abscess were reported.[6]

Higher incidence of foreign body ingestion occurs in pediatric population in between six months to six years of age while in adult population foreign body impactions more commonly occur among patients with known mental retardation, mental impairment caused by liquor and old age and psychiatric illnesses as reported by Lee et al.[7] Usually, two types of foreign bodies are encountered, true foreign bodies (coins, buttons) and food related foreign bodies. Most Foreign body impactions are seen in children at the narrowest portion of the alimentary tract which is the cricopharyngeus that lies 15cm from the upper central incisors.[1,8]

Majority of impacted esophageal foreign bodies (80%–90%) pass spontaneously without any surgical intervention.[9,10] However, approximately 10%–20%

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of cases of foreign body impactions require rigid or flexible endoscopic removal under general or local anesthesia, whereas, less than 1% will need open surgery for foreign body removal or to treat complications.[10,11] American Society of Gastrointestinal Endoscopy (ASGE) guideline, for management of impacted foreign bodies, suggests immediate surgical intervention for patients who are having absolute dysphagia.[12] If the patient is not in distress, they are observed for 24 hours, before opting for any invasive procedures.[13]

Many pharmacological or non-pharmacological prokinetic agents have been used to dislodge the impacted food bolus with variable success.[14,15] A survey conducted in UK showed that the majority of practitioners did not immediately proceed to rigid endoscopy; rather, they preferred antispasmodic drugs (83%), the most common being hyoscine butylbromide (Buscopan) and diazepam, that usually allows the esophageal lumen to relax and facilitate the passage of the impacted bolus.[16] Rate of complications increase in the hands of an inexperienced surgeonin managing unrecognized distal esophageal food bolus impactions.[17] In a study, about 80% of cases, the impacted bolus may pass uneventfully through the gastrointestinal tract without endoscopic aid.[18]

The purpose of this study was to determine the frequency of patients passing the impacted esophageal meat bolus by conservative method alone in local population. Previously the available literature on this is scarce, so our study will not only be a useful addition to the existing literature, but will also provide us with local statistics. As in majority of our setups, the patients with impacted meat bolus do not take the conservative trials, instead they are subjected to endoscopic removal or surgery, thus the results of our study will encourage the clinicians to develop a conservative approach in these particular patients, hence avoiding the invasive procedures in order to reduce the morbidity of the affected.

Methods

This was a descriptive, case series study conducted in the Department of Otorhinolaryngology Unit I, Services Hospital, Lahore, from 2nd September 2017 to 1st March 2018. The calculated sample size was 62 cases with 95% confidence level, 10% margin of error and taking frequency of patients passing the impacted esophageal meat bolus by conservative method alone as 80.0%5 by using following formula.

sample size = n

$= (Z\_(1-\alpha/5\ P(1-P)\ )\hat{}2)/d\hat{}2$

Non-probability, Consecutive sampling was used.

Study cases between age of 20-50 years of both genders were selected according to the following criteria. Patients with clinical suspicion of impacted esophageal food bolus (Presence of any food bolus in esophagus on x-ray (radiolucent shadow) and with dysphagia (difficulty in swallowing), odynophagia (painful swallowing), anorexia (sense of vomiting) on history, andduration of symptoms of ≤24 hours were included in the research.

Patients with known esophageal abnormalities like stricture, web or growth on either barium swallow or esophagogastroduodenoscopy (OGD), patients with history of peptic ulcer (assessed on history and medical record) and patients with history of gastroesophageal reflux disease (assessed on history and medical record) were excluded from the study.

After ethical approval and written informed consent from 62 patients presenting to ENT emergency of Services Hospital Lahore, who fulfilled the inclusion and exclusion criteria were recruited. A single intravenous dose of Buscopan 20mg was given to each patient. Each patient was followed by the researcher himself for 24 hours to assess the passage of food. The patients who continued to exhibit symptoms of impaction for more than 24 hours, were taken totheatre for endoscopic removal under GA. All patients who were able to eat and drink without any difficulty were discharged from the ward. This research data was recorded on a specially formulated proforma which consisted of two parts. Part 1 includes the patient's bio-data; part 2consists the study variables.

Statistical Analysis

The data was processed using SPSS version 22 and analyzed. The results were presented as mean and standard deviation for quantitative variables i.e. age

and duration of symptoms. Frequency and percentage were calculated for qualitative variables like gender, type of food bolus (meat/chicken/other including non-organic foreign bodies), site of impaction in esophagus (upper/middle/lower), previous history of food impaction (yes/no) and passage of impacted esophageal food bolus (yes/no).

Effect modifiers like age, gender, duration of symptoms, type of food bolus (meat/chicken/other), site of impaction in esophagus (upper/middle/lower) and previous history of food impaction (yes/no) were controlled through stratifications. Post-stratification chi square was applied to see their effects on outcome and p value ≤ 0.05 was considered as significant

Results

Age range in this study was from 20 to 50 years with mean age of 34.10 ± 7.63 years. Majority of the patients, 32 in number(51.61%) were between 20 to 35 years.

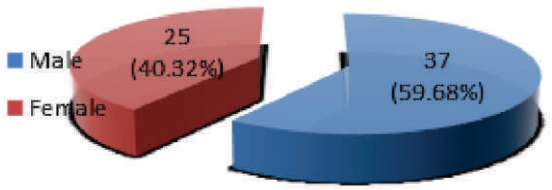

Figure I: *Distribution of Patients According to Gender (n=62).*

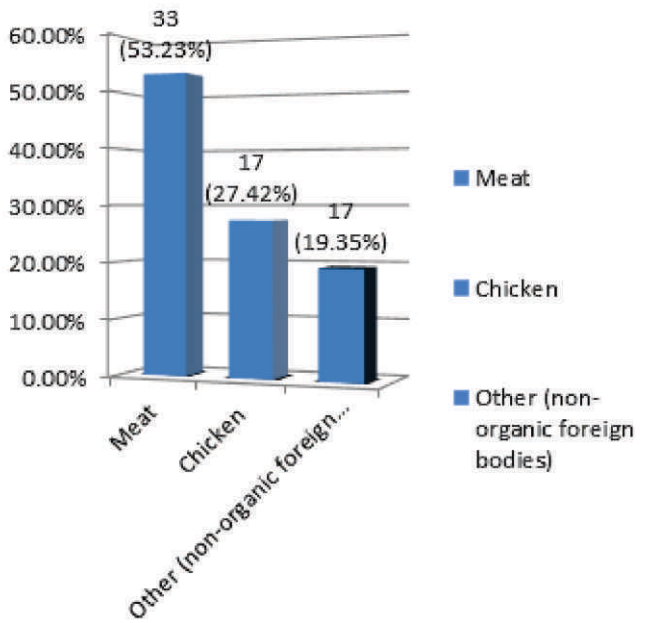

Figure II: *Distribution of Patients According to the Type of Bolus(n=62)*

Out of 62 patients, 37 (59.68%) were male and 25 (40.32%) were females with male to female ratio 1.5:1 as shown in Figure I. Mean duration of symptoms was 11.53 ± 5.68 hours. Distribution of patients according to the type of bolus as shown in Figure II.

In our study, Frequency of patients passing the impacted esophageal food bolus by conservative management was found in 51 (82.26%) patients.

Table I & II have shown the stratification of passage of impacted esophageal food bolus with respect to site of impaction and type of food bolus respectively.

Table 1: *Stratification of Passage of Impacted esophageal Food Bolus with Respect to Site of Impaction in Esophagus.*

Site of impaction in esophagus	passage of impacted esophageal food bolus		p-value
	Yes	No	
Upper	16	04	
Middle	18	05	**0.607**
Lower	17	02	

Table 2: *Stratification of passage of impacted esophageal food bolus with respect to type of food bolus.*

Type of food bolus	Passage of impacted esophageal food bolus		p-value
	Yes	No	
Meat	28	05	
Chicken	15	02	**0.277**
Other (non -organic foreign bodies)	08	04	

Discussion

Foreign body (FB) ingestion and esophageal food impactions are a common ENT emergency. In adults, FB ingestion occurs more commonly in those with psychiatric illnesses, alcohol intoxication, and incarcerated individuals in quest of secondary gain.[19-22] A research conductedon 262 adult individuals with FB ingestion and impaction cases, 92% were deliberate, and 85% of patients had an underlyingmental health issue. Patients with underlying esophageal pathology often present with food bolus impaction. Known cases of congenital malformations are also at increased risk for FB impaction. Certain occupations like carpenters and tailors have higher chances of FB ingestion as they hold nails and pins in their mouth while working.[23]

We have conducted this study to determine the

frequency of patients passing the impacted esophageal meat bolus by conservative method alone. Age range in this study was from 20 to 50 years with mean age of 34.10 ± 7.63 years. Majority of the patients 32 (51.61%) were between 20 to 35 years of age. Out of 62 patients, 37 (59.68%) were male and 25 (40.32%) were females with male to female ratio 1.5:1. In our study, Frequency of patients passing the impacted esophageal meat bolus by conservative method was found in 51 (82.26%) patients. A survey conducted among UK practitioners showed that the majority did not usually proceed immediately to rigid endoscopy for removal of meat bolus impaction; rather, they gave precedence to use of antispasmodic drugs (83%), to try to induce spontaneous passage of the impacted meat bolus.[16] In a study, in about 80% of cases, the ingested material passes uneventfully through theupper gastrointestinal tract.[18]

Success rate by conservative management alone was 68% better than the endoscopic approach in the study conducted by Basavaraj and Penumetcha. The literature search revealed one case study and two retrospective cohort studies comparing hyoscine butylbromide against no invasive treatment for esophageal meat bolus impaction. Another study has shown 82% success rate of conservative management using intravenous hyoscine. Hyoscine butylbromide is widely used in the management of esophageal meat bolus impaction. With the total of 74 subjects, the abovementioned studies concluded that there was no significant difference in disimpaction rates between those patients treated with hyoscine butylbromide and those who received no treatment. The lack of statistical supremacy to small sample sizes suggests further studies are needed.[23-25] The evidence for hyoscine butylbromide as a treatment for esophageal soft food bolus obstruction is questioned in a publication from 2007. The evidence backing the use of hyoscine butylbromide appears to stem from a recommendation in a 1997 textbook that misquotes a 1991 study detailing 10 out of 16 patients which were given “antispasmodics”, were spontaneously relieved of the obstruction. The study is questioned as a cohort of only 16 patients, which provides results of low statistical power and more relevantly, none of the 5 different “antispasmodic” drugs used in the study actually included hyoscine butylbromide.

A literature review showed that four retrospective cohort studies and one case report were acknowledged. These case studies stated disimpaction rates of 100%, 100%, 100%, 80% and 65%, with prokinetics alone respectively. One patient suffered a mucosal tear to the oesophagus. The prokinetic agents vary in each study, the literature on the use of fizzy drinks in esophageal soft food bolus obstruction has a small patient number. Nevertheless, the results of the studies were positive, with 79% of cases experiencing disimpaction with a prokinetic agent alone or with barium meal for imaging. This combination therapy has not been formulated in a larger study. Larger trials are required to provide evidence in favor of their use. However, considering the fact that carbonated drinks are inexpensive, safe and apparently effective to some extent, their use in the management of esophageal soft food bolus disimpaction may be recommended.[24]

Other known pharmacological agents include glucagon, which reduces esophageal motility and relaxes the lower esophageal sphincter. However, it is not recommended to be effective in treating impacted esophageal coins in pediatric population, but it has been used in the managing esophageal soft food bolus obstruction. A comprehensive research revealed a randomized controlled trial showing no significant difference when comparing glucagon combined with diazepam against placebo for management of esophageal soft food bolus impaction. Two studies investigating 92 and 222 cases of esophageal soft food bolus obstruction were carried out. In the first study, all 92 patients were given glucagon and 30 were dis-impacted without endoscopy. 10 out of 106 patients were given glucagon and 20 out of 116 patients that were given no medication, dis-impacted without further interventionin the second study.[21] The results suggest that administration of glucagon gives similar results in relieving esophageal soft food bolus obstruction as oppose to when no medication is given.

A large number of clinicians dealing with this emergency are not well versed with the protocols of treating patients suffering from food bolus impaction. This is the reason that small number of patients were taken to the OR within 12-hours observation, or they could not get any medical treatment. Such patients are exposed to unnecessary endoscopy and anesthesia related risks. Therefore, operating rooms and surgeons become overworked.

Conclusion

This study concluded that there is a high frequency of patients passing the impacted esophageal meat bolus by conservative method alone. So, we recommend that conservative approach should be encouraged in these particular patients and avoid the invasive procedures in order to lessen the morbidity associated with rigid endoscopies.

Author's Contributions

DA: Data Collection
SHS: Introduction, literature review, Disscussion
GM, AAA: Article references
MQN: Statistical Analysis
MAA: Edited

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Association of Serum Vitamin D levels with Hypertension

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Abstract

Objectives: The objective of our study was to identify the effect of low serum vitamin D levels on hypertension & to make a comparison of levels of vitamin D in hypertensives and healthy individuals.

Materials and Method: A cross-sectional comparative study carried out in Cardiology Department of Shaikh Zayed Hospital and Punjab Institute of Cardiology, which involved measurement and comparison of serum Vitamin D levels in 64 subjects, categorized in two groups; hypertensives and normotensives, in order to establish a potential association between vitamin D levels and hypertension.

Results: Our study showed that Serum Vitamin D was equally sub-optimal in all participants of study, including both hypertensive group and the healthy controls. As a result of this finding, a clear pattern of association of vitamin D deficiency with hypertension could not be seen. Mean ±SD Vitamin D levels was 19.5±10.0 ng/L in hypertensives and 19.5±13.6 in healthy individuals. This study did not lead to establishment of an association between hypertension and vitamin D levels.

Conclusion: Because of deficiency of Vitamin D in general population in this region, our study failed to show an association between Vitamin D and hypertension. Further exploration is needed in this regard.

Key words: Hypertension, serum Vitamin D levels

Introduction

Vitamins are a class of chemical substances that are present in small amounts in food. It can be classified both as a nutrient as well as a vitamin. It is naturally synthesized in the skin in the presence of ultraviolet B radiations of sunlight during mid-day, particularly at high altitudes.[1,2]

Till recent past, vitamin D was considered to be involved in calcium metabolism, causing increased absorption of calcium from intestine, thereby promoting bone growth and mineralization.[3] Vitamin D deficiency can cause reduction of bone mass, thereby resulting in osteoporosis and osteomalacia in adults and rickets in children.[2] With further advancement in research, now vitamin D is considered to play remarkable role in improving muscle strength, prevention and improvement in survival of cancers, regulating immune mediated disorders like rheumatoid arthritis, multiple sclerosis, diabetes mellitus, systemic lupus erythematosus and inflammatory bowel disease.[4]

Besides other important metabolic effects of vitamin D, it is considered to play a very important role in regulation of renin-angiotensin system of blood pressure regulation. This is the major blood pressure control mechanism.[5] It is believed that vitamin D deficiency, somehow, causes the upregulation of renin angiotensin system, thereby, increasing the probability of development of hypertension. Similarly, vitamin D produces direct effects on vasculature, protecting its endothelium from damaging effects of advanced glycation end products and decreasing the atherosclerotic and inflammation causing factors.[6] Vitamin D deficiency associated with hyperparathyroidism can also lead to arterial calcification, thereby, contributing to hypertension.[7]

All these effects indicate widespread presence of vitamin D receptors at sites like leucocytes, vascular

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smooth muscle cells, vascular endothelium and even juxtaglomerular cells of kidneys.[8]

Since vitamin D deficiency is very common in our part of the world owing to high amount of melanin in skin, which can actually decrease synthesis of vitamin D in response to ultraviolet B radiation by 99%, it is very important to understand all its implication.[9] This study aims to identify the possible effect of vitamin D deficiency in pathogenesis of hypertension so that its supplementation can be instituted, if such an association is established.

Methods

This cross-sectional comparative study was carried out in Cardiology Department, Shaikh Zayed Hospital & Punjab Institute of Cardiology and Physiology Department of Shaikh Zayed Postgraduate Medical Institute, Lahore, after seeking permission from concerned authorities. The study population consisted of hypertensive patients above 40 years of age and age & gender matched healthy controls while the patients of renal disorders or those on vitamin D supplementation were excluded from the study.

A sample population of 32 hypertensive and 32 healthy control subjects was used to compare their vitamin D levels. A convenient, non-probability sampling technique was used and blood samples of patients visiting outpatient department were taken after detailed history and examination. A detailed informed consent was taken from participants of study and later on, report of their serum vitamin D levels was mailed to them.

Estimation of vitamin D levels was done using ELISA technique after centrifuging & separating serum.

Results

The study was conducted on 64 participants. Of these, 32 participants were hypertensive (HTN), and 32 were healthy controls without any known cardiovascular disease. Results were analyzed with the help of SPSS (version 20). Data for levels of serum vitamin D was expressed by using Mean + SD in case of both groups.

Variables among two groups were compared by using t-test. Data pertaining to deficiency of vitamin D was shown in terms of percentage and frequency. Vitamin D levels were categorized for comparison with the help of chi-square test.

Mean age in case of hypertensives and controls was 52.8±6.4 and 46.9±6.8 years respectively. No significant difference was seen in gender distribution between the groups(p-value 0.453).

As shown in fig.1, body mass index ranged from a minimum of 22.6 to a maximum of 34 in hypertensive group, which is quite comparable to BMI ranging from 19 to 33.4 of healthy control group. This difference was insignificant with p-value 0.157. These statistical findingsare tabulated in table 1.

History of hypertension in family was seen for 25(78.1%) of healthy participants and for 18(56.2%) cases of hypertension.

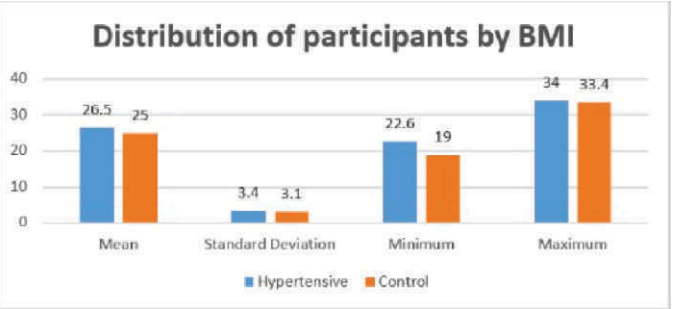


Fig.1: *Distribution of Participants According to BMI*

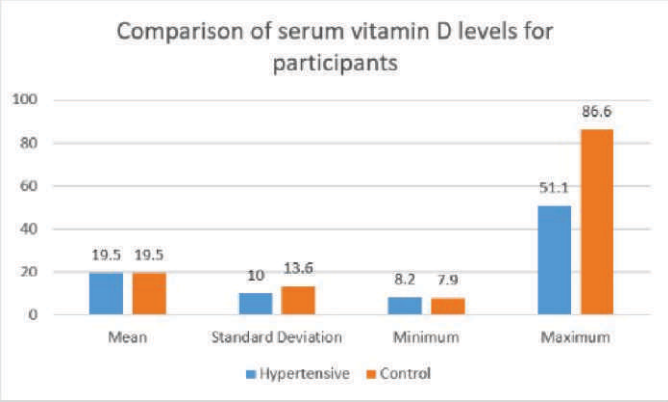
As shown in fig. 1 & table 2, mean level of vitamin D was 19.5±10.0 in hypertensive group and 19.5±13.6 ng/ml in control group. Therefore, no significant difference was found among two groups with a p-value of 0.983. For further analysis, vitamin D level was divided in three categories, i.e. <15, 15-25 and ≥ 25 and comparison was made using chi-square test, as shown in table 3. There were 12(37.5%) hypertensives with deficient vitamin D levels and similarly, 13(40.6%) healthy participants showed deficient levels. In short, no difference in vitamin D status was evident between two groups with p-value 0.976.

Fig.2: *Showing Comparison of Serum Vitamin D Levels in Two Groups*

Discussion

This is one of the pioneer studies in our setup to explore the physiological effects of vitamin D. In this study, we aimed to compare the serum levels of

25(OH)D in 2 groups which were age and gender matched. One group included hypertensive patients and other one comprised of healthy control subjects.



Serum vitamin D levels were found to be low in both hypertensive patients and healthy controls, thereby not suggesting any association of deficiency in cases and healthy subjects. In this study, mean vitamin D level was measured to be 19.5±10 ng/ml in hypertensive patients and 19.5±13.6 ng/ml in healthy controls.

Table 1: *Distribution of Participants According to BMI*

	BMI			
	Mean	**Standard Deviation**	**Minimum**	**Maximum**
Hypertensive	26.5	3.4	22.6	34
Control	25	3.1	19	33.4

Table 2: *Showing Comparison of Serum Vitamin D level Between Two Groups*

	Mean	**Standard Deviation**	**Minimum**	**Maximum**
Hypertensive	19.5	10	8.2	51.1
Control	19.5	13.6	7.9	86.6

Table 3: *Showing Comparison of Categorized Vitamin D Levels Using Chi-square Test*

Group	**SERUM VITAMIN D LEVELS (ng/ml) (Binned)**							
	< 15.0		**15.0 - 25.0**		...		**Total**	
	n	%	n	%	n	%	n	%
Hypertensive	12	37.5	14	43.8	6	18.8	32	100.0
Control	13	40.6	14	43.8	5	15.6	32	100.0
Total	25	39.06	28	43.75	11	17.18	64	100.0

Optimal serum vitamin D level, according to various studies is considered to be more than 30 ng/ml.[10] One study suggests optimal level of vitamin D of around 40ng/ml.[11] Few studies recommend an even higher optimal level but overall,30ng/ml is considered to be the lowest cut-off point. This study found the level of vitamin D in healthy controls equal to 19.5±13.6 ng/L, which is certainly sub-optimal.This level is considered to be in insufficient range according to most studies.[12,13] Nowadays, deficiency of vitamin Dis a common health problem worldwide which can be a consequence of insufficient vitamin D in diet, less exposure to sunlight, obesity, age, over use of sunscreens & other medication usage that can impair vitamin D absorption.[14] A study carried out at Washington University, revealed vitamin D levels to be insufficient/deficient in 57.5% subjects.[15] In addition to the global problem, South Asian population is even at higher risk of Vitamin D deficiency. This is due to the presence of more melanin beneath the skin that impairs synthesis process of vitamin D, insufficient sunlight exposure particularly in female gender, owing to social and cultural issues, sub-optimalfood quality and lastly, selection of improper food that lacks in required vitamins reflecting poverty and ignorance.

Numerous studies conducted so far, have indicated a potential link between vitamin D deficiency & hypertension, still none of such studies have been done in South Asian region. One of such studies was carried out in Iran, trying to establish a relationship between serum vitamin D levels and hypertension. This study revealed 67% hypertensive subjects having vitamin D deficiency. Further, the severity of hypertension was relatable to deficiency of vitamin D levels.[16] A cohort study conducted by Form an et also revealed vitamin D levels to be inversely proportional to incident hypertension and this relationship was unaffected by BMI, age, race, physical exertion and menopausal status.[6] One such study was carried out on American Blacks which highlighted drastic improvement in blood pressure control after supplementation of vitamin D, for three consecutive months.[9] Likewise, one more study conducted on White population of American revealed a significant inverse link of vitamin D level and category of hypertension, in the range from normotensive to stage 2 hypertension.[17] Another study done recently by Wang et al revealed that vitamin D less than 15ng/ml is related to increased hypertension rate(p=0.015). Detailed analysis revealed an even stronger relationship to exist between vitamin D and risk of cardiovascular events in hypertensives (p=0.003).[18] Multiple prospective studies have been conducted

with measurement of initial vitamin D level in order to explore long term risk of cardiovascular complications in subjects lacking prior history of cardiovascular problems. One such study revealed a 2-fold increased rate of myocardial infarction in subjects with vitamin D deficiency (levels<15ng/ml) during a follow up of 10 years.[19] Similarly, a large Framingham Studyalso revealed an association between low vitamin D levels and serious cardiovascular disease events, with risk reaching 53%-80%.[20] On the contrary, certain researches failed to provide any inverse relationship between vitamin D and hypertension. Infact, one study even highlighted a positive correlation to exist between vitamin D levels&blood pressure.[19] Undoubtedly, different studies reveal variable impact of vitamin D on hypertensive and normotensive individuals. This shows that effect of vitamin D on hypertension is still an area of concern which will require a drastic exploration & multiple comprehensive researches, before a final deduction is made.[16]

This study could not establish a inverse association between risk of hypertension and serum vitamin D levels, which is attributed to sub-optimal levels of serum vitamin D even in healthy population.

Conclusion

This study resulted in following conclusions:

1) Serum vitamin D is generally deficient or insufficient in our population.
2) The association between serum vitamin D level and hypertension could not be established.
3) Exploration of effects of vitamin D deficiency needs further large scale studies.

Limitations:

Our study had a few limitations:

1) Sample size was not large enough to give more conclusive results.
2) To obtain more reliable results, all other possible risk factors of cardiovascular diseases must be excluded from the study.

Author's Contributions

MR: Conducted and presented the research at a conference
TK: Questionaire design, conduction
MI: Initial Draft of manuscript
AF: Reviewed and improved the initial draft of manuscript
AM: Table and graph Design,Interpreted results
QM: Planned, Conducted and supervised the research

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Periodontitis: A Risk Factor for Preterm Labour

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Abstract

Objective: To determine the relationship between periodontitis and preterm labour in pregnant women presenting to a tertiary care hospital in Lahore.

Methods: This case control study was conducted at Obstetrics & Gynecology Unit 4 of Sir Ganga Ram Hospital, Lahore for six months. The delivering women, who consented to participate, were divided into two case and control groups. For each case one control was enrolled who met the inclusion criteria, so total sample size was 380 women. Women delivered before 37 weeks of gestation were case group and those delivered after 37 weeks were control group. A patient was considered having periodontitis if she had probing pocket depth of ⩾3mm in at least 3 sites. Data was collected and analyzed on SPSS version 21.

Results: In this study the mean age of the case group patients was 28.52±6.45 years while of the control group was 28.67±6.35 years. The mean value of probing depth pocket in the case group was 3.872±1.37 while the mean value probing depth pocket of the control group was 3.58±1.52. Out of 380 patients the periodontitis was found in 275 patients. The odds of having periodontitis in case group was 1.85 times higher than control group i.e. OR=1.85[1.17-2.92].

Conclusion: Periodontitis is a preventable risk factor of preterm labour in women presenting at a tertiary care hospital.

Keywords: Preterm Labour, Periodontitis, dental hygiene, preterm delivery

Introduction

Preterm delivery is also called as premature birth and it is delivery of a baby before 37 completed weeks of gestation. Preterm delivery is major cause of perinatal mortality and morbidity worldwide. About 15 million infants are born preterm (before 37 weeks of gestation) annually and they have low birth weight (LBW<2,500 g). The incidence of Preterm delivery has been reported in the range from 5% to 7% of live births in some developed countries, but the same is much higher in developing countries.[1] Premature infants are at greater risk of many mental and physical problems like cerebral palsy, delays in developmental mile stones, hearing loss, poor digestion, weak immune system and perinatal mortality. Women with preterm infants also face many psychological and physical stresses. The prolonged hospital stay, multiple treatment interventions and fear of losing a baby may make them prone to postpartum depression.[2] Since preterm delivery is a challenge in obstetrics therefore it is necessary to identify the risk factors. The exact cause of preterm labour is often not known but some of the risk factors include vaginal infections, diabetes, high blood pressure, multiple pregnancy, over or underweight, smoking and psychological stress. Among all the above said risk factors for preterm labour, maternal infection is the major one.[3]

Periodontal disease is caused mainly by gram-negative microaerophilic and anaerobic bacteria. They colonize the subgingival area and produce pro-inflammatory mediators like Prostaglandin E2, Tumour Necrosis Factor alpha (TNF-α), Interleukin 1 beta (IL-1β) and IL-6. These pro-inflammatory mediators have systemic effects on the host.[4] Periodontal diseases are gingivitis and periodontitis. Gingivitis is gingival inflammation without loss of

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connective tissue attachment. Periodontitis is gingival inflammation at sites where there has been apical migration of the epithelial attachment on the root surfaces by the loss of connective tissue and alveolar bone. In the last twenty years many studies have shown the relationship between periodontitis and preterm labour. Periodontitis is a risk factor for preterm labour due to presence of bacteria and pro-inflammatory cytokines in blood that can affect the distant organs.[5,6]

Rationale of this study is to determine the frequency and association of periodontitis with preterm labour in women presenting in a tertiary care hospital. In literature, the relationship of periodontitis with preterm labour is still not clear. Therefore, we conducted this study to get local evidence and implement the results of this study in local settings. Therefore, in future we can recommend the antenatal screening of pregnant women for periodontal diseases.[7,8]

Objective

To determine the relationship between periodontitis and preterm labour in pregnant women presenting to a tertiary care hospital in Lahore.

Methods

Study Design: Case control study

Setting: Obstetrics & Gynecology Unit 4 ofSir Ganga Ram Hospital, Lahore

Duration: 6 months (8-5-2019 to 8-11-2019)

Sample Size: Sample size was 380 women. 190 women in control and the same number in case groups were calculated with 85% power of test with 5% level of significance and taking expected percentage of periodontitis i.e. 86% in case and 76% in control groups.

Sampling Technique: Non-probability, consecutive sampling

Inclusion Criteria: Women of age 18-40years, parity < 5 presenting at gestational age >28 weeks (by first trimester scan) were included. Cases were those women in preterm labour (>3contractions in 10 minutes, Bishop score >4 and cervical dilation >4cm before completion of 37weeks of gestation). Controls were those women in labour at term (gestational age >37weeks).

Exclusion Criteria: Women with previous history of preterm labour, cervical incompetence, chronic or gestational hypertension, pre-eclampsia, eclampsia, diabetes, multiple pregnancy, abnormal placental implant (accrete, previa, increta) or placental abruption, amniotic fluid index <5cm or >21cm or women already taking treatment for periodontitis or other dental problems were excluded.

Data Collection Procedure: After taking informed consent, demographic profile was noted. Then women were divided into two groups i.e. cases in preterm labour and controls in term labour. After delivery the women were assessed for periodontitis by a single senior dentist having at least 4 years residency experience. Probing pocket depth was assessed and periodontitis was labeled according to WHO criterion for periodontitis i.e. probing pocket depth ≥ 4 mm in at least 3 sites, in different teeth. All this information was recorded on proforma. SPSS version 21 was used to enter and analyze the collected data. Odds ratio was calculated to measure association of periodontitis and preterm labour. OR>1 was considered as arisk of preterm labour.

Results

The mean age of the cases group patients was 28.52±6.45 years while the mean age of the control group was 28.67±6.35 years. The mean gestational age of the cases group patients was 34.48±1.74 weeks while in control group was 38.92±0.79 weeks. There were 65(17.11%) nulliparous women, 62(16.32%) had one child, 115(30.26%) had two children, 85(22.37%) had three children and 53(13.95%) women had four children. The mean BMI of the cases group patients was 24.84±5.054 kg/m^2 while in control group was 26.50±5.45 kg/m^2. This difference was statistically significant i.e. p-value=0.002. According to this study the mean probing pocket depth of periodontitis in the cases group was 3.872± 1.37 while in control group was 3.58±1.52. This difference was statistically significant i.e. p-value= 0.050. (Table-1). The results of this study show that out of 380 patients the periodontitis was found in 275(72.37%) patients (Fig-1). In cases group the periodontitis was found in 149(78.4%) respondents while in control group the periodontitis was found in 126(66.3%) respondents. The odds of having periodontitis in cases group is 1.85 time higher than control group i.e. OR=1.85[1.17-2.92]. (Table-2)

Table 1: *Demographic Features of Patients*

	Study Groups	
	Case	Control
n	190	190
Age (Years)	28.52±6.45	28.67±6.35
Gestational age (weeks)	34.48±1.74	38.92±0.79
BMI (Kg/m^2)	24.84±5.05	26.50±5.45
Probing depth	3.87±1.37	3.58±1.52
Primiparous	61	66
Multiparous	129	124

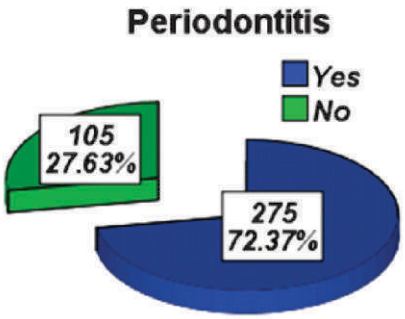

Figure-1: *Distribution of Periodontitis*

Among patients with age ≤ 30 years the odds of having periodontitis is 2.28 time higher in cases group than control groups i.e. OR=2.28[1.22-4.26]. Among patients with gestational age > 36 weeks there is insignificant difference found between the study groups with periodontitis i.e. p-value=0.068. Among

Table 2: *Association of Periodontitis with Preterm Labour*

		Study Groups		Total	OR [95% CI]
		Case	Control		
Periodontitis	Yes	149	126	275	1.85 [1.17-2.92]
		78.4%	66.3%	72.4%	
	No	41	64	105	
		21.6%	33.7%	27.6%	
Total		190	190	380	
		100%	100%	100%	

multi-parity patients the odds of having periodontitis is 2.23 time higher in cases group than control groups i.e. OR=2.23[1.27-3.89]. Among patients with over-weight & obese BMI status the odds of having perio-dontitis is 2.19 time higher in cases group than control groups i.e. OR=2.19[1.12-4.28]. (Table-3)

Discussion

In this study cases and controls were recruited with intent to conduct a case-controlstudy with cases being mothers who experienced preterm labor and controls being mothers without preterm labour and having infants weighing more than 2500 grams. These cases and controls came from same pool of patients delivering in Sir Ganga Ram Hospital Lahore in Gynae Unit 4. Counseling was done and informed consent was taken during early labour so all cases could be enrolled with a comparable number of controls. The advantage of the study is that all

Table 3: *Association of Periodontitis with Preterm Labour Stratified by Effect Modifiers*

Age (Years)	Period on titis	Study Groups		Total	OR (95% CI)
		Case	Control		
⩽30	Yes	95	75	170	2.28 [1.22-4.26]
		82.6%	67.6%	75.2%	
	No	20	36	56	
		17.4%	32.4%	24.8%	
>30	Yes	54	51	105	1.41 [0.71-2.79]
		72.0%	64.6%	68.2%	
	No	21	28	49	
		28.0%	35.4%	31.8%	
Gestational age 32-36 weeks	Yes	132	0	132	--
		84.6%	0%	84.6%	
	No	24	0	24	
		15.4%	0%	15.4%	
Gestational age>36 weeks	Yes	17	126	143	0.51 [0.24-1.061]
		50.0%	66.3%	63.8%	
	No	17	64	81	
		50.0%	33.7%	36.2%	
Primiparous	Yes	47	48	95	1.25 [0.56-2.82]
		77.0%	**72.7%**	**74.8%**	
	No	14	18	32	
		23.0%	**27.3%**	**25.2%**	
Multiparous	Yes	102	78	180	2.23 [1.27-3.89]
		79.1%	**62.9%**	**71.1%**	
	No	27	46	73	
		20.9%	**37.1%**	**28.9%**	
BMI<24.9	Yes	74	49	123	1.69 [0.88-3.24]
		74.7%	**63.6%**	**69.9%**	
	No	25	28	53	
		25.3%	**36.4%**	**30.1%**	
BMI>24.9	Yes	75	77	152	2.19 [1.12-4.28]
		82.4%	**68.1%**	**74.5%**	
	No	16	36	52	
		17.6%	**31.9%**	**25.5%**	

periodontal examination was done in a standardized way by trained medical practitioners.

In our study the mean age of the cases group patients was 28.52±6.45 years which was not significantly different from controls 28.67±6.35 years. This result is similar to other study having the mean age for case 25 ± 6.3 (SD) years, while the mean age of the control group was 22 ± 3.4 years.[9] There was no significant

difference among the parity between cases and controls, and the mean gestational age of preterm labour was 34 weeks which is similar to other studies.[10] High or low BMI was not significantly associated with preterm birth and was same in both cases and control groups.[11]

In current study out of 380 patients the periodontitis was found in 275(72.37%) patients in total. In the cases group the periodontitis was found in 149(78.4%) participants and in control group the periodontitis was found in 126(66.3%) participants. According to this study the odds of having periodontitis in case group is 1.85 time higher than control group i.e. OR=1.85[1.17-2.92]. The results of this study are similar to the results of a study conducted by Chokkaiyan et al.[12] in which periodontitis among cases was 86% and among controls it was 75%. Although the reported difference was significant (P=0.001) yet the frequency of periodontitis is not negligible in control group.

The study conducted by Offenbacher et al.[13] reported a link between poor maternal periodontal health and preterm delivery. As per the said study pregnant women with periodontitis have 7.5 times more risk of developing preterm labour as compared to controls. This result is higher than our study result.

Another study published in 2018[14] showed that the mothers in the periodontitis group delivered preterm infants at eight-fold higher frequency and low birth weight infants with ten-fold higher frequency as compared to control group. The studies conducted in USA show significant relationship between periodontal disease and preterm delivery among African-American racial/ethnic groups and those women who smoke during pregnancy.[15,16] Another study by Jeffcoat et al[17] demonstrated that there is beneficial effect on preterm labour if periodontal treatment is successful. As per logistic regression analysis there is significant relationship between successful periodontal treatment and full-term birth (adjusted odds ratio 6.02; 95% CI 2.57–14.03). The subjects, refractory to periodontal treatment were significantly at higher risk to have preterm labour.

On the other hand, a study by Lohsoonthorn et al[18] on Thai women does not provide enough evidence that periodontal disease is associated with preterm labour. Lohsoonthorn et al. reported that among cases 25.3% women had periodontitis while among controls 22.7% women had periodontitis. The reported difference was insignificant (P>0.05), thus showing a non-significant relationship between periodontitis and preterm labour.

Two studies conducted in the United Kingdom have failed to determine significant relationship between periodontal disease in pregnancy and risk of preterm delivery.[19,20] In addition, Martinez-Martinez et al.[21] suggested that Preterm birth is because of many other reasons therefore periodontal pathogens are not sufficient to cause Preterm birth.

There are many cohort studies reported in literature showing an association among periodontitis and preterm birth, low birth weight or preterm pre-labour rupture of membranes. In 2016, a hospital-based prospective study on 790 pregnant women found that periodontitis was a risk factor for preterm birth and low birth weight.[22] Recently periodontitis was also found to be associated with pre-eclampsia and PROM as common causes of preterm birth.[23]

A meta-analysis done by Vivares-Builes[24] reviewed 99 observational studies. Most of them have highlighted association among maternal periodontitis and a higher risk of low birth weight, preterm delivery and pre-eclampsia.

There is a need of more multicenter studies to be conducted to reach a definite association between periodontitis and preterm labour. For the time being, routine ante-natal dental evaluation can be practiced and patients having periodontitis should be treated to prevent preterm labour.

Conclusion

Our study has concluded that periodontitis is associated with preterm labour in women who presented at a tertiary care hospital of Lahore, Pakistan.

Author's Contribution

SIM: Original Idea, Conception of work
FN: Paper writing
AA: Designed Analysis
MG, NR: Data Collection
NK: Analytical interpretation of results

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Morphological Spectrum of Lesions Seen in Thyroidectomy Specimens At A Tertiary Care Institute

Iram Nadeem Rana[1], Samra Sameen[2], Sahar Iqbal[3], Tazeen Anis[4]

Abstract

Objective: To determine the morphological spectrum of thyroid lesions encountered in thyroidectomy specimens at a tertiary care institute.

Methods: It was a retrospective study conducted in Pathology Department, Allama Iqbal Medical College, Lahore. A retrospective manual collection of data was done from record registers, for the years 2012 & 2013.

Results: A total of 307 cases were retrieved with age range of 16-70 years. Amongst them, 47 were males and 260 were females. Non neoplastic conditions outnumbered the neoplastic lesions as 229(75%) cases were of colloid goiter. Hashimoto thyroiditis was present in 12(3.9%) specimens and associated hyperplastic changes were seen in 15(4.9%) cases. There were 19(6.2%) cases of papillary carcinoma, 3(0.9%) cases of follicular carcinoma, 3(0.9%) cases of medullary carcinoma, 1(0.3 %) case of insular carcinoma and 2(0.6%) anaplastic carcinoma. Papillary microcarcinoma was seen in 4(1.3 %) cases and medullary microcarcinoma in 1(0.3%) case. Follicular adenoma comprised 29(9.4%) cases and Hurthle cell adenoma 3(0.9%) cases. Study data also showed 1(0.3%) rare case of hyalinizing trabecular tumor.

Conclusion: Non neoplastic thyroid diseases are more common as compared to neoplastic lesions. Papillary carcinoma is most common thyroid malignancy encountered in our setting.

Key Words: Thyroidectomy, Colloid goiter, papillary carcinoma

Introduction

The thyroid gland is responsible for secretion of two crucial hormones Thyroxine and Calcitonin.[1] The incidence of thyroid diseases is rising due to increase in aging population and an increased use of cross sectional imaging of head, neck and chest.[2] Effected patients may remain relatively asymptomatic, may present with symptoms of hyperfunction, hypofuction or a mass in front of the neck. Diffuse thyroid lesions involve the entire gland, such as hyperplasia and thyroiditis. Nodular lesions are those disorders that produce a clinically palpable nodule which may be solitary or multiple.[3] Around 10-15% of thyroid nodules turn out to be cancerous on investigations. So it is recommended that all nodules larger than 1-1.5cm must be evaluated. For such patients early detection and treatment are associated with excellent prognosis.[2] Thyroidectomy is mainstay of treatment in malignant thyroid diseases. For benign disorders, surgery resorted to for cosmetic or pressure symptoms.

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Objective

To determine the morphological spectrum of thyroid disorders in thyroidectomy specimens recei-ved in department of Pathology of Allama Iqbal Medical College (AIMC), over a period of 2 years.

Methods

It is a retrospective study spanned over 2 years, conducted in Histopathology section of Department of Pathology, AIMC, Lahore. Demographic data was collected from Record Registers for the years 2012 & 2013 for all the thyroidectomy specimens (either total

thyroidectomy, partial thyroidectomy or lobectomy). A total of 307 samples of thyroid surgeries were received during this period. Slides were retrieved for verification of the morphological diagnosis. Relevant clinical data was retrieved. In case of a neoplastic diagnosis, second consultation from another Histopathologist in the department was taken. Data was entered and analyzed by using Microsoft excel 2010 and the results were prepared.

Results

Youngest patient included in study was 16 years old and eldest was 70 years old. Maximum 149 (48 %) patients were within age range of 11-30 years, while 131 (43%) patients were in age range of 31-50 years and 27 (9%) patients were in age range of 51-70 years. Out of 307 cases, 47 (15%) were male patients and 260 (85%) were female patients thus making female to male ratio of 5.5:1 as shown in figure 1.

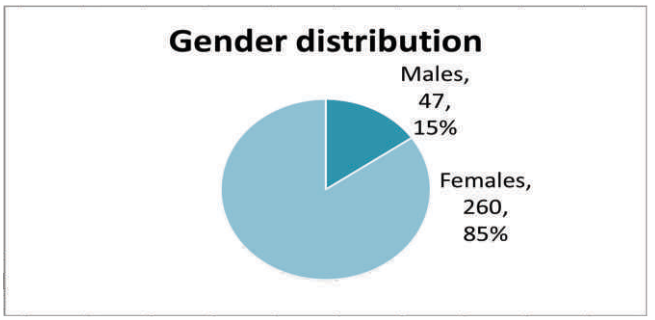


Fig.1: *Gender Distribution of Thyroid Diseases*

Histopathology revealed non neoplastic lesions in 241(78.5%) specimens and neoplastic lesions in 66(21.5%) cases. Amongst non neoplastic entities, majority 229(95%) cases comprised of colloid goiter and 12(5%) cases showed histologic evidence of Hashimoto thyroiditis.

Out of these 66 neoplastic lesions, there was equal contribution of benign 33 (50%) and malignant 33(50%) cases. Diagnosed benign entities were follicular adenoma 29 (88%) cases, Hurthle cell adenoma 3(9%) cases and there was 1(3%) rare case of hyalinizing trabecular tumor (Table 1).

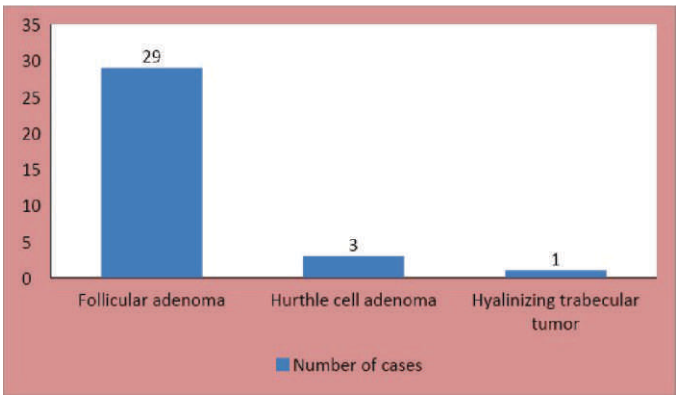
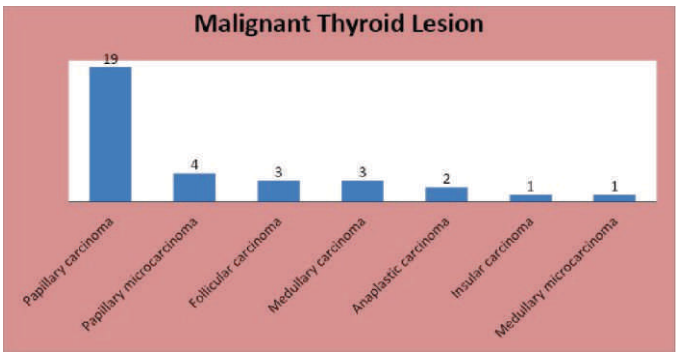


Fig. 1: *Benign Neoplastic Thyroid Lesions*

Malignant thyroid cases diagnosed during the period were as follows (Table 2); papillary carcinoma 19(58%), papillary microcarcinoma 4(12%), follicular carcinoma 3(9%), medullary carcinoma 3(9%), anaplastic carcinoma 2(6%), insular carcinoma 1(3%), and medullary microcarcinoma 1(3%).

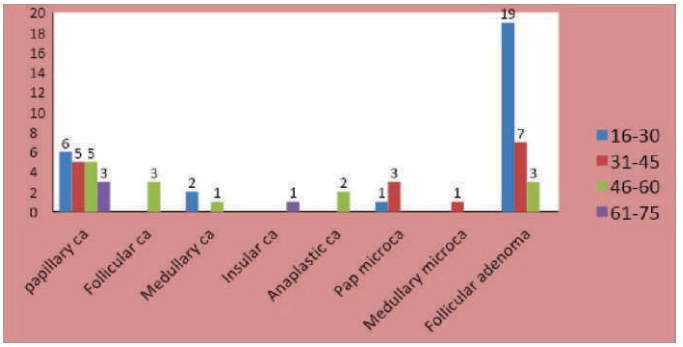
Fig. 2: *Malignant Thyroid Lesions*

Papillary carcinoma was seen in all age groups with



maximum number of cases[6] seen in age group of 16-30 years. Follicular and anaplastic carcinoma were seen in age group of 46-60%. Insular carcinoma was seen in 61-75 years of age while follicular adenoma also showed maximum number in younger population. Table 3 shows correlation of age with various benign and malignant thyroid diseases.

Fig.3: *Correlation of Age with Histopathologic*



Categories

Discussion:

Thyroid gland is amongst the most common endocrine gland inflicted by various pathologies. Thyroid mass lesions may be diffuse or nodular, caused by a variety of benign and malignant lesions. Prevalence of palpable thyroid nodule in general population is reported as 4-7 %, rising to 10-41%, when discovered incidentally on ultrasonography.[4,5] Thyroid diseases mostly effect younger population as seen in our study where the maximum number of cases (48%) were within age range of 11-30 years. This is similar to cases reported by Itagi et al in which maximum number of patients with thyroid nodules were seen in age range of 21-30 years.[6]

Thyroid lesions predominantly affect females. In our study 85 % were female patients and only 15% were male patients thus making female to male ratio of 5.5:1. This ratio is similar to that reported by Singh et al in India.[7] Musani et al had 78% of females in their study while there was strong female predominance (89%) in a study conducted by Fatima et al.[3,8]

After detailed histopathologic examination, 78.5% of specimens showed non neoplastic entities while 21.5% had neoplastic lesions. Sanjeeva et al had more number of non neoplastic entities amounting to 91% in their study conducted in India in 2015.[9] In our study, multinodular colloid goiter (Figure 2) was the commonest non neoplastic enlarged thyroid entity (95%) . Hashimoto thyroiditis was detected in 5 % cases on histopathology.

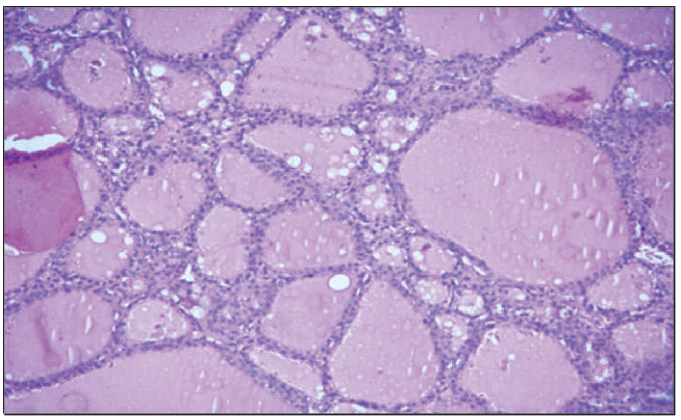


Fig.4: *Microscopic Picture Showing Multinodular Colloid Goiter with Multiple Colloid Filled Cystic Spaces and Benign Histology*

In neoplastic benign entities follicular adenoma was commonest accounting 88% of cases. This is followed by 9% cases of Hurthle cell adenoma, which has been reported as variably between 3-10% in literature.[10] There was a minor contribution by one rare case of hyalinizing trabecular tumor diagnosed in a young 28 years old female. (Figure 3) Literature shows variable reports on this rare entity ranging from 0.44-1.3% of all thyroidectomies.[11]

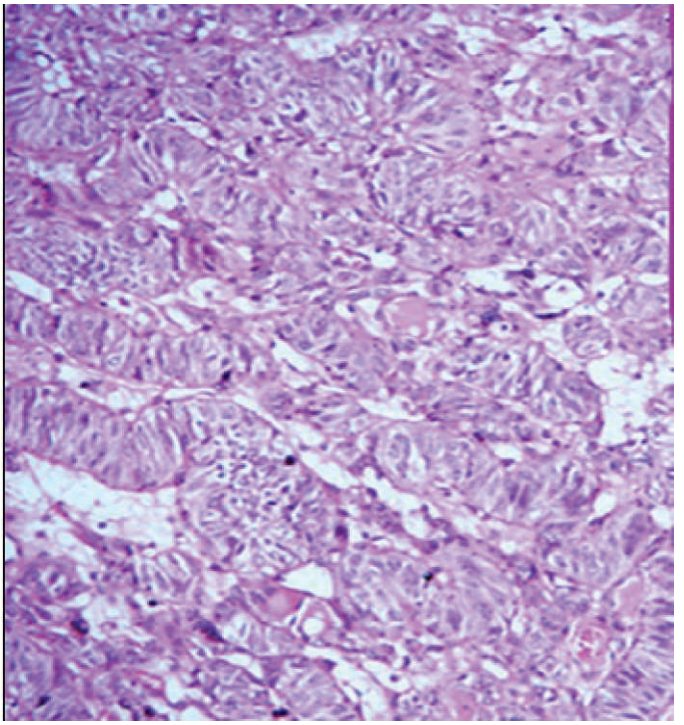


Fig.5: *Microscopic Morphology of Rare Hyalini-zing Trabecular Tumor of Thyroid*

In malignant thyroid lesions, papillary carcinoma outnumbered other malignancies reaching a toll of 58% in our study. (Figure 4)

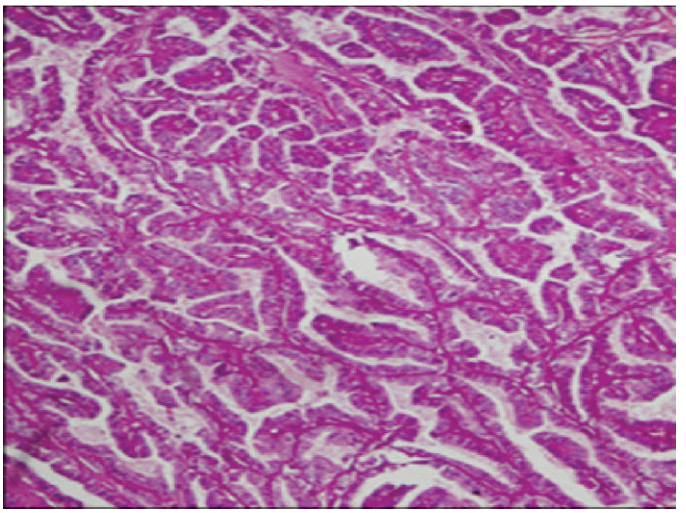


Fig.6: *Papillary Thyroid Carcinoma*

This is comparable to study by Burgess et al who reported 65% papillary thyroid carcinoma in their

large study including 3452 patients.[12] Follicular and medullary carcinoma contributed as 9% each in our study as compared to Bukhari et al who reported 2% cases of follicular carcinoma and 4.5% cases of medullary carcinoma in a large study from Karachi including 998 patients.[13] Papillary microcarcinoma was seen in 12 % of thyroidectomies performed for malignancy and medullary microcarcinoma contributed as 3% of all malignant cases. Microcarcinomas are smaller tumors with diameter less than 1 cm. Literature reports papillary microcarcinoma ranging between 7.1-16.3% and medullary microcarcinoma around 2%.[14,15]

Conclusions

To sum up thyroid gland diseases are more common in younger age group and in females. Non neoplastic lesions are far more common than neoplastic lesions. Papillary thyroid carcinoma is the most common thyroid malignant tumor and hyalinizing trabecular tumor is a rare benign thyroid tumor.

Author's Contribution

INR: Author
SS: Conceived and designed the analysis, reporting of cases
SI: Data Collection, data analysis
TA: Data collection, reporting of cases

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Agreement Between Waist Hip Ratio and Total Cholesterol to HDL Ratio in the Diagnosis of Raised Total Cholesterol in Post Menopausal Women

Muhammad Asif,[1] Abida Pervaiz,[2] Wajiha Fatima,[3] Naseer Umer Bhatti,[4] Muhammad Iftikhar Yousaf,[5] Ayesha Mahmood Malik[6]

Abstract

Objective: To establish the presence of hypercholesterolemia in post-menopausal women by checking an agreement between waist hip ratio (WHR: at a cut off 0.84) with total cholesterol to HDL ratio (TC/HDL at a cut off 4).

Methods: This cross-sectional descriptive study was conducted at the department of medicine over a period of 6 months. 225patients fulfilling the inclusion criteria were recruited after explaining the procedure and taking informed consent. 5 ml. of an eight hours fasting blood drawn in the serum vial and sent to the laboratory for the analysis of total cholesterol and HDL cholesterol according to the hospital laboratory protocol. Waist and hip measurements taken via a reference point at umbilicus and 5 c.m below it via a measuring tape.

Results: 112(49.78%) individuals were from 61-65 years, 69 (30.67%) between 56-60 and only 44(19.55%) were between 51-55 years of age. Frequency of agreement between WHR and TC/HDL ratio was calculated which revealed 72.44%(n=163) as positive and 27.56%(n=62) as negative. Conclusion: It was established that WHR and TC/HDL remains a strong indicator in preventing major cardiovascular events.

Key words: waist hip ratio, total cholesterol to HDL ratio, post-menopausal.

Introduction

Post menopause refers to cessation of menstrual flow due to reduced endogenous production of hormones mainly estrogens and progesterone by gonads. These hormones are believed to be protective against atherosclerotic and major cardiac events. Males have relatively more incidence of cardiovascular events in the form of coronary heart disease (CHD) as compared to women due to favorable effects of estrogen on lipids[1,2] but women with post-menopause have high chances of cardiovascular events.[3] As deficiency of estrogen leads to hypercholesterolemia. One proposed mechanism is changes in the fat cells leading to not only the accumulation of total cholesterol, triglycerides and HDL but changes occurred at the cellular levels as well. Likewise, in premenopausal due to influence of estrogen women fat distribution is more inclined towards the thigh and gluteal region which changes to abdominal type after menopause due to lack of estrogen.[4] Obesity is an identifiable and curable risk factors for majority of cardiovascular events both fatal and non-fatal. Obesity predisposes one towards metabolic syndrome that includes hyperuricemia, hypertension, impaired glucose tolerance and dyslipidemias. The location of fat deposition is extremely important to establish the relation between disease and obesity.[5] Various tools available for diagnosing obesity including waist hip ratio, abdominal fat and LDL-c levels.[6] Serum TC/HDL-C ratio is important in establishing risk of CHD. Ratio of ≥ 4.6 considered threatening for cardiovascular events so an optimal value of 3.3 is suggested.[5] Frequency of raised total cholesterol to HDL ratio in postmenopausal women is 30%[8]. Our study was conducted to screen the post-menopausal

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females who can be at risk of getting cardiovascular disease by assessing WHR (at a cut-off value of 0.84) and TC/HDL-C ratio as statistical gold standard (at a cut-off point of 4.7) as an index to determine the risk of CHD in postmenopausal women. In a study it was observed that the sensitivity and specificity of waist hip ratio (at a cut-off point of 0.84) is 78% and 77% respectively in the detection of raised total cholesterol to HDL cholesterol (TC/HDL-C) in postmenopausal women by taking TC/HDL-C at a cut-off point of 4 as gold standard7 and the agreement of WHR (at a cut off 0.84) and total cholesterol to HDL ratio (at a cut off 4) is 78%.[5]

We can use waist hip ratio as a screening tool as it is relatively easy to conduct. This will help early management of patients having raised waist hip ratio to initiate early management of dyslipidemia to prevent coronary heart disease.

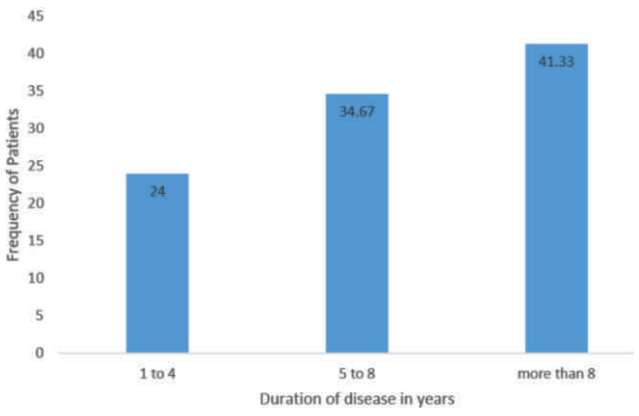
Methods

This descriptive cross-sectional survey was conducted at outpatient and in-patient medical unit # IV of Jinnah hospital, Lahore over a period of 6 months via a non-probability purposive sampling, after approval from a local ethical committee. A total of 225 individuals 95% confidence level, 10% margin of error and taking expected percentage of agreement i.e. 78%, b/w waist hip ratio (at a cut off 0.84) and total cholesterol to HDL ratio (at a cut off 4). 225 post-menopausal women of age 51-65 years, with a 1-year history of cessation of menstrual flow and having 8 hours of overnight fasting were enrolled after getting informed consent. Females with a history of Diabetes mellitus, renal dysfunction and intake of lipid lowering drugs were excluded from the study. A 5m.l. blood sample taken in a serum vial was obtained by phlebotomist after aseptic measure. Samples were centrifuged at 5 degree centigrade for 15 minutes after incubation of 20 minutes for extraction of serum. The sera were analyzed for total cholesterol, HDL Cholesterol and their ratio by enzymatic calorimetric method using chemistry auto analyzer. Waist and hip measurement were taken by researchers at an umbilicus and another 5 cm below it after explaining to the patient. The data was entered and analyzed using SPSS version 21.0. Frequencies and percentages were computed for qualitative variables like agreement b/w WHR and TC/HDL ratio and mean plus minus SD was calculated for quantitative variables as age and lipid profile. Data was stratified for the duration of post-menopause to address effect modifiers. Kappa statistics were used to determine the strength of agreement b/w WHR (at a cut off 0.84) and TC/HDL-C ratio (at a cut off 4).

Results

225 patients were recruited after fulfilling the inclusion/exclusion criteria to determine the agreement between WHR (at a cut off 0.84) and TC/HDL ratio (at a cut off 4) for the presence of hypercholesterolemia in post-menopausal women. 49.78%(n=112) were between the age group 61-65 years, 30.67% (n=69) from 56-60 years and 19.55% (n =44) were between 51-55 years of age. Duration of post menopause (in years) was calculated as percentages shown in Fig #1a which shows 24%(n=54) between 1-4 years, 34.66%(n=78) between 5-8 and 41.33%(n=93) were recorded with >8 years of duration of menopause.

Frequency of agreement between WHR and TC/HDL ratio was calculated which revealed in 72.44% (n=163) as positive and 27.56%(n=62) as negative



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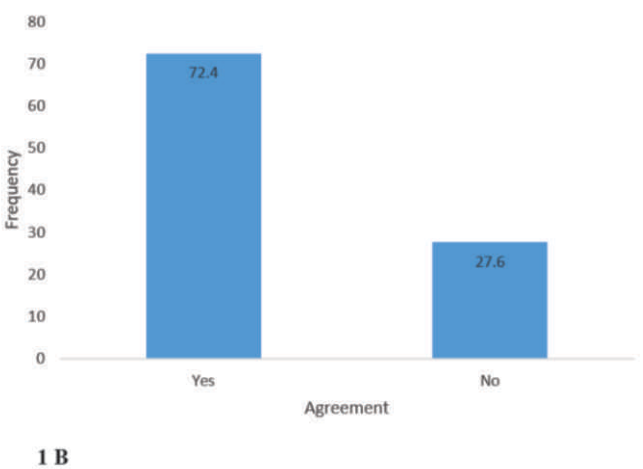

1 B

(illustrated in Fig # 1b). where Agreement was defined as Positive when a post-menopausal woman having increased WHR i.e. equal or above 0.84 and raised TC/HDL ratio i.e. equal or above 4. Agreement was said to be negative when postmenopausal woman having decreased WHR i.e. below 0.84 and decreased TC/HDL ratio i.e. below 4.

Table 1: *Stratification of Agreement as Positive between Whr and Tc/hdl Ratio with Regards to Duration of Disease. (n=163)*

Duration of disease i.e. post menopause (in years)	No. of patients	No. of patients (%)
1-4	54	30(18.40%)
5-8	78	50(30.67%)
>8	93	83(50.92%)
Total	**225**	**163**

Discussion

Metabolic syndrome, obesity and dyslipidemias emerged as a predictor of fatal and non-fatal cardiovascular events. CHD tends to rise in post-menopausal women.[7] Estrogen has a protective role in the prevention of thrombosis with anti-inflammatory properties. We thought to assess the risk of cardiovascular events in post-menopausal women. The current study revealed that the duration of post-menopausal had a linear relationship between WHR and TC/HDL ratio. 163 patients had a positive agreement between these ratios. The frequency of agreement between WHR and TC/HDL ratio was calculated in 72.44% (n=163) as positive and 27.56% (n=62) as negative. Our results were consistent with a study that showed an agreement in 78% of the patients for detection of raised total cholesterol to HDL cholesterol (TC/HDL-C) in postmenopausal women by taking TC/HDL-C at a cut-off point of 4 as gold standard and the agreement by WHR(at a cut off 0.84) and total cholesterol to HDL ratio (at a cut off 4).[5]

Various studies purposed the active role of peripheral fat mass in the modulation of metabolic and cardiovascular risk in postmenopausal women.[10] Excessive fat in thigh region, even in generally obese women with excessive truncal fat, can provide protective effects against lipid over accumulation, insulin resistance, type 2 diabetes, and atherogenesis. There are multiple modifiable risk factors of CVD, among all the major one remains the association observed in women with the deranged serum lipid levels and lipoproteins.[12] Certain studies have proposed an increase in the release of free fatty acids into circulation due to high-fat accumulation leading to raised hepatic triglycerides synthesis.[13] There is a rise in plasma lipoprotein lipase (LPL) and hepatic TG lipase activity post-menopause leading to a decrease in estrogen levels.[14] HDL-C was markedly reduced in post-menopausal women as shown in the past studies which is in tandem with the findings of our study. Available evidence shows that as HDL-C increases by 0.026 mmol/ml, there is a reduction in risk of cardiovascular diseases, with a 4.7% decrease in mortality rate of CVD.[15] Variation in serum lipids remains to increase the incidence of CVD following menopausal transition.[13]

The available data is scanty, while different studies revealed that WHR can serve as an easy screening adjunct used in conjunction with other proven measures to detect those at increased risk of coronary heart disease (CHD).[8,9] Waist circumference and waist hip ratio have been used as measures of central obesity (where visceral adipose tissue is stored), and body mass index has been used as a measure of general obesity.[10]

There is a need for more trials for determination of agreement between waist ratio (at a cut off 0.84) and total cholesterol to HDL ratio (at a cut off 4) in the diagnosis of raised total cholesterol in post-menopausal women are required so that we can use waist hip ratio as a screening tool to detect raised total cholesterol to HDL ratio in post-menopausal women. It will help early management of patients to prevent coronary heart disease.

Conclusion

It is concluded that post-menopausal state might be a predictor of metabolic syndrome leading to cardiovascular events. The early pharmacological intervention can minimize this risk, so we can stratify the population at risk without any identifiable risk factors.

Author's Contributions

MA, WF: Data Collection
AP: Supervision of research work
NUB, MIY: Data Analysis.
AMM: Review of manuscript

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The Frequency of Intranasal Synechiae Formation between Nasal Septum and Lateral Nasal Wall after Endoscopic Sinus Surgery Among Patients with Sinonasal Polyposis

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Abstract

Objectives: To determine the frequency of intranasal synechiae formation between lateral nasal wall and nasal septum after (ESS) Endoscopic Sinus Surgery among patients with Sino nasal Polyposis

Methods: After obtaining approval from the ethical committee of our Hospital, a total number of 150 subjects fulfilling the study criteria were recruited in the research which was conducted in the department of Otorhinolaryngology, Services Hospital, Lahore. Demographic information (name, age, gender, contact details) was also obtained were included in this study. All the patients underwent ESS and were followed up post operatively at the end of 1st, 2nd, 3rd and 4th weeks respectively, to observe the formation of synechiae.

Results: Age range in this study was between 21-40 years out of which a small number of patients were < 20 years old. Mean age of the patients was 35.30±10.54 years. Male patients were 80 (53.3%) while female patients were 70 (46.7%). Intranasal Synechiae formation was observed in 28 patients (18.7%).

Conclusion: Intranasal Synechiae formation between lateral nasal wall and nasal septum was found in 18.4% of the patients after endoscopic sinus surgery.

Keywords: Sino nasal polyposis, ESS, Intranasal Synechiae Formation

Introduction:

Nasal polyps are presence of an abnormal pedunculated lesions that arise from the diseased-mucosa of paranasal sinuses which later manifest themselves in the nasal cavity. They commonly have solid and cystic components[1], 4-6% of the general population has Sino nasal polyps.[2]

Sino nasal polyposis is thought to be a multifactorial disease of the nasal mucosa, which is considered clinically by the presence of non-neoplastic translucent swellings in the nasal cavity and paranasal sinuses. It is found in a varied number of diseases and has various histological components that is determined by the underlying disease state. Henceforth, it may embody a common pathological end point innumerous disease processes.[3]

The predominance of nasal polyps in the general populace remains uncertain. However, the reported incidence seems to differ between 0.2% and 4.3% of the population.[3-5] A study conducted in Denmark that lasted over a 6-year period by Larsen and Tos, identified 252 nasal polyposis patients (78 females and 174 males) to study its prevalence in the background population of 223449 occupants. Larsen and Tos projected an occurrence of 0.627 per thousand per year in Denmark.[6]

Klossek et al described an overall frequency of 2.11% in France.[7] In their study, 10033 subjects were scanned for presence of nasal polyps by use of anauthenticated and structured questionnaire. There is an over-all agreement amongst ENT clinicians that the prevalence increases with rising age and that there is a strong male predominance.[6,7] Remarkably, a far greater incidence of nasal polyps were reported when autopsy specimens were examined, with nasal polyps

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found in 26-42% 8,9. It is probable that small sized or sessile polyps rarely manifest themselves clinically in the nasal cavity during life. Polyps normally remain asymptomatic, until they progress to such a size as to obstruct the opening of the sinus ostia with subsequent development of symptoms of unremitting nasal obstruction and rhino sinusitis.

There are many disorders that have a recognized incidence of nasal polyps. The reported frequency of nasal polyps in asthmatic patients varies between 6.7%, and 13%[10] respectively while the incidence of asthma in patients with Sino nasal polyps has been stated as high as 45%.[11] In 1968, Samter defined the Aspirin triad, consisting of Aspirin sensitivity, Atopic Asthma and Sino nasal polyposis.[12] Hypersensitivity to Aspirin is present in up to 5% to 10%[13] of asthmatic patients and the disease manifestation in such patients is particularly severe. The incidence of nasal polyposis is also higher in the Aspirin tolerant and asthmatic population. The documented prevalence of nasal polyps in this group of patients ranges from 36% to 95% respectively.[14]

There are a number of important clinical associations in patients with Sino nasal polyposis, namely CRS, Cystic Fibrosis which should be considered in children with nasal polyps, although the diagnosis will have normally been made in early childhood and Allergic Fungal Rhino sinusitis. The association of nasal polyposis in AFRS is not completely understood. AFRS is associated with thick eosinophilic mucus, lack of fungal invasion into tissues and Type I Hypersensitivity to fungi. The condition is also characterized by bony erosions of the sinus walls seen on CT imaging.[15]

Etiology is still uncertain, chronic inflammatory changes mediated by eosinophils and to some lesser extent neutrophils. Atopy is also implicated in its pathogenesis.[2] Mainstay of treatment is medical and the most effective treatment of nasal polyps is with topical nasalcorticosteroids and management of the underlying allergy.[1,2] Patients recalcitrant to medical therapy are treated with endoscopic sinus surgery.[16]

Endoscopic sinus surgery (ESS) is an intranasal surgical procedure, that is performed under direct vision which is negligibly invasive with remarkable improvement of symptoms. Adhesions form due to medialization of the middle and inferior turbinates on the lateral nasal wall and crusting with scarring which results in blockade of the middle meatus and recurrent rhino sinusitis, dictating further surgery.[16] Factors promoting synechiae formation include history of previous nasal surgery and inexperienced surgical techniques.[16]

Although ESS is considered an extraordinary advancement in nasal surgery, intranasal adhesion formation is an inevitable accompaniment which causes recurrence of disease and dictates a revision surgery. In a literature review by Shamoon et alvariable results of synechiae formation after ESS were reported which concluded that 16.6% synechiae formation occurred after ESS in a study conducted on 60 patients.[17] Baradaranfar et al concluded 32.4% synechiae formation after ESS in a study done on 37 patients.[18]

Intranasal adhesion formation is a distressing complication of ESS. Previous studies conducted were on smaller sample sizes i.e. 37[18], 60[17] cases, and we wanted to conduct this study on a larger sample size i.e. 150 cases. Literature showed variable and controversial results. As this surgical procedure is rapidly gaining popularity in our country and no such study has ever been carried out in our set up, so this research has determined the actual rate of intranasal synechiae formation after ESS. The results of this study helped us in determining whether this procedure should be continued in future or some reforms in the surgical technique is needed.

Methods

This was a descriptive case series study carried out in the department of ENT Unit I, Services Hospital, Lahore, from 03.10.2014 to 02.04.2015. The calculated sample size was 150 cases with 6% margin of error, 94% confidence level taking expected percentage of synechiae formation between lateral nasal wall and nasal septum i.e. 16.6%. Non-probability consecutive sampling was used.

Study cases between age of 16-60 years of both genders were recruited according to the following criteria. All patients with nasal polyps as confirmed on physical examination and computed-tomography (CT). These patients were examined by the ENT consultants in the post-operative follow-up visits and

labelled as positive for synechiae formation between lateral and medial nasal walls, 4 weeks after ESS, were included in the study. Patients having recurrent nasal polyps with intracranial and intraorbital extension, having previous history of surgery for any nasal pathology and patients with a histologically known Sino nasal malignancy were excluded from the study.

After ethical approval and obtaining written informed consent from 150 patients presenting to ENT Outpatient department of Services Hospital Lahore. A proforma was formulated to record the demographic data for research purpose. All the patients that were treated by ESS were followed up post operatively at the end of 1st, 2nd, 3rd and 4th week respectively, and observed for the development of synechiae formation. The patients were categorized as Yes or No for synechiae formation in the Proforma.

Statistical Analysis

All the collected data was entered into SPSS version 10 and analyzed. The qualitative data like demographics (sex, male or female) and presence of synechiae formation (yes or no) was presented as frequency distribution. Quantitative data like age (in years) was presented as mean and standard deviation.

Results

Majority of the patients in this study were between 21-40 years of age and minority of the patients were < 20 years old. Mean age of the patients was 35.30± 10.54 years (Table-1).

Male patients were 80 (53.3%) while female patients were 70 (46.7%) in number respectively.

Synechiae formation was observed in 28 patients (18.7%) (Table-2). Stratification with regard to age and sex was carried out in tables3&4 respectively.

Discussion

Table 1: *Distribution of Cases by Age*

Age (Year)	Number	Percentage
≤ 20	12	08.0
21-40	93	62.0
41-60	45	30.0
Total	**150**	**100.0**
Mean±SD	**35.30±10.54**	

Table 2: *Distribution of Cases by Synechiae Formation*

Synechiae formation	Number	Percentage
Yes	28	18.7
No	122	81.3
Total	**150**	**100.0**

Table 3: *Stratification of Age with Regard to Synechiae Formation*

Age (Year)	Synechiae formation		Total
	Yes	No	
≤ 20	04	08	12
21-40	15	78	93
41-60	09	36	45
Total	**28**	**122**	**150**

Table 3: *Stratification of Age with Regard to Synechiae Formation*

Gender	Synechiae formation		Total
	Yes	No	
Male	13	67	80
Female	15	55	70
Total	**28**	**122**	**150**

Nasal polyps remain a significant challenge to the treat for an otorhinolaryngologist. Association between nasal polyps and chronic rhino sinusitis is unclear but nasal polyps should be regarded as an accompaniment of chronic inflammation of the Sino nasal mucosa.[19]

The management of nasal polyps includes both medical and surgical options following the evaluation of the patient, but main stay of treatment is medical. Surgery alone cannot accomplish or sustain healthy Sino nasal mucosa. In surgery, unhealthy mucosa is removed that did not initially respond to preoperative medical therapy. Surgery may be able to reestablish mucociliary clearance, remove diseased mucosa, refining sinus ventilation and permitting access to topical nasal corticosteroids, but surgery alone cannot alleviate Sino nasal disease. Patients need to be encouraged to continue persistent medical treatment postoperatively in order to achieve unsurpassed results which may need prolonged medical management after surgery with regular follow up visits.

Surgical treatment encompasses intranasal polypectomy which has an extraordinary recurrence rate, intranasal ethmoidectomy – a blind procedure that also results in complications like reappearance of disease and external ethmoidectomy, with its charac-

teristic complication of an external scar. All these limitations are surpassed by the progression of ESS, which is fast becoming afetching surgical treatment of choice for Sino nasal polyposis.[20]

Endoscopic sinus surgery (ESS) has become the customary treatment of choice for the management of medically recalcitrant chronic rhino sinusitis and nasal polyps. The most common complication ofESS is postoperative synechiae formation with a prevalence ranging from 1% to 36%[21] respectively. Retained secretions,mucosal damage, scar formation, and excessive nasal crusting aids in intranasal synechiae formation. Adhesions can impede the normal mucociliary clearance of the sinuses and results in a relapse. Numerous surgical practices like partial resection of the middle turbinate, and placement of intranasal biodegradable packing materials, have helped to lessen the incidence of postoperative synechiae formation.[22] Conventional nasal packing agents, such as Vaseline gauze strips and expandable polyvinyl acetate (Merocel) are non-absorbable and new biodegradable packing materials with various grades of effectiveness have also been developed, for example, Floseal, MeroGel/Meropak, Nasopore and carboxymethylcellulose.[23] Use of Mitomycin C during surgery has also helped decrease Synechiae formation after ESS.[24]

Largely, the incidence of intranasal synechiae formation after ESS varies significantly from trial to trial, and the ideal material for nasal packing is still a matter of debate.

In the present study, majority of the patients 93 (62%) in the age group of 21-40 years who underwent ESS, were consistent with the findings of other studies (70%).[25-27]

In the existing study, intranasal synechiae formation after endoscopic sinus surgery was observed in 18.7% of the patients. Our findings are similar with the study carried out by Shumon et al.[17] Baradaranfar et al differ with our findings, as they confirmed 32.4% synechiae formation after ESS.[18]

Conclusion

Intranasal Synechiae formation was established in 18.4% of the patients who were subjected to endoscopic sinus surgery. Endoscopic sinus surgery has delivered a safe and effective method for dealing with various Sino nasal diseases. Most frequently, this procedure can be carefully and effectively done under a local anesthesia. Rigid nasal endoscope offers a well-lit view into the nasal cavity and the osteomeatal complex which is the cornerstone of ESS, so that Sino nasal illnesses can be faredwell with a high rate of success and improvement of symptoms with trivial morbidity. Postoperative follow up visits are as important as surgery that should be personalized according to the patient's requirements.

Author's Contributions

DA: Data Collection
SHS: Introduction, literature review, Disscussion
GM, AAA: Article references
MQN: Statistical Analysis
MAA: Edited

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Comparison of Efficacy of Topical Ciprofloxacin Ear drops (0.6%) Versus a Combination of Systemic with Topical Ciprofloxacin in Treating Chronically Discharging Ears

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Abstract

Objective: To compare the efficacy of topical ciprofloxacin alone, versus a combination therapy ofsystemic with topical ciprofloxacin(0.6%) in achieving dry ears in active mucosal chronic otitis media after two weeks of treatment.

Methods: After obtaining permission from ethical committee of Hospital, an over-all of 150 patients (with 75 subjects each, divided into two groups) were included in this study.

In Group-A: Topical Ciprofloxacin ear drops (0.6%) 3-4 drops were instilled three times a day, 8 hours apart for 2 weeks.

In Group-B: Tab Ciprofloxacin 500mg was given twice a day, 12 hours apart for 14 days along with topical Ciprofloxacin ear drops (0.6%) 3 drops were used thrice a day, 8 hours apart for 14 days.

Results: Patients ranged between 15-45 years of age. Mean age of the patients was 30.3±7.4 and 29.2±7.7 years. In group-A, there were 41 males (54.7%) and in group-B 49 males (65.3%). Females were 34 (45.3%) in group-A and 27 (36%) in Group-B. Mean duration of ear discharge was 5.3±1.1 months in group-A while 5.5±1.4 months in Group-B. We could not find any substantial variation among the two group in terms of efficacy (p=0.249). Stratification with regard to age, gender and duration of ear discharge was also carried out.

Conclusion: Results of this study showed that topical ciprofloxacin ear drops (0.6%) were equally effective as systemic ciprofloxacin combined with topical ciprofloxacin (0.6%), for treating chronically discharging ears.

Keywords: CSOM, ciprofloxacin, nature of discharge

Introduction

Persistently wet ears arerelated to an underlying presence of a permanent ear drum perforation and Chronic suppurative otitis media is one of the commonest causeof treatable hearing deficit around the globe, specifically in the non-affluent population with poor socio-economic conditions and limited primary health care access. Various time related definitions have been applied to CSOM; however, generally a perforation present for more than 3 months is deemed chronic. Chronic otitis media is defined as chronic inflammation of the middle ear cleft including mucosa, tympanic membrane, and ossicles.[1] This type of CSOM can be further classified into active or inactive based on the incidence of ottorhoea. The inactive group includes a persistent dry perforation (failure to heal after otitis media), and retraction pockets. Active CSOM (non-cholesteatomatous) is associated with intermittent or constant ottorhoea. Most commonly isolated bacterial organisms are Staphylococcus aureus or Pseudomonas aeruginosa respectively.[2] Pain is not a feature of CSOM, as the discharge can drain freely from the

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middle ear cleft through a pre-existing or non-healing tympanic membrane perforation. The WHO definition requires that ear discharge present for more than 2 weeks' duration, manyENT clinicians contemplate the diagnosis of CSOM, despite treating it for a period wavering from 6 weeks to over 12 weeks' duration.[3,4] Medical treatment should be sought for controlling the acute inflammation of CSOM.

Patients with Chronic inflammation of the middle ear cleft, present with an unremitting ear discharge through a pre-existing tympanic membrane perforation with epithelialized margins. The infection commonly begins in early childhood[5] as an accompaniment of unresolved Acute Otitis Media at some point later in life.[6] The infection usually begins during the first 5 years of a child's life, with a peak incidence under 2 years of age.[7] The fact that how AOM progresses to CSOM is still debatable. Usually, patients with permanent ear drum perforations that continue to express mucoid aural discharge for periods ranging from 6 to 12-weeks duration8, in spite of adequate medical intervention, are categorized as CSOM cases. The WHO criteria for aural discharge in CSOM states, ottorhoea of 2 weeks duration9, but ENT clinicians are usually inclined towards adopting a lengthier duration of more than 12 weeks of active mucosal disease.[10]Proliferation of sub epithelial connective tissues of middle ear mucosa and upsurge of vascularization further enhances mucus production that hamper the penetration of topical antibiotic ear drops deep into the diseased middle ear mucosa. Because of this fact, most ENT physiciansfavorthe use topical antibiotic ear drops. Topical Ear drops having Quinolones display exceptional role in eliminating Pseudomonas and are not ototoxic.[11] The aim of treatment is to make the discharging ears dry and avert problems like repeated infections and hearing impairment. Out of the treatment choices, the effectiveness of using topical ciprofloxacin alone as opposed to a combination of systemic withtopical ciprofloxacin are most uncertain. In an international publication by Shia et al.; (2010) the study showed resolution of ear discharge in 70% of patients with the use of combination ciprofloxacin as compared to 50% of patients where ear discharge was resolved when topical ciprofloxacin ear drops were used for 2 weeks.[12] Whereas study conducted by Renukananda et al.;(2014) showed no major difference between the two groups.[13] There are no local studies available so far about this comparative research.

The objective of our research was comparison of the effectiveness of topical ciprofloxacin 0.6% ear drops alone, versus a combination of systemic ciprofloxacin 500 mg twice daily with topical ciprofloxacin drops 0.6% thrice daily for a period of 14 days in terms of achieving dry ears in chronic otitis media. The foundation of our study was to compare the outcome of topical ciprofloxacin dropsversusa combination therapy (systemic and topical ciprofloxacin), as the afore-mentioned international studies show variations and there is controversy regarding which statement is better.

Methods

The study design opted for the present research was randomized controlled trial, conducted in the department of Otorhinolaryngology Unit-I, Services Hospital Lahore, over the period of six months, from 23-06-2016 to 22-12-2016. The sample size consisted of 150 cases, which was calculated with 80% power of test, 5% level of significance and taking expected percentage of efficacy in both groups (75 patients in each group respectively) i.e. 70% in combination group vs 50% in topical ciprofloxacin (0.6%) group in achieving dry ears in active mucosal chronic otitis media after 2 weeks of treatment.

GROUP A: 75 patients were given topical ciprofloxacin (0.6%) 3 drops 8 hourly for 14 days.

Group-B: 75 patients were given Tab. Ciprofloxacin 500mg twice daily and topical Ciprofloxacin (0.6%) drops 8 hours apart for 14 days.

Non probability consecutive sampling technique was used.

Patients between the age of 15 to 45 years were selected according to the following criteria which were: All patients of either gender presenting with an ear discharge of more than 2 weeks duration based on history,unilateral or bilateral COM of active mucosal variety diagnosed on Examination Under Operating Microscope (EUM). Established acute otitis media cases (< 2weeks' duration) with tympanic membrane perforation diagnosed on history and clinical

examination along with inactive mucosal, active squamosal, inactive squamosal and tympanosclerosis on EUM findings and pregnant or lactating mothers were excluded from the study.

Approval from the Ethical committee of the hospital was obtained along with a written informed consent from 150 patients presenting in ENT Outpatient Department, Services Hospital, Lahore.

Written informed consent was taken from each patient at the first visit. A proforma was used for recording information of each individual in the study. Patient's biodata along with the hospital registration number was recorded in the proforma. After obtaining the informed consent, patients were arbitrarily placed into 2 groups by picking out patients' name slips from a draw box. Aural discharge was collected with a sterile ear swab from the external auditory canal. Using a sanitized aural speculum, to avoid contamination of the specimen, the sample would immediately be taken to the Pathology Lab for culture and sensitivity. The specimen was immersed in glucose growth and subsequently inoculated into Blood Agar (enriched medium) and Mckonkey Agar (differential medium) after which they were cultured for 24 hours. Culture and sensitivity of isolates was established by the Kirby-Bauer disc diffusion method. Only those patients were selected who were sensitive to ciprofloxacin.

Patients were requested to avoid water from entering into the diseased ear while showering and dry mopping of the discharge prior to putting in the ear drops was advised. The correct method of putting in the ear drops with intermittent tragal pressure for 5 minutes was advised. Patients were allowed to clean discharge from deep external meatus themselves. In the follow up visit, on 5th day of treatment, complaints were assessed. Subjective assessment was done by finding out from the patients about the absence or persistence of discharge. Objective assessment was done by otoscopic examination. If the discharge of patient failed to improve after 5th day of treatment, such patient was given systemic antibiotic other than ciprofloxacin according to culture and sensitivity of aural swab test. Results were recorded in patient proforma. Finally, patients on the line of improvement with ciprofloxacin were again evaluated for ear discharge on the final 14th day and results were added in their respective proforma.

Statistical Analysis

Statistical Data was fed into SPSS version 10 and analyzed. Descriptive statistics were calculated for both quantitative and qualitative variables. Quantitative variables e.g. age and duration of ear discharge was presented as mean±SD. For qualitative variables like gender and efficacy, frequency and percentage were calculated. Confounders like age, gender and duration of ear discharge was controlled through stratification. Post stratification Chi- square test will be used to compare the efficacy in two groups and $p \leq 0.05$ was considered significant.

Results

Patients age range in this study was between 15-45 years. Mean age of the patients was 30.3±7.4 and 29.2±7.7 years. In group-A, there were 41 males (54.7%) and in group-B 49 males (65.3%). Females were 34 (45.3%) in group-A and 27 (36%) in group-B. Mean duration of ear discharge was 5.3±1.1 months in group-A while 5.5±1.4 months in group-B. There was no substantial variation between the two study groups in terms of efficacy (p=0.322). Stratifi-

Table 1: *Distribution of Patients by Age*

Age (Year)	Group-A (Ciprofloxacin drops)		Group-B (Tab. Ciprofloxacin)	
	No.	%	No.	%
15-30	40	53.3	48	64.0
31-45	35	46.7	27	36.0
Total	**75**	**100.0**	**75**	**100.0**
Mean±SD	**30.3±7.4**		**29.2±7.7**	

Table 2: *Duration of Ear Discharge*

Duration (month)	Group-A (Ciprofloxacin drops)		Group-B (Tab. Ciprofloxacin)	
	No.	%	No.	%
≤ 6	64	85.3	59	78.7
> 6	11	14.7	16	21.3
Total	**75**	**100.0**	**75**	**100.0**
Mean±SD	**5.3±1.1**		**5.5±1.4**	

Table 3: *Distribution of Patients by Efficacy*

Efficacy	Group-A (Ciprofloxacin drops)		Group-B (Tab. Ciprofloxacin)	
	No.	%	No.	%
Yes	40	53.3	46	61.3
No	35	46.7	29	38.7
Total	**75**	**100.0**	**75**	**100.0**

Chi Square =0.981P value=0.322

cation with regard to age, gender and duration of ear discharge was also carried out.

Discussion

Chronic otitis media is defined as a chronic inflammation of the middle ear cleft including mucosa, tympanic membrane, and ossicles presenting with ear discharge through a pre-existing perforation.[14,15]

CSOM is the most common reason of juvenile hearing disability in developing countries.[16] Correct diagnosis relies on a high index of doubt, operating micro-otoscope examination and a sensible use of screening as required.[17,18]

Although, its incidence has fallen in the developed world, but in developing countries, the CSOM and its sequelae still account for a major proportion of the clinical workload. Complications arise when the patient develops associated hearing disability and the social stigma of a foul smelling discharge draining from the affected ear. The morbidities associated with CSOM arises once intracranial complications ensue.[16]

Diagnosis depends upon reliable history taking. The main symptom is prolonged (>3 months) painless otorrhea. Another common symptom is hearing impairment in the diseased ear. Adequate examination of a discharging tympanic membrane perforation will confirm the diagnosis.[19]

An audiogram usually shows conductive hearing loss. Bacterial cultures may not be required to ascertain the diagnosis of CSOM since 90–100% of chronically discharging ears harvest two or more segregates of both gram negative aerobes and anaerobes. Early and effective treatment based on the knowledge of causative microorganisms and their sensitivity, results in a good clinical recovery and development of complications.[20,21]

The most frequently isolated organism in active chronic suppurative otitis media is Pseudomonas Aeruginosa.[22]

Staphylococcus Aureus is the second commonest organism isolated from chronically discharging middle ears.[22]

Patients with CSOM respond more potently to topical rather than systemic treatment. Topical preparations can produce concentrations many times greater in the targeted tissue than those, that are not possible using systemic treatment.[23]

Ciprofloxacin is a second-generation FDA approved quinolone for treatment of COM in adults. Ototopical Ciprofloxacin has several advantages over Neomycin. It has the advantage of having pH of 6.5, so it does not burn on administration. Its systemic absorption from topical usage is minimal, suggesting a low possibility of inducing systemic toxicity. Thus, the adverse reactions to topical Ciprofloxacin are generally mild.[24]

The outcomes of the current research revealed that the study groups were nearly the same in relation to age, gender and duration of ear discharge. The patients were predominantly male in both the groups. There was no majorvariation between the two study groups in terms of efficacy. Patients who received topical ciprofloxacin ear drops (0.6%), 53.3% of them demonstrated dry ears within 2 weeks, while in patients taking oral ciprofloxacin 500mg showed efficacy in 61.3%. These findings are comparable with the study of Masum and Fakir.[6]

Conclusion

It is therefor, concluded that the topical ciprofloxacin ear drops (0.6%) alone, was equally effective as a combination of oral and topicalciprofloxacin in treating chronically discharging ears.

Author's Contribution

SHS: Introduction, Literature, review, Discussion
DA: Data Collection
GM, AAA: Article Reference
MQN: Statistical Analysis
MAA: Edited the article

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Assessment of Antibacterial Activities of Leaves Extract of Some Citrus Fruits Against Pathogenic Bacteria

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Abstract

Objectives: Study was planned to assess the Antibacterial Activities of leave extract of some Citrus Fruits against Pathogenic Bacteria.

Methods: The fresh leaves of Citrus grandis, Citrus reticulata, and Citrus limon plant were collected. The plants were recognized phenotypically and confirmed for taxonomic character by P.C.S.I.R Laboratory Lahore. Microbial Strains including strains of Staph. aureus and Salmonella typhi,which were taken from clinical Laboratory of Fatima Jinnah Medical University Lahore. The antimicrobial activity of the powdered form of Citrus leaves was tested against the strains of bacteria through disc diffusion method and the zone of inhibition was noted.

Results: Antibacterial activities by ethanol extracts of C. lemon and C.reticulate were observed with inhibition zone 2.75 mm and activity index 0.675 against S.aureus. However, low antibacterial activities of C. paradisi were noted against S.aureus and S.typhi. On the other hand, low antibacterial activity of C. lemon and C.reticulata was observed against S. typhi.

Conclusion: The results obtained in the study show that the leaves of C. lemon and C.reticulate exhibit higher antibacterial activity as compared to C.paradesi, which may be due to the presence of large amounts of flavonoid and phenolic compounds.

Key words: Citrus fruits, antibacterial activity, S. aureus, Salmonella typhi

Introduction

Medicinal plants are used to treat the ailment of several microbial and non-microbial diseases and also for the formation of new drugs.[1] These become popular due to the limited aptitude of antibiotics and other drugs used for treatment of diseases. The affordability, reliability, accessibility, and low toxicity of herbs used as medicine made them quite favorable and useful worldwide for health care.[2,3] According to WHO, about 80% of people worldwide use herbs as medicine for health care.[4]

Infections due to mirco-organisms are the major health problem that may lead to disabilities and death worldwide in all age groups. Among the pathogenic bacteria, Escherichia coli, Staph aureus and Salmonella typhi are highly prevalent and cause infection while resisting many drugs.[5] Staphylococcus aureus is a main reason for food poisoning through the secretion of enterotoxins.[6] Salmonella typhi causes a water and food borne disease and is related to typhoid fever and problems of gastrointestinal tract. These bacteria form colonies in the epithelium of intestine by the phagocytosis using proteins of effector type, resulting in the reorganization of the cytoskeleton of host.[7] In general, micro-organisms have many genetic modes of actions to attain resistance against antibiotics. This has increased the need for antimicrobial herbs for the treatment of diseases.

The genus of Citrus links to the family Rutaceae has a

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number of biological metabolites active against gram negative and gram positive bacteria.[5] Citrus sinensis (Orange), Citrus paradise (Grapefruit), Citrus limon (Lemon) and Citrus aurantium (Sour orange) are some fruits of genus Citrus. Precisely, the Citrus peels are a possible source of important metabolites of plant.[9]

Lemon leaf has antispasmodic and sedative properties. These can be used to treat neurological problems such as nervousness, insomnia and palpitation. The alkaloid form of citrus plants shows antibacterial and anticancer properties using the extract of its root, stem, leaves, and flowers.[10,11]

Bacterial cells attack the lipid bilayer of the membrane of the cell and alter the activity of cell enzymes. Plants are rich in a wide variety of secondary metabolites, such as tannins, terpenoids, alkaloids, and flavonoids, which have been found in vitro to have antimicrobial properties and these may inhibit the bacterial growth by a diverse mode of action as compared to antibiotics.[12]

The resistance due to microorganisms is rapidly increasing and this creates a hurdle against the proper treatment of infectious ailments. Additionally the side effects of antibiotics is also a big problem. Thus, there is a need to find the antibacterial activity of herbs, which might become an important part in treatment of diseases.

Objectives: The purpose of this study was to evaluate antimicrobial activity of leaf extract of Citrus plants against the strains of Staphylococcus aureus and Salmonella typhi.

Methods

Collection of plant samples:

The fresh leaves of Citrus grandis, Citrus reticulata, and Citrus limon were collected in the local market of Lahore city. The plants were recognized phenotypically and confirmed for taxonomic character by P.C.S.I.R Laboratory Lahore. Duration of study was March 2016 to August 2016. Leaves of plants were washed thoroughly, dried and homogenized to form a powder and stored in an airtight glass bottle at 4°C.

Preparation of leaves extract of Grapefruit/ orange fruit / Lemon fruit:

Leaves were dried in shade and powdered in a mechanical blender. Five hundred grams of powder was soaked in 500 mL of 99 % ethanol (Merck, Germany) as a solvent in a ratio of 1:4 (w/v) and incubated at 37°C for a period of 24 hours and later filtered by Whatman filter paper. Ethanol was allowed to evaporate and the extract was concentrated using evaporator and stored at 4°C until used.[13]

Preparation of sample:

Samples for antimicrobial activity were prepared by dissolving 100 mg of each extract in 1 ml of dimethyl sulphoxide (DMSO).

Microbial strain used:

Microbial Strains including strains of Staph. Aureus and Salmonella Typhi were taken from the clinical Laboratory of Fatima Jinnah Medical University Lahore. Sub-culturing of strains was carried for further use. The stock cultures were kept on the medium of nutrient broth medium with 10% glycerol at -20°C.

Preparation of bacterial suspension:

Colonies of strains of bacteria Staphylococcus aureus and Salmonella typhi were transferred to the nutrient broth and were incubated at 37°C for 24 hr and preserved in sterile flasks until their use.

Antibacterial activity by agar well diffusion method:

The antimicrobial activity of metabolites of Citrus leaves was applied against the strains of bacteria by using the disc diffusion method or Kirby-Bauer method. Bacterial strains were allowed to grow separately in plates of agar (Merck, Germany) for four hour at 37°C. Spreading of inoculum was carried out on the agar plate for getting an even growth of bacteria. Disc labeled as test was loaded with extract of citrus leaves of three species. Disc loaded with 10 µL of 80% methanol was taken as control. Incubation of plates was done at 37oc for a period of 24 hours. After the period of incubation, the antibac-terial activity was found by measuring the diameters of the zone of growth inhibition in mm of micro-organism6. The positive control and negative control wells were

filled with Ampicillin (4 µg/ml) and DMSO respectively.

Activity index for each leaf extract was calculated by the following formula (Dharjia):

Activity index (AI)= Inhibition Zone of the sample/ Inhibition Zone of the standard.

Statistical analysis:

Data was analyzed by SPSS 20. Variables were expressed as mean ± standard deviation for each microbial strain. Student 't' test was applied for comparison and p values were taken as significant at $p < 0.05$.

Results

Most Antibacterial activities of ethanol extracts of C. lemon and C.reticulata were observed with inhibition zone 2.75±0.09, AI was 0.675 against S.aureus. However, low antibacterial activities of ethanol extracts of C. paradisi was observed with inhibition zone 1.0± 0.01, AI was 0.25 against S.aureus. On the other hand, low antibacterial activities of ethanol extracts of C. lemon and C.reticulata was observed with inhibition zone 1.2±0.02, AI was 0.50 against S. typhi. Very low antibacterial activity of ethanol extracts of C. paradisi was observed with inhibition zone 1.0±0.01, AI was 0.32 against S.typhi

Discussion

About 80% of the population of the world relies on medicine derived from plants for healthcare and it is believed that these herbal medicines have no side effects. In the United State, roughly 25% of allopathic drugs contain one or more ingredients from plants.[3] Medicine derived from plants has strong antimicrobial effects and may offer a harmless and economical treatment against infections caused by viruses, bacteria or fungi1.[5]

According to our study, maximum antibacterial activities by ethanol extracts of C. lemon and C.reticulata were observed against S.aureus. Our study is supported by another study, which reported that extracts of plants, especially citrus fruit plants are more active against Gram-positive microbes like S.aureus as compared to Gram-negative and seem to be a significant alternative to antibiotic resistance and managing the disease[16,17]. It is proposed that the leaves of citrus limon are potential sources of antioxidants. The activity of antioxidants may depend on their concentration and amount. The activity of antioxidants may be due to flavonoid and phenolic compounds present in extract.[18] It is suggested that phenolics and flavonoids were higher in other parts of citrus plant in comparison with citrus juice, which is why the peels are more effective than juice.[16]

A group of workers also studied the antibacterial role of extract of citrus lemon and of Citrus aurantium (sour taste orange). According to their study, both of these showed a significant effect on food borne micro-organism.[18] It is reported that the extract of all citrus fruits showed very high antibacterial activity against S.aureus.[19] Our results fall in line with another study which found that extracts of leaves of Citrus paradisi do not show antibacterial activity against S. aureus, E. coli and Salmonella typhi.[20]

We observed low antibacterial activities of ethanolic leaf extracts of C. lemon and C.reticulata, against S. typhi. A study also found that Gram-negative bacteria showed resistance to the extract. The reason may be the difference in the structure of cells of Gram negative and Gram positive bacteria. Study stated that the outer side of cell membranes of Gram-negative bacteria act as a barrier towards microorganism from entering in the cells.[16]

A study demonstrated that medicinal herbs including

Table 1: *Antibacterial Activity (Zone of Inhibition) of Extracts of Citrus Fruits*

Leaf Extract	Concentration (mg/ml)	Zone of Inhibition of Staph aureus (mm)	Zone of Inhibition of S typhi (mm)	Activity Index (AI) Of Staph aureus	Activity Index (AI) of S typhi
Citrus lemon	100	2.75 ±0.09	1.2 ± 0.02	0.675	0.48
Citrus reticulate (orange),	100	2.75 ± 0.08	1.3 ± 0.02	0.675	0.52
Citrus paradisi (grape fruit)	100	1.0 ± 0.01	0.8 ± 0.01	0.25	0.32
Dimethyl sulfoxide	1 µl/ml	-	-	-	-
Ampicillin	10 (µg/ml)	4 ± 0.19	2.5 ± 0.06		

citrus plants show bacteriostatic effects on the enzymes which are related to production of energy. Besides, they have the ability to alter the permeability of cell walls and protein denaturation.[6]

Limitation of study: A need to find the toxicity of these citrus fruits and use other solvents for extracting polar compounds that may have bactericidal activity.

Conclusion

The results obtained in the study show that the leaves of C. lemon and C.reticulate exhibit higher antibacterial activity as compared to C.paradesi, which may be due to the presence of large amounts of flavonoid and phenolic compounds. However, further research is required to use other solvents that dissolve more polar compounds and give better results than the present one.

Authors' Contributions

RK: Article writing/ Experiment design/conduct
LA: Data interpretation/ Literature survey
SS, SR: Experiment performance
AS: Proof reading
HA: Data collection

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Frequency of Hepatitis A & E Infections in Adult Patients of Acute Hepatitis

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Abstract

Objective: To study the frequency of Hepatitis A Virus and Hepatitis E Virus infections in adult patients of acute hepatitis in a Tertiary Care Hospital in Lahore.

Methods: All samples received from medical units (indoor and outdoor) of Mayo hospital Lahore from 26 Feb.2019 to 26.Sept.2019, for Hepatitis A & E IgM antibody testing by ELISA were included in the study. The results and other relevant information were recorded on proforma.

Results: Out of 690 study subjects, 62% were male and 38% were female. The mean age ± SD was 33.8 ± 7.4years. The percentage of HAV or HEV infected cases was 59%,and 41% were not infected with HAV or HEV. The frequency and percentage of Hepatitis A Virus was 62(15%),whereas the frequency and percentage of HEV was 327(80%) and that of co-infection with HAV and HEV was 21(5%). The mean ± SD age of Hepatitis AVirus was 35.2 ± 5.0,whereas the mean ± SD age of Hepatitis E Virus and co-infection with Hepatitis A and Hepatitis E Virus were 31.45 ± 2.3 and 22.6 ± 6.3 years, respectively.

Conclusion: Hepatitis E Virus is the commonest cause of acute hepatitis in our study,followed by hepatitis A Virus and coinfection of HAV and HEV.

Key words: Frequency, Hepatitis A infection, Hepatitis E infection, Co- infection Hepatitis A & Hepatitis E.

Introduction

Acute viral hepatitis is a grave public health problem. Presently, six hepatotropic viruses, classified as hepatitis A, B, C, D, E and G are the prime cause of its pathogenicity.[1-3]

The prevalence of hepatitis varies globally and also within countries. Hepatitis A virus (HAV) and hepatitis E virus (HEV) are transmitted via fecal-oral route and infection usually resolves after causing acute hepatitis. Exposure to contaminated blood and its products and body fluids are responsible for the transmission of Hepatitis B, hepatitis C and hepatitis D viruses and the incidence of chronic hepatitis is very high. HAV-HEV co-infection is also common. According to WHO, every year 1.4 million new cases of HAV and 20 million cases of HEV are reported around the world, with 100,000 deaths per year due to acute HAV and 60,000 deaths due to HEV infection.[2,4-8]

Most cases of the acute hepatitis due to A and E infections cannot be distinguished from other causes of acute hepatitis on clinical grounds. For the appropriate diagnosis of acute viral hepatitis, deranged liver function tests (LFTs) and positive serological markers for the suspected virus are required. In acute hepatitis A infection, anti-HAV IgM antibodies rise immediately after the onset of the disease, and antibody titres declines to zero in 3–6 months, while anti-HAV IgG antibodies appear within 2–3 months after the onset of acute infection and persist longer. IgG antibodies provide long term protective immunity, whereas IgM antibodies against HAV and HEV detected by ELISA technique are used to diagnose acute infection.[9]

The greatest risk for HAV and HEV infection in developing countries is poor hygiene and sanitation. Contamination of water resources is the main cause of

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spread.[5] In Pakistan 3.5 to 4% cases of acute hepatitis in adults and 50 to 60% in children are caused by Hepatitis A virus. Majority children are exposed to this virus during their early age and remain immune afterwards.[2,4,7-12] HAV was previously considered an acute self-limiting infection in children,[5,9,14] but Hamid et al conducted a study on 233 cases of chronic liver disease and found that 97.8% of his study population was exposed to HAV.[14] In another study conducted on a series of 2,735 confirmed cases of acute HAV, from a Tertiary Care Hospital in Pakistan, it was observed that 232 children required hospitalization and out of these 36.7% died.[5]

In developing countries including Pakistan, hepatitis E virus causes outbreaks as well as sporadic cases (7,13). Unlike HAV, HEV causes acute hepatitis in 20 to 22% of adults and 2.4% of children.[14] Once infected the individuals remain immune for 8-10 years, but can be reinfected later. It is a self limiting disease, but in pregnancy, the outcome can be fatal, and in the last trimester mortality rate as high as 16-33% has been reported.[2,5,18]

Studies report a benign course of HAV and HEV coinfection, but fulminant liver failure may occur in pregnant patients.[16] When more than one viral infection occurs, patients are usually older males, they have risk factors for contracting the disease, and the disease outcome is often worse.[17]

Preventive measures like better sanitary conditions, availability of clean water, education of public regarding the spread of the disease and its prevention can be helpful in reducing the disease burden.

Methods

It was a descriptive study conducted at Central Diagnostic Laboratory (CDL), Mayo Hospital/ King Edward Medical University, Lahore, after approval of Institutional Review Board. All samples sent to CDL for anti HAV & HEV IgM testing from medical units (indoor and outdoor)of Mayo hospital, Lahore, were included in the study. The relevant information of patients like age, gender were noted on proforma. Improperly labeled and inadequate samples were excluded from the study.

The samples were collected in yellow top vaccutainer, centrifuged and serum was separated and stored in refrigerator at -20°C to run in batches. After calibration, ELISA was performed using AutoBio and Diapro kits for anti HAV & HEV IgM respectively on Dia 710 ELISA microplate reader. The results were marked as positive or negative and recorded on proforma.

All collected data was entered and analyzed by using Statistical package for social sciences (SPSS version 20). Quantitative variable like age was presented as mean±SD. Qualitative variables like gender, infected and non-infected, positive results for Hepatitis A, E & co-infection were presented as frequency and percentage.

Results

The total numbers of patients (N) included in the study with the suspicion of acute hepatitis were 690. The mean ± SD age of patients was 33.8 ± 7.4 years. The male: female was 62:38; 428 males and 262 females.

Figure 1: *Frequency& Percentage of Infected and Non-Infected Cases (N=690).*

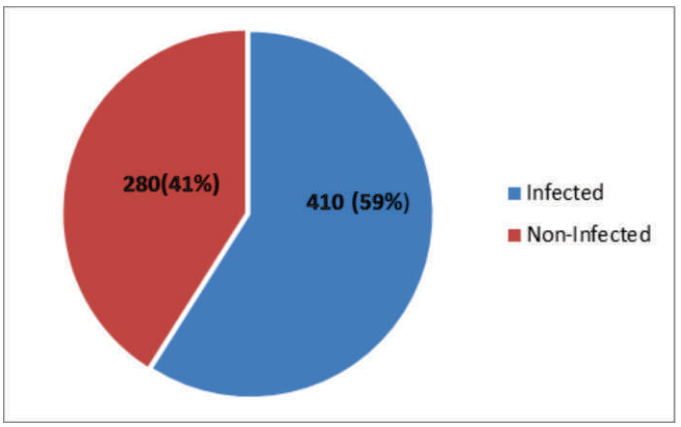
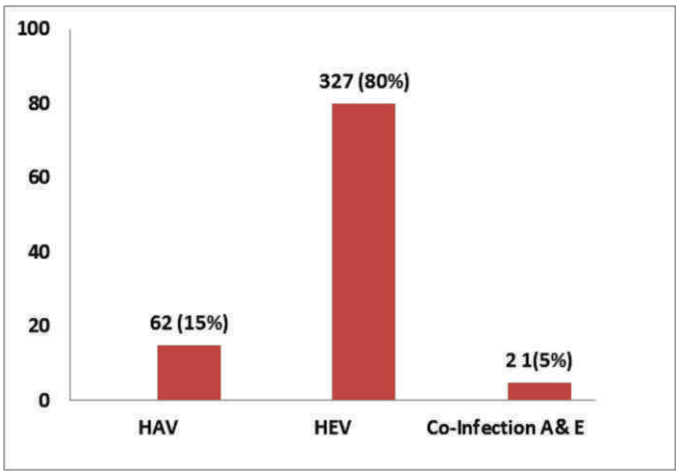


Figure 2: *Frequency& Percentage of Hepatitis A, E and Co-Infection A&E (N=410).*

Figure 3: *Percentage of male and female in HAV, HEV and co- infection A&E.*

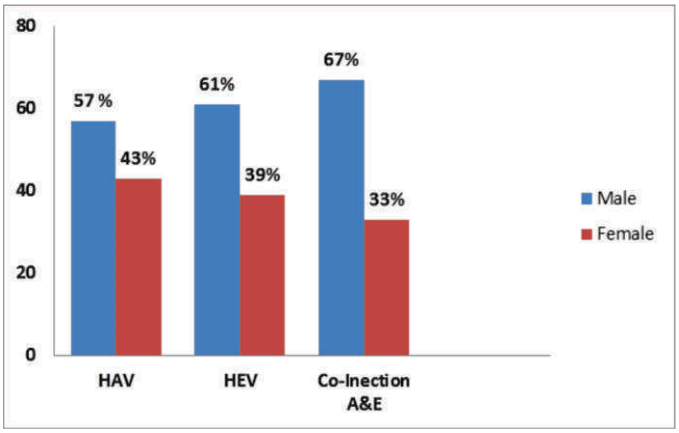
Out of 62 HAV infected patients, there were 35 males



and 27 females. There were 201 males and 126 females out of 327 HEV infected and 14 males and

Table 1: *Age of Patients with HAV, HEV & Co-infection A&E.*

Sr. No	Type of Infection	Mean ± SD Age (years)
1	Hepatitis A infected	35.2 ± 5.0
2	Hepatitis E infected	31.45 ± 2.3
3	Co-infection Hepatitis A& E	22.6 ± 6.3



and 7 females among 21 patients co- infected with A&E.

Discussion

Pakistan has a high disease burden of hepatitis A to E, with maximum morbidity in hepatitis A and E and maximum mortality in hepatitis B, C and D.[2]

Since acute viral hepatitis due to HAV and/or HEV is common, it is a challenge for the government and healthcare providers. This study was conducted at the time when there were increasing number of cases of acute hepatitis in Lahore. In our study, 690 patients with the suspicion of acute viral hepatitis were included. Among these patients, 410(59%) were infected with Hepatitis A & E and 280(41%) were not infected with HAV or HEV(Fig.1).

Among the infected patients, 62(15%) were infected by HAV (Figure 2). Despite Pakistan being high endemic zone for HAV, its frequency is less than HEV infection in our study.[9,10] This difference can be attributed to the age of study population which was 33.8±7.4 years (Table.1). Our study population comprised of adults and HAV infection is more common in children and since it gives lifelong immunity, it is possible that many adults might have acquired immunity as a result of previous infection. Previously it was considered that by the age of 14 years almost 100% of children have been exposed to hepatitis About recent studies show that there is a change in the trend of occurrence of hepatitis A, and now all age groups are affected.[14] This change in trend can be due to improvement in hygienic conditions or better understanding by the parents to maintain a good standard of hygiene, and children are exposed to contaminated food as they grow older.[8,15]

The frequency of HEV infection was 327(80%) (Fig.2). It is comparable to studies conducted in Pakistan and other countries where HEV was the major cause of outbreaks.[1,13,14] HEV affects mainly young and middle age individuals and this trend is seen in our study also in which the mean age of patients with HEV infection was 31.45 + 2.3 . This is similar to study by Bosan A et al in which Hepatitis E mainly affects the adult population.[2] Like HAV, HEV also produces a mild self-limiting disease in majority of the patients, but in a few cases, it may lead to fulminant hepatic failure.[1,15] In pregnant women, the mortality rate is significant, ranging between 20 and 29.3%.[14,19,22]

In the present study, 21(5%) of the infected individuals were co-infected with HAV & HEV(Fig.2). Co-infection with HAV-HEV is a not uncommon.[20] The infection is usually self-limiting but atypical manifestations such as fulminant hepatic failure have also been reported.[15]

In our study, the frequency and percentage of male: female HEV infected patients, were 201(61%) and 126(39%) respectively (Fig.3). The frequency and percentage of male: female HAV infected patients were 35(57%) and 27(43%) respectively (Fig.3). Both HAV and HEV infections were more common in males, probably because of outside eating habits. This is comparable with a survey performed in 2009, by

the Pakistan Field Epidemiology and Laboratory Training Program (FELTP), in collaboration with CDC's Division of Viral Hepatitis and Ministry of Health observing that the incidence of HAV in males was 69.5% and that of HEV was 72.4%.[14]

Since there is increasing risk of acute hepatitis in the community, provision of safe water and educating public about the modes of spread is the need of the day. Early vaccination of children for HAV can reduce the morbidity and mortality. Since no vaccine is commercially available for HEV infection, preventive measures need to be propagated. Policies should be formulated to provide hygienic basic facilities and better sanitary conditions to our population.

Conclusion

1. In our study, HEV is the most common cause of acute hepatitis.It is followed by HAV and co-infection with HAV and HEV.
2. HAV, HEV and co-infection with HAV and HEV is more common in adult males less than 40 years old.

Author's Contribution

RG: Conceived, designed and writing of manuscript
RD: Statistical Analysis
QA, SAS: Data Collection
HA: Data Collection and Statistical Analysis
H.S: Writing of manuscript

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Hyperglycemia and Its Impact on Length of Stay in Patients Hospitalized with Community-Acquired Pneumonia

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Abstract

Objectives:

1. To determine the frequency of hyperglycemia in hospitalized patients with community acquired pneumonia
2. To compare mean hospital stay in patients with and without hyperglycemia admitted with CAP.

Methods: It was a descriptive, case series done at Department of Medicine, Services Hospital, Lahore, in 2016. With non-probability, consecutive sampling technique a sample size of 150 cases is calculated with 95% confidence level, 8% margin of error and talking expected percentage of hyperglycemia as 38.2% in hospitalized patients with community acquired pneumonia.

Results: Out of total 150 cases of CAP there were 85 (56.67%) males with mean age of 47.61±14.66 years. Hyperglycemia was seen in 46 (30.67%) patients with CAP. There was equal distribution of hyperglycemia with respect to gender and age groups with p= 0.56 and 0.24 respectively. Hyperglycemia was more in those having temperature more than 101oF however this difference was not significant with p= 0.32. There was significant difference seen in terms of length of hospital stay,4.07±1.51 days in hyperglycemic and 2.85±1.31 days in normoglycemics with p= 0.001. The length of hospital stay was near significant high in males,4.31±1.56 days (p= 0.08), while non -significant in females with p= 0.30. There was no significant difference in terms of age groups in cases with or without hyperglycemia with p= 0.56 and 0.78. The length of hospital stay was longer in those that had temperature more than 101oF,4.29±1.26 days with hyperglycemia as compared to 2.88±1.34 days in normoglycemics with p= 0.13.

Conclusion: Community acquired pneumonia is an important infectious health concern. It is associated with high blood glucose and the length of hospital stay is found significantly high in cases of hyperglycemia.

Key words: Community acquired pneumonia, Hyperglycemia, hospital stay

Introduction

Community acquired pneumonia (CAP) is a major cause of morbidity and mortality in low and middle income countries. In the last decade, there have been several advances and new interventions resulting in a substantial reduction in pneumonia incidence and its improved outcomes.[1] Hyperglycemia has been established as an independent predictor of morbidity and mortality in patients admitted with acute coronary syndromes, ischemic stroke, trauma, heart failure, and coronary artery bypass graft, as well as admission to surgical and medical intensive care units[2]. Although hyperglycemia leads to impaired host immune responses, its impact on the outcomes (e.g. mortality, length of stay (LOS), and readmission) is not clear in CAP. The relative impact of glycemic control on LOS among CAP patients has not been well established. Evidence that hyperglycemia affects the outcomes suggests a need for its evaluation in

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the context of CAP – hospitalized patients.[1,2]

Appropriate initial management of pneumonia and subsequently the outcomes depend on an accurate assessment of disease severity. To support clinical assessment, several severity-scoring indices like CURB 65 (confusion, urea, respiratory rate, blood pressure, and 65 years of age or older) or qSOFA score (quick sequential organ failure assessment) on presentation have been developed, which facilitate the prompt identification of individuals with severe disease and allowing rapid institution of intensive care interventions.[2] However, many such tools may actually underestimate disease severity in young people[1,2]. Similarly, differences in population comorbidity burden and etiological spectrum of pneumonia may reduce the prognostic performance of most pneumonia severity assessment tool that were almost exclusively developed and validated in well – resourced setting.[1,2] There is an urgent need for the development of validated severity assessment tools that can support clinical management decisions in low socioeconomic countries like Pakistan. Glycemic status at admission is readily available for all patients, and might provide a potentially useful predictive factor for outcomes and utilization of care.[3]

Objectives of the Study

1. To find frequency of hyperglycemia in hospitalized patients with community acquired pneumonia
2. To compare mean hospital stay in patients with and without hyperglycemia admitted with CAP.

Methods

It was a descriptive, case series done at Department of Medicine, Medical Unit III, Services Hospital, Lahore, in 2016. With non-probability, consecutive sampling technique a sample size of 150 cases was calculated with 95% confidence level, 8% margin of error and taking expected percentage of hyperglycemia as 38.2% in hospitalized patients with community acquired pneumonia.

Inclusion Criteria

- All patients hospitalized with CAP aged between 17 and 80 years of both genders.

Exclusion Criteria

- Antibiotics initiated for respiratory symptoms within 3 weeks prior to hospitalization.
- Hospital discharge <30 days preceding present hospital admission date (to rule out nosocomial pneumonia)
- History of suspected aspiration, pulmonary tuberculosis or pneumocystis carinii pneumonia within 1 year prior to admission, use of immunosuppressive agents or steroids
- Acquired Immune Deficiency Syndrome or human immunodeficiency virus infection
- Tracheostomy
- Patients with interstitial lung disease, chronic obstructive airway disease, chronic kidney disease, congestive cardiac failure andpregnancy

Date Collection Procedure

A total of 150 patients with CAP fulfilling the inclusion and exclusion criteria aged between 17 and 80 years were selected. Bio data was collected after informed consent. Random blood sugar level (BSR) at admission was measured using a glucometer. Patients were labeled as normoglycemia (BSR <140mg/dl) and hyperglycemia (BSR > 140mg/dl). Temperature record was maintained. Axillary temperature was recorded 12 hourly. Length of stay was calculated for all patients.

Data Analysis Procedure

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 16. Qualitative data like gender and hyperglycemia were presented as frequencies and percentages. Quantitative data i.e. age, blood glucose level and length (duration) of hospital stay were presented as means and standard deviations. Independent sample t test was used to compare the mean hospital stay in patients with or without hyperglycemia. A p value of ≤0.05 was considered as significant. Data was stratified for age and gender to deal with effect modifiers. Post stratification independent sample t test was applied to see the effect of effect modifiers on length of stay and p value of ≤ 0.05 was considered as significant.

Results

In this study out of total 150 cases of CAP, 85

(56.67%) were males and 65 (43.33%) females, table1. The mean age was 47.61±14.66 years while mean BSR, temperature and length of hospital stay were 110.4±31.61 mg/dl, 100.81±1.58°F and 3.22± 1.48 days respectively, tables 2and 3. Eighty (53.33 %) cases were having age 50 years or less while 70 (46.67%) were more than 50 years, tables 4 and 5. Out of 150 cases, 100 (66.67%) had temperature of 101oF or less, table 6. Hyperglycemia (uncontrolled diabetes) was seen in 46 (30.67%) cases of CAP, table 5. There was equal distribution of hyperglycemia with respect to gender and age groups with p= 0.56 and 0.24 respectively, table 1and 5. Hyperglycemia was more in cases that had temperature more than 101°F however this difference was not significant with p= 0.32, table 6.There was significant difference seen in terms of length of hospital stay i.e.,4.07±1.51 days in hyperglycemic and 2.85±1.31 days in normoglycemics with p= 0.001, table 4. The length of hospital stay was near significant high in males,4.31±1.56 days (p=0.08), while it was non-significant in females with p=0.30, table 07. There was no significant difference in terms of age groups in cases with or without hyperglycemia (tables1 & 4) with p= 0.56 and 0.78. The length of hospital stay was longer in those that had temperature more than 101°F, 4.29±1.26 days with hyperglycemia as compared to 2.88±1.34 days in normoglycemics with p= 0.13, table 6.

Discussion

Table 1: *Hyperglycemia with Respect to Gender*

GENDER	HYPERGLYCEMIA		Total
	Yes	No	
Male	26 (30.59%)	59 (69.41%)	85 (100%)
Female	20 (30.77%)	45 (69.23%)	65 (100%)
Total	**46 (30.67%)**	**104 (69.33%)**	**150 (100%)**

Chi square= 0.001, p= 0.56

Table 2: *Study Variables (Age & BSR)*

		VARIABLES	
		Age	BSR
Mean		47.61	110.4
95%Confidence Interval for Mean	Lower Bound	45.25	104.94
	Upper Bound	49.98	115.14
Median		45.00	98.00
Std. Deviation		14.66	31.61
Minimum		18	69
Maximum		80	190

Community-acquired pneumonia (CAP) is the infection of the lung parenchyma, which is acquired from the organism present in the community. It is a common infection and can be managed in outpatients, in patient and ICUs depending upon the severity of the illness. It is associated with considerable morbidity and mortality, particularly in elderly

Table 3: *Study Variables (Duration of Hospital Stay & Temperature)*

		VARIABLES	
		Duration of hospital stay (days)	Temperature (F)
Mean		3.22	100.81
95% Confidence Interval for Mean	2.98	45.25	100.56
	3.46	49.98	101.07
Median		2.00	101.00
Std. Deviation		1.48	1.58
Minimum		2	99
Maximum		8	104

Table 4: *Stratification for Length of Hospital Stay in Patientswith or without Hyperglycemia with Respect to Age Groups*

Age groups (years)	Hyperglycemia	Length of hospital stay		p value
		n	Mean ± SD	
50 or less	Yes	27	3.81±1.41	0.09
	No	53	2.32±0.87	
> 50	Yes	19	4.42±1.61	0.78
	No	51	3.39±1.47	

Normoglycemics with p= 0.001

Table 5: *Hyperglycemia with Respect to Age Groups*

AGE GROUPS (years)	HYPERGLYCEMIA		Total
	Yes	No	
50 or less	27 (23.75%)	53 (66.25%)	80 (100%)
> 50	19 (27.14%)	51 (72.86%)	70 (100%)
Total	**46 (30.67%)**	**104 (69.33%)**	**150 (100%)**

Chi square= 0.76, p= 0.24

Table 6: *Stratification for Length of Hospital Stay in Patients with or without Hyperglycemia with Respect to Temperature*

Temperature	Hyperglycemia	Length of hospital stay		p value
		N	Mean ± SD	
101 or less	**Yes**	29	3.93±1.64	0.41
	No	71	2.83±1.30	
> 101	**Yes**	17	4.29±1.26	0.13
	No	33	2.88±1.34	

Chi square= 0.39, p= 0.32 for hyperglycemia with temp >101

Table 7: *Stratification for Length of Hospital Stay in Patients with or without Hyperglycemia with Respect to Gender*

Gender	Hyper-glycemia	Length of hospital stay		p value
		N	Mean ± SD	
Male	Yes	26	4.31±1.56	0.08
	No	59	2.90±1.34	
Female	Yes	20	3.75±1.41	0.30
	No	45	2.78±1.27	

patients and those with significant comorbidities. Various other factors affect the length of hospital stay and pose a huge burden over the patients as well as the health care system of the community. Hyperglycemia was seen in 46 (30.67%) cases admitted with community acquired pneumonia. Similar pattern was seen in other studies that also had higher number ranging from 30 to 40%.[4-7]

Why the cases in our study had relatively lower number of hyperglycemia as compared to other studies? It may be because this study was conducted in medical wards as compared to other studies which were conducted in pulmonology departments where serious cases are admitted and have a higher chance of getting hyperglycemia. This also reflects the disease process that greater the stress of the disease and higher are the chances of counter regulatory hormones to be released and leading to increased level of glucose.

Hyperglycemia was slightly higher in females where it was seen in in 20 (30.77%) cases as compared to males having 26 (30.59%) cases in their respective groups with p value of 0.56. However this difference was not statistically significant. Similar pattern was observed by Sarkar M and Trifirò G et al.[8-9]The higher level of glucose in females can be due to hormonal differences as compared to males and secondly the impact of infections in females lead to more anxiety and again increasing the counter regulatory hormones.

Hyperglycemia in age group of 50 year or more was seen in 19 (27.14%) of cases as compared to 27 (23.75%) with age less than this with an insignificant p value of 0.24. This was in contrast to few studies done in the past by Laheij RJ et al and Almirall J et al that found this more in the younger age groups.[10-11] The reason for this higher number in older age group can be explained by the fact that in such cases they get more severe infection and that can be a cause of hyperglycemia as was seen in present study as a marker of severe infection. On the other hand contradicting results can be the involvement of the other mechanisms as well. As in old age the reflex mechanisms are slowed down and on the other hand the chances of serious infection due to immune compromised state of old age can also lead to adrenal crises which can also end up with relatively lower levels of serum sugars.

In cases with temperature more than 101 F, the hyperglycemia was seen in 17 (34%) of cases in contrast to 29 (29%) with temperature less than this with p= 0.32. Similar was seen by Wunderink RG et al and Johansson N et al.[12-13]This again strengthens the belief that higher the temperature and higher is the stressful condition and more are the chances for glucose to be raised.

Mean hospital stay in males with hyperglycemia was 4.31±1.56 days as compared to normoglycemics having 2.90±1.34 days with p= 0.08 while the difference of this glycemic levels infemales was not significant with p= 0.30. Similar was seen by Marrie TJ et al Aujesky D et al.[14-15] They also did not find any significant association with this. The reason of male patients to have prolonged hospital stay can be explained by the presence of co morbid factors like smoking which is not only a risk factor to predispose to infection but also lead to delayed recovery.

A non-significant statistical difference was seen regarding mean length of hospital stay in patients with or without hyperglycemia in both the age groups; however this difference was more seen in cases that had age 50 years or less having stay of 3.81±1.41 days as compared to normoglycemics having stay of 2.32± 0.87 days with p value of 0.56. Moreover, the overall stay was higher in cases with age groups more than 50 years. Similar trends were seen in a study done by Suter-Widmer I et al[16] who also had longer hospital stay in their study with significant p value of 0.001 but the cute off value for age in their study was 60 years. However, studies conducted by Kaysar M et al and Labarere J et al did not reveal any significant association but still the cases with higher age groups had a longer hospital stay just like our study.[17-18] Why the cases with higher age had a longer stay because of the

multiple factors like at older age the immunity is suppressed due to reasons like malignancies, malabsorption or other co morbid conditions which add up to the primary diagnosis of CAP and lead to a further stay. Moreover the patients with old age can also be socially deprived and factors like good care at hospital can also prolong their stay. In contrast to this the younger ones with good immunity and mental strength to cope up with infection lead to shorter hospital stay.

There was significant difference seen in terms of length of hospital stay where it was 4.07±1.51 days in hyperglycemic and 2.85±1.31 days in normoglycemics with p= 0.001. Similar was seen by a study done by Godar DA et al who found mean hospital stay of 4.2 days as compared to 3.9 with normal glucose level which was found statistically significant with p value of 0.04.[19] Studies done by McAlister FA et al and Latham R et al who also had it more in patients with hyperglycemia though this difference was not statistically signifcatn.[20-21] Why the length of stay was longer with hyperglycemia? It can be due to severity of the disease, which was not measured by any score in this study. The association of multiple factors like high glucose, high temperature and longer hospital stay all reflect a severer form of disease process. Moreover the effects of hyperglycemia like weakness and polyuria also lead to extra set of symptoms to the previously suffering patients with symptoms of pneumonia and lead to further delay in discharge.

There were many strengths of this study. Considering the burden posed by CAP patients in medical wards, no study was carried out. Moreover we evaluated the factor of BSR which is recently worked up to look for its impact and this study also assessed the wide range of age group.

However there were few limitations of this study as well. The cases were not assessed for the severity of pneumonia over any score hence it was difficult to assess which group had the more severe cases. Furthermore the co-morbid conditions like diabetes mellitus, hypertensionand malignancies were not assessed.

Further studies with larger number of patients, better description of pneumonia severity and with co-morbid conditions can explore the impact of hyperglycemia in length of hospital stay.

Conclusion

Community acquired pneumonia is an important infectious health concern. It is associated with high blood glucose and the length of hospital stay is found significantly high in cases of hyperglycemia.

Author's Contribution

MN: Data Collection, Statistical Analysis, Manuscript writing
MNA: Write up, Statistical Analysis
TR: SR: Statistical Analysis
TS: Editing, Review
MAN: Designed, Writing, Editing

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Iron Deficiency Anemia & Adverse Events After ST Elevation Acute Myocardial Infarction

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Abstract

Objectives: Study objective was to look for the frequency of iron deficiency in ischemic heart disease patients presenting with acute ST elevation myocardial infarction and to see the association of adverse coronary events with iron deficiency among these patients

Methods: It was a cross-sectional study conducted on three hundred and seventeen patients at coronary care unit/Medical unit of services hospital Lahore. Serum ferritin, iron, and transferrin were measured by using automated immunoassays in patient admitted with acute myocardial infarction and adverse events developed after myocardial were recorded at 5th day of admission. Frequency of iron deficiency anemia was determined in these patients. Adverse events after acute myocardial infarction such as development of recurrent MI, unstable angina, arrhythmias, pericarditis, (EF <50%), adverse outcomes in the form of mechanical complications (ventricular septal defect or mitral regurgitation, and significant impairment of left ventricular functions, stroke and death rate was studied in these patients. Chi-square test was used to see association of iron deficiency anemia with adverse events developed after myocardial infarction.

Results: Frequency of iron deficiency was 82% among patients suffering from acute myocardial infarction. There was significant association of anemia with Post myocardial infarction heart failure (P=0.006), Low EF <50 %(P=0.00), increased mortality (0.076) and pericarditis (P= 0.069).Iron deficiency was associated with of adverse outcomes after myocardial infarction.

Conclusion: Increased frequency of iron deficiency anemia was recorded in patients suffering from acute myocardial infarction and it was significantly associated with the post myocardial infarction adverse events.

Keywords: Iron deficiency anemia, Acute myocardial infarction, Adverse outcomes

Introduction

Acute myocardial infarction is causing significant morbidity and mortality in patients suffering from cardiovascular diseases. Iron is essential for all physiological processes in body. Iron is not only required for erythropoiesis but is also important in oxygen storage & transport, Synthesis of deoxyribonucleic acid and so for the erythropoiesis, electron transport, oxygen transport and synthesis/ degradation of muscle protein. All the muscles in body including cardiac myocytes require iron for proper functioning.[1] Iron deficiency is of two types, one in which the iron stores are exhausted but the iron homeostasis is preserved, the second type of iron deficiency is called functional iron deficiency in which the total iron reserves are normal but the iron supply is not sufficient to fulfill the demands of body.[2] In functional Iron deficiency value of serum ferritin is normal but the transferrin saturation is low.[3]

Among cardiovascular diseases iron deficiency is seen in heart failure and in patients suffering from acute myocardial infarction.[4] Like many nontraditional novel cardiovascular risk factors, role of iron deficiency was studied in patients with cardiac illnesses.[5] There are many pathophysiological mechanisms for anemia in coronary artery disease. The hyperdynamic state contribute to left ventricular hypertrophy and arterial wall thickness if anemia is not get corrected.[6]

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Anemia is a risk factor for ischemic heart disease and mortality associated with it.[7] Adverse prognosis is found in patients of anemia with acute coronary syndrome irrespective of type of anemia.[8] Effect of anemia on outcome is independent of other etiological factors and it can predict the survival in patients with cardiac diseases.[9] Myocardial necrosis resulting from acute obstruction of coronary artery results in acute myocardial infarction suggested by typical history ST segment elevation in two consecutive chest or limb leads or elevated cardiac biomarkers.[10] Heart failure is a clinical syndrome presenting with symptoms of dyspnea, paroxysmal nocturnal dyspnea, edema feet and signs such as elevated jugular venous pressure, and bibasilar crepitation. It is caused due to structural heart disease such as ischemia or due to any functional cardiac abnormality which is causing decreased in stroke volume.[11]

In this study we assessed the presence of iron deficiency and its association of with adverse outcomes/ events after acute myocardial infarction. Our aim was to look for the of iron deficiency in patients of ischemic heart disease presenting with coronary ischemia and to see the association of iron deficiency with adverse coronary events in these patients.

Methods

It was an observational cross-sectional study; the study duration was twelve months. The sample size for the study was calculated by taking most probable prevalence of iron deficiency as 29% and with 95% confidence interval. Three hundred and seventeen 317 patients were included in the study. These patients were admitted in coronary care unit of services hospital Lahore from July 2018 to July 2019 with acute ST elevation myocardialinfarction? Patients with cardiomyopathies, on anticoagulation therapy, cancer and fever were excluded. Informed consent was obtained by all and ethical approval was taken from institutional review board of services hospital Lahore.

Any hemoglobin level <12.0 g/dL is defined as anemia. Iron deficiency anemia was defined as hemoglobin level <12.0 g/dL in female and <13.5g/dl in male. Serum ferritin is a parameter for iron deficiency. Normal serum ferritin is 30-300ng/ml. Serum ferritin is an acute-phase reactant, and diagnosis of iron deficiency anemia was made if patient is anemic and serum ferritin was less than 30 ng/ml or serum ferritin less than 12 ng/dl.[12]

Baseline information was taken from hospital charts. Coronary artery disease was diagnosed as patient presenting with signs/symptoms of myocardial infarction, ECG changes, raised cardiac enzymes and Troponin I levels.[13] Other routine laboratory values were recorded. Complete blood count with red blood cell morphology and indices, Serum ferritin and iron was measured by using automated immunoassays on 5th day of admission. Adverse events/outcomes the patient developed after ST elevation myocardial infarction at 5th day of admission were recorded. The complications or adverse events after myocardial infarction studied were, recurrent Myocardial Infarction MI, unstable angina, arrhythmias(premature atrial & ventricular contraction, ventricular tachycardia, ventricular fibrillation and atrial fibrillation) stroke, pericarditis, significant impairment of left ventricular functions (EF <50%), the mechanical complications such as ventricular septal defect or mitral regurgitation due to papillary muscle ruptured and death. ECG changes, Troponin I and echocardiography was used to diag-nose the adverse events. The definition of iron deficiency was based on serum ferritin and hemo-globin levels.[14]

Results

Out of three hundred and fifty patients, mean age of patients was 54 years. 53%patients were male and 47%patients were female. Mean hemoglobin of patients was 10g/dl and mean serum ferritin was 25ng/dl. Mean ejection fraction of these patients was 45%. 88% of patients were found to be anemic. 82% patients had serum ferritin less than 30ng/dl and 18%patients has more than 30ng/dl(Table 1)

After myocardial infarction 62.1%patient developed adverse events like arrhythmias in the form of premature ventricular contractions (35%), atrial fibrillation (20%), ventricular tachycardia (23%), APC'S (10%) and ventricular fibrillation (7%), 23% patient had stroke, 15.5% patient had recurrent acute myocardial infarction, 97.1 %patient had unstable angina, 5% patient died, 20.5% patient had pericarditis, 74% patient had clinical heart failure and among these 68% patient had impairment of LV functions on echocardiography (EF <50%) (FIG.1), 0.3% patient patients had ventricular septal defect, 1.9% patient had mitral regurgitation due to papillary muscle ruptured. The complications are listed in

Table 1: *Descriptive Statistics of Study Population*

Study parameters	N=total patients	Range	Minimum	Maximum	Sum	Mean		Std. Deviation	Variance
						Statistics	Std err		
Age	317	70	20	90	172.5	54.42	.867	15.435	238.245
Hemoglobin	317	8	6	14	3177	10.02	.115	2.042	4.171
Serum ferritin	317	152	4	156	8963	28.28	1.399	24.901	620.045
Ejection Fraction	317	55	9	64	14405	45.44	.388	6.913	47.792

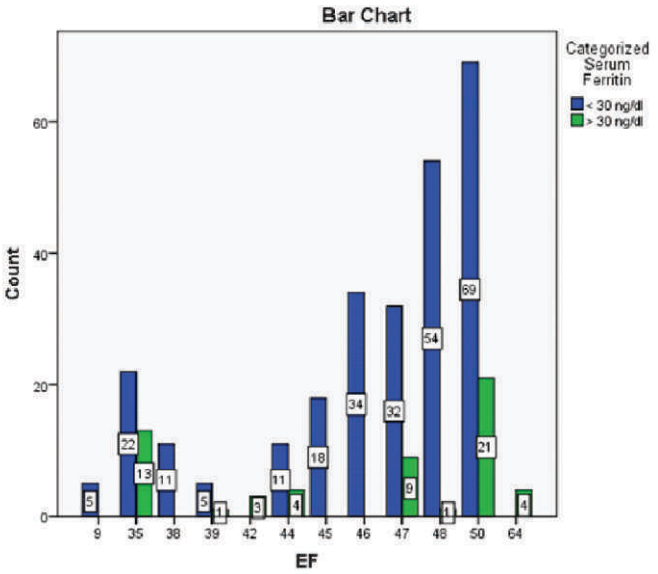

Figure 1: *Serum Ferritin and Ejection Fraction (P=0.00)*

Table: 2

Recurrent acute myocardial infarction had no significant association with anemia (P=0.12). There was significant association of anemia with gender and males were having the significantly low levels of serum ferritin (P = 0.07), patients with diabetes mellitus were not found to have significantly low hemoglobin (P= 0.22). Stroke was not significantly related with serum ferritin levels (p=0.77), increased mortality was not seen in patients who were found to be anemic and had low serum ferritin (0.076). Hypertension was significantly related with anemia (P= 0.006). Obesity was not significantly related with anemia (P= 0.14).

The frequency of anemia in these patients was found to be high and significant association of anemia was found with adverse events after myocardial infarction.

Table 2: *Anemic Patients Who Developed Complications after Myocardial Infarction*

Study parameters	Serum Ferritin		Total no of patients	Types of Myocardial infarction
	N=< 30 ng/dl	N=> 30 ng/dl		
Diabetes mellitus	123	30	153(48.3%) P=(0.22)	Anterior wall myocardial infarction Total No of patient = 178(56.2%)
Hypertension	122	37	159(50.2%) P=(0.006)	
Obesity	24	11	45(14.2%) P=(0.14)	
Unstable Angina	224	52	276(97.1%) P=(0.11)	Inferior wall myocardial infarction Total No of patient = 8(2.5%)
Recurrent acute Myocardial infarction	37	12	49(15.5%) P=(0.12)	
Death	13	0	13(5%) P=(0.076)	
Pericarditis	58	7	65(20.5%)	Lateral wall myocardial infarction Total No of patient = 8(2.5%)
Clinical heart Failures	199	38	237(74%)	
Mechanical complications	7	0	7(2.3%)	
Stroke	63	11	74(23.3%) P=(0.77)	Posterior wall myocardial infarction Total No of patient = 8(2.5%)
Arrhythmias	159	38	197(62.1%)	

Discussion

Results of our study showed high frequency of iron deficiency anemia in patients with acute myocardial infarction and significant association was found between anemia and adverse events after myocardial infarction. It is shown in the previous studies that iron deficiency is associated with adverse coronary outcomes. These patients are prone to develop cardiovascular diseases in future and the role of iron replacement is not clear in these patients.[15]

A cross sectional study done on stable patients of ischemic heart disease by obtaining bones marrow aspirates. The results of the study showed bone marrow depletion of iron stores in patients with ischemia but not in control group.[16]

It has been shown in some studies that intravenous iron replacement helps to alleviate the symptoms of heart failure in patients suffering from iron deficiency. This suggests that early correction of iron deficiency after myocardial infarction can reduce the adverse outcomes in these patients.[17]

Iron deficiency is seen in patients with heart failure and is causing increased morbidity. The role of anemia in progression of disease is not clearly understood. Erythropoietin treatment did not improve the clinical status and associated complications. Anemia is common in patients with heart disaeses. This leads to poor outcomes in these patients. Whether to take anemia as markers of heart failure severity or a factor that mediate heart failure progression is not entirely clear. Erythropoiesis-stimulating agents did not lead to clinical improvement and at times causing the serious side effects. Treatment of anemia was studied in patients both with absolute and functional iron deficiency. It is seen that treatment of iron deficiency is beneficial in patients with absolute iron deficiency and it appears to be unclear whether we should treat the functional iron deficiency or not.[18] All these findings are supporting the results of our study. Hemoglobin abnormalities have been described as a cause of poor prognosis in patients with ischemic heart disease based on retrospective cohort studies.[19] Our study also showed increased mortality in patients who was suffering from anemia due to iron depletion.

In a patients of chronic kidney disease hemoglobin abnormalities can lead early coronary intervention.[20] It is an independent risk factor for prediction of risk of recurrent myocardial infarctions and bleeding during the procedure. Anemia is also an important factor for risk stratification of these patients. Incresed risk of recurrent ischemic events demands for early correction of anemia.[9]

In patients who undergo coronary stenting after myocardial infarction, hemoglobin, serum creatinine levels and ADP induced residual platelet activity is found to be an independent factors for in hospital adverse cardiovascular outcomes.[21]

It is an observation in a study that patients of pulmonary hypertension and heart failure and coronary artery disease undergoing bypass surgery, one third to half of patients were affected by iron deficiency and symptomatic improvements was shown after intravenous iron administration even in the absence of anemia. There is increased risk of early hospital readmission associated with absolute iron deficiency.[22]

The patient undergoing percutaneous coronary intervention after myocardial infarction does not get benefited from erythropoietin and increase risk of thrombotic events were observed in these patients and iron preparations are recommended only in those patients who are having the iron deficiency or the blood loss.[23]

A study done in patients with heart failure and pulmonary hypertension showed that one third of patients with heart failure and fifty percent patients with pulmonary hypertension demonstrated iron deficiency. This observation suggests that iron deficiency is a risk factor for all cardiovascular events.[8]

Sixty one percent prevalence of iron deficiency in patients of coronary artery disease was seen and it persisted at some point in next thirty days. This effect appears to be associated with antiplatelet treatment and increased inflammation. High frequency of iron deficiency in patients of acute myocardial infarction need to deter-mine the hemorrhagic risk factors in patients. Anti-platelet treatment and subsequent coronary interven-tion can be a cause of iron deficiency in these patients. Also there is a need to determine the choice of modalities for treatment of anemia in these patients. Correction of anemia is required for those patients who are requiring early

coronary intervention.[7]

It has been shown that red cell distribution width is a risk factor and is poor prognostic factor after coronary events. Ferritin level is a marker of inflammation and poor prognostic factor for left ventricular systolic function. Coronaryy artery disease is associated with increase in other markers of inflammation such as C - reactive protein. [24]

Conclusion

The frequency of iron deficiency anemia is very high in patients suffering from acute myocardial infarction and it is associated with significantly increased complications after myocardial infarction.

Limitations of Study: The patients were only followed during hospital stay. Further studies are required for post myocardial infarction follow up and risk stratification in patients with iron deficiency anemia.

Author's Contribution

NM: Data Collection
MR: Research Proposal, writing discussion
ZS: Statistical Analysis & Research Proposal writing

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Postpartum Psychiatric disorders –A neglected Issue

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Abstract

Postpartum period along with pregnancy are considered to be emotionally susceptible periods. The association between emotional or psychiatric disorders and postpartum period has been documented since Hippocratic times. Hormonal changes have been implicated, along with multiple factors in the development of depression associated with postpartum period. Moreover, maternal depression can have devastating effects on neonate as well. This study explores an important area to assess the magnitude of problem in our setup, so that appropriate evaluation of mental health status and up-to-date management can be planned.

Objective: To find out psychiatric morbidity among females presenting during postpartum period at a tertiary care hospital in Lahore.

Methods: A cross-sectional study was done in Department of Obstetrics and Gynaecology of Central Park Teaching Hospital, Lahore. One Hundred women presenting in peripartum period were included in the study, using purposive sampling technique. After an informed consent participant's bio data was recorded. A structured proforma was used for psychiatric evaluation of the cases, which contained social and demographic details along with questions from Edinburgh postnatal depression scale. Psychiatric diagnosis was made according to DSM-5. Severity of illness was assessed using Hamilton rating scale for depression and Hamilton anxiety rating scale.

Results: Postpartum follow up of 100 females revealed that 18% developed psychiatric morbidity. 13 had major depressive disorder and 5 females had anxiety disorder. There was no case of puerperal psychosis in any of the females postpartum in this study. Psychiatric morbidity and age group between 18-25 years (20.6%) showed significant correlation. Similarly, higher incidence of psychiatric morbidity was observed in women living in nuclear household (24.1%).

Conclusion: Psychiatric morbidities are common among females during postpartum period. Major depression is the commonest one. Therefore assessment for depression should be included in routine obstetric follow-ups.

Key Words: psychiatric morbidity, major depression, anxiety disorder, puerperal psychosis, postpartum females.

Introduction

Childbirth brings multiple challenges to the mother, e.g. loss of sleep, emotional and physical trauma, initiation of breast feeding, adjustment with life relationships and socially isolated routine. How-ever, bonding with the newborn is the most important psychological process. Postpartum period along with pregnancy are considered to be emotionally and psy-chologically vulnerable periods.[1] In many instances, childbirth brings joy in the family, but it could be a stressful event for a few women, severe enough to provoke a mental breakdown.[2] The association bet-ween emotional or psychiatric disorders and postpar-tum period has been documented since Hippocratic times.[3]

The placenta is an endocrine organ of fetal origin and dysregulation of placental corticotropin releasing hormone(CRH) may play a role in development of postpartum depression[4]. Many studies show that a

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woman has an increased risk of admission in a psychiatric ward of hospital within the first month after childbirth than any other time[5,6]. Around 12.5% of women admission in a psychiatric ward occur generally during the postpartum time period [7].

Postpartum mental disorders are generally divided into three broad categories, i.e. non psychotic postpartum depression, puerperal psychosis and postpartum blues. All three of these have distinct clinical features but affect female population in all social classes and have not been associated with any biological or psychological variable.

Postpartum blues manifest as mild depressive symptoms that develop within 2-3 days of delivery and are self-limiting that resolve within 2 weeks of onset of symptoms. Postpartum blues develop in around 50% of the females but the pathogenesis is unknown.[8-11] Postnatal decrease in estrogen level which increases the level of monoamine oxidase A (enzyme) can be one of the factors.[12] Women with postpartum blues have 4-11 times greater risk of developing postpartum major depression and 4 times increased risk of anxiety disorder.[9] Symptoms include low mood, crying, anxious behavior, irritability, insomnia, exhaustion and loss of concentration. Postpartum blues is not recognized as a diagnostic entity by American Psychiatric Association's Diagnostic and Statistical Manual.[13] Thus, it just represents as a prodromal phase of depressive and anxiety syndromes.

The etiology of postpartum depression is a complex interaction of psychological, social and biological factors, in addition to genetic and environmental factors. Maternal sensitivity, attachment with the newborn and style of parenting is essential for a healthy development of an infant's cognitive and behavioral skills. Mothers who are depressed display less attachment with the infant and harsh parenting style. This results in adverse outcomes in child's development. A retrospective study of women with postpartum onset of major depression found that in 54% cases onset of PPD was within 4 weeks postpartum.[14] The most consistent risk factor, which has the largest effect, is past history of either perinatal or non-perinatal depression.[15]

The clinical picture of postpartum psychosis includes hallucinations and delusions, abnormal behavior, disorientation and delirium. Postpartum psychosis is a medical emergency and requires immediate hospitalization, along with comprehensive psychiatric evaluation and medical management.

Methods

The study was conducted in the Department of Obstetrics & Gynaecology of Central Park Teaching Hospital affiliated with Central Park Medical College, Lahore. Hundred women were included in the study. They were admitted for delivery either from OPD or Emergency after screening for fulfillment of criteria of inclusion. All participants were explained the nature and purpose of study and a written informed consent was obtained. The study was ethically approved by Institutional review board of Central Park Teaching hospital. Women less than 18 years of age and above 40 years, females having any associated systemic disease and mental disorder were excluded from the study. Cases with intrauterine fetal death were also not included in the study. All females were evaluated on first postnatal day, at 2 weeks' time period and afterwards at 4 weeks postpartum. A structured proforma containing social and demographic details was used to enter the basic details of the participants. Psychiatric evaluation was done on the basis of information collected on the above mentioned proforma and questions from Edinburgh postnatal depression scale.[16] Psychiatric diagnosis was made according to DSM-5. Severity of illness was assessed using Hamilton rating scale for depression[17] and Hamilton anxiety rating scale.[18]

Results

63% of females were in the age range of 18-25 years, followed by 20% in the age range of 26-33 years and 17% in 34-40 years. Majority of the females were illiterate i.e. 55%. 27% had received primary education whereas 12% had completed secondary education and only 6% of them were graduates. Out of all the women 73% were housewives and the rest of 27% were working women. 53% belonged to semi-urban society and 25% were from rural background. 22% of women belonged to urban background. Majority of women (75%) belonged to lower socioeconomic class as our hospital is a charity hospital catering to the needs of surrounding village population. 18% belonged to middle class and only 7% belonged to

upper class. 71% of the females lived in a joint family set with good family support and 29% lived as a nuclear family.

Out of the 100 females 64 were multipara and 36 were primipara. As far as mode of delivery is concerned out of the 100 deliveries 58 were normal vaginal deliveries and 42 were lower segment cesarean sections. There were 97 singleton births and 3 twin deliveries. Out of the 97 singleton births 38 women gave birth to male babies and there were 59 births of female babies.

Table 1: *Socio-Demographic Profile*

Variables		% (N=100)	Psychiatric morbidity N(%)
Age(years)	18-25	63	13 (20.6)
	26-33	20	03 (15)
	34-40	17	02 (11.7)
Education	Illiterate	55	10 (18.1)
	Primary	27	06 (22.2)
	Secondary	12	02 (16.6)
	Graduate	6	
Occupation	Housewife	73	14 (19.1)
	Working	27	04 (14.8)
Residence	Urban	22	03 (13.6)
	Semi-urban	53	12 (22.6)
	Rural	25	03 (12)
Economic status	Upper	7	01 (14.1)
	Middle	18	02 (11.1)
	Lower	75	15 (20)
Type of Family	Nuclear	29	07(24.1)
	Joint	71	11(15.4)

Postpartum follow up of 100 females revealed that 18 developed psychiatric morbidity. 13 had major depressive disorder and 5 females had anxiety disorder. There was no case of puerperal psychosis in any of the postpartum females.

Among the 13 females diagnosed with major depressive disorder 46.1% had mild depression, 30.7% had moderate depression, 15.3% had severe depression and 7.6% had very severe depression according to Hamilton rating scale for depression (HRSD). In anxiety disorder group out of 5 women 4(80%) had moderate anxiety and 1(20%) had severe anxiety.

Psychiatric morbidity and age group between 18-25 years (20.6%) showed significant correlation. Similarly, higher incidence of psychiatric morbidity was observed in women living in nuclear household (24.1%). There was no correlation between education of women, their dwelling whether rural, urban or semi-urban and economic status with psychological status. Multiparity had significant correlation (18.7 %) with development of postpartum psychiatric disorders and same is the observation in case of cesarean delivery (23.8%). Postpartum depression was seen in 23.7% of women who gave birth to female babies.

Table 2: *Obstetric Profile*

Variable		% (N=100)	Psychiatric morbidity(%)
Parity	Primipara	36	06 (16.6)
	Multipara	64	12 (18.7)
Mode of delivery	Vaginal	58	08 (13.7)
	Cesarean	42	10 (23.8)
Babies born	Male	38	04 (10.5)
	Female	59	14 (23.7)
	Twins	3	0

Table 3: *Distribution of Psychiatric Morbidity*

Psychiatric morbidity	% (N=100)	Severity	No cases	Score
Major depressive disorder	13	Mild	6	8-13
		Moderate	4	14-18
		Severe	2	19-22
		Very Severe	1	>23
Anxiety disorder	5	Moderate	4	18-24
		Severe	1	>25
No Psychiatric morbidity	82			

Discussion:

This study was aimed to investigate that how females without any past psychiatric history develop psychiatric illness. This ruled out the major known determinant of development of postpartum psychiatric morbidity i.e. past history[19] and let us get an insight of other risk factors.

One of the most challenging aspects of postpartum depression is that how affected population remains undetected. Mothers try to hide their feelings because of the social stigma attached with psychiatric disorders. These mood disorders can have devastating effects on mothers as well as the newborn.

Risk factors that are frequently associated with postpartum depression are poor social and financial support,[20] age <25years, multiparity , intimate partner violence, poor perinatal physical health.[21] Psychiatric illness was observed in almost 18% of the females in

their postpartum period during follow up. Out of these, 13% were diagnosed as having major depressive disorder and rest had anxiety disorder. Ramchandani et al and Wan et al have reported prevalence of postpartum mood disorders as 16.4% and 15.5% respectively.[22,23] Britton along with his colleagues reported prevalence of anxiety as 24.9% during postpartum period out of which only one percent had diagnosis of severe anxiety.[24]

In our study majority (63%)of females were in the age range of 18-25 years and the incidence of psychiatric morbidity was highest (20.6%)in this age group as compared to 15% in the age range of 26-33years and 11.7% in age range of 34-40 years. In the 73 housewives 19.1% developed psychiatric morbidity as compared to 14.8% in working women. A prospective cohort study conducted in University of Washington School of Medicine including 1423 pregnant women showed that women with postpartum depression were significantly younger ($p<0.0001$) and more likely to be unemployed($p=0.04$)[25].

Our study showed psychiatric morbidity of 20% in women belonging to lower socioeconomic group in comparison to 14.1% and 11.1% in upper and middle socioeconomic group respectively. A Chinese survey revealed that postpartum depression was more common in low income group.[22]

Our study exhibited an increased risk of postpartum psychiatric disorders in multiparous (18.7%) women in comparison to primiparous women(16.6%).It was also found that psychiatric morbidity was 23.8% in case of cesarean delivery as compared to 13.7% in the vaginal delivery group. Sword et al,[26] also deduced in their prospective cohort study that multiparity has strong correlation (OR 1.59; 95% CI 1.22-2.08)with postpartum psychiatric morbidity, but mode of delivery was not found to be independently associated with postpartum depression in their study. Contrarily Irfan and Badar[27] reported that major proportion of females developing mental illness were primiparous. Amr and Balaha reported that 22.6% of the study population who delivered via cesarean section were having psychiatric illnesses.[28]

Further research is needed to understand these mythical morbidities, as still there is a lot to understand as to why and how are psychiatric disorders so closely related to pregnancy and postpartum period.

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Bacteriological Profile and Antibiotic Sensitivity Pattern in Infected Diabetic Foot Ulcers

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Abstract

Objectives: To identify the common bacterial pathogens responsible for infection in diabetic foot ulcer and their sensitivity pattern to different antibiotics.

Methods: This prospective observational study was conducted from 24th June 2019 to 27th December 2019 at Services Institute of Medical Sciences Lahore. Specimens of discharge from diabetic foot ulcers (DFU) were received from Diabetes Management Centre (DMC). Cultures were put up and bacteria isolated were identified by standard methods. Antibiotic sensitivity was determined by Kirby-Bauer disc diffusion method.

Results: Samples from DFU of 50 patients were processed. Thirty-six (72%) samples were from males and 14(28%) were from females; mean age of patients was 53±9.5 years. Forty-nine (98%) patients had unsatisfactory glycemic control. Forty three (86%) samples were growth positive while 07(14%) were bacteriologically sterile. Monomicrobial infection was observed in 38 (76%) cases while polymicrobial infection was seen in 12 cases (24%). The most common isolates were Staphylococcus aureus 14(28%), Pseudomonas species 11 (22%) and Proteus species 10 (20%). Forty three percent of Staphylococcus aureus, were methicillin resistant (MRSA). All MRSA remained sensitive to vancomycin and linezolid. In Pseudomonas species, resistance to third generation cephalosporins, ceftazidime , was 27%, while resistance to imipenem was seen in 3 (9%) of isolates. In Proteus species, resistance to third generation cephalosporins was 90% while to imipenem resistance was 60%. Resistance to commonly prescribed quinolones was more than 70% among all the bacterial isolates.

Conclusions: Common Gram positive and Gram negative organisms responsible for infection in DFU were Staphylococcus aureus, Pseudomonas species and Proteus species. The isolates were multi-drug resistant (MDR). Resistance to antibiotics used as empiric therapy was high.

Keywords: Diabetic foot ulcer, antibiotic resistance, empiric therapy

Introduction

Diabetes mellitus is a growing health care concern in Pakistan. The prevalence of the disease was 26.3% in the National Diabetes Survey of Pakistan (NDSP) in 2016-17, an increase of 17.6% from the previous survey carried out in 1994-98.[1] It is the fourth leading cause of death in developed countries, while Pakistan ranks at seventh position currently. This significant increase in the prevalence of diabetes is attributed to an aging population, unhealthy dietary practices, sedentary life style, obesity and smoking.[2]

Diabetic foot ulcer (DFU) is a common and serious complication in diabetic patients. Most hospitalizations in diabetic patients are due to diabetic foot ulcers.[3] Approximately 15% of diabetics develop foot ulcer at some point in their lives which can lead to infection, tissue destruction and may result into amputation if inadequately treated. The rate of amputation in diabetic foot ulcers accounts for 50% of all

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non-traumatic amputations carried out. The rate of recurrence of diabetic foot ulcers is similarly high, reoccurring in 50% of patients within three years.[4] Risk factors for the disease include peripheral arterial disease, peripheral neuropathy and foot deformaties.[5] Different classifications are used to describe the lesion on the foot, but the most commonly used classification is of Meggitt-Wagner. In this classification the ulcer is graded from 0 to 5, first four grades describe physical depth of the ulcer while last two describe the extent of gangrene.

Diabetic foot infection (DFI) management involves empirical antibiotic therapy and supportive care initially followed by definitive antibiotic regimen based on culture and antibiotic sensitivity reports.[3,6] DFI are mostly polymicrobial including both Gram positive and Gram negative organisms.[6,7] Patients with diabetic foot ulcers are exposed to several antibiotics that is the leading cause of development of resistance to antibiotics.[8] Early diagnosis and appropriate antibiotic therapy in DFI can minimize the complications.[6,7]

Microorganisms isolated and their sensitivity pattern in DFI vary in different regions and different institutions[9,10], therefore it is essential that empirical antibiotic therapy is based on local guideline which takes into account the prevalence of different microorganisms and their sensitivity patterns to antibiotics. This will ensure that empirical antibiotic therapy provides appropriate coverage. It will also reduce the use of multiple antibiotics and resistance to antibiotics. The purpose of present study is to contribute to this field of research by identifying the bacteriological profile and antibiotic sensitivity patterns in patients with DFI.

Methods

This prospective observational study was done in collaboration with Diabetes Management Centre (DMC) of Endocrinology Department and Microbiology Pathology Department of Services Institute of Medical Sciences & Services Hospital Lahore. Prior approval was obtained from institutional review board. Patients with diabetes mellitus type 2 presenting to DMC with infected foot ulcer were included after informed consent from patients. Fifty specimens of discharge from ulcer were received in Amies transport media. A filled performa containing information regarding patient identification, ulcer grade according to Meggitt-Wagner's classification of diabetic foot ulcer based on depth of wound[12], antibiotics prescribed and HbA1c results were received from 24th June 2019 to 27th December 2019.

All specimens were inoculated on blood agar and MacConkey agar plates. Incubation was done aerobically at 35°C for 24 hours. Identification was based on colony morphology, Gram stain reaction and biochemical tests. For Gram positive organisms catalase test and DNAse were done. For Gram negative organisms oxidase test was done and for oxidase negative colonies urease, citrate utilization, motility and triple sugar iron tests were performed. If results were ambiguous API20E was set up.[13]

Antibiogram was performed on Mueller Hinton agar (Oxoid,UK) by Kirby Bauer disc diffusion method. OxoidTM antibiotic discs were used.[14]

For Gram positive organisms antibiotics applied were penicillin (P10µg), Cefoxitin (FOX30µg) Vancomycin (VA30µg), Gentamicin (CN10µg), Amikacin (AK30µg), Erythromycin (E15µg), Doxycycline DO(30µg), Ciprofloxacin (CIP5µg), Clindamycin (DA2µg), Trimethoprim-Sulphamethoxazole (SXT1. 25/23.75µg), Linezolid (LZD30µg). Cefoxitin was used as surrogate for methicillin sensitivity. Sensi-tivity of Gram negative organisms were tested against Ampicillin (AMP10 µg), Amoxacillin – clavulanate (AMC 20/10 µg), Piperacillin-tazobactam (TZP100/ 10 µg), Cefuroxime (CXM30 µg), Cefotaxime (CTX 30 µg), Ceftriaxone (CRO 30µg), Ceftazidime (CAZ 30µg), Imipenem (IPM 10 µg), Meropenem (MEM10 µg), Gentamicin (CN10 µg), Amikacin AK (30µg), Doxycycline (DO30µg), Ciprofloxacin (CIP5µg), Trimethoprim-Sulphamethoxazole SXT(1.25/ 23.75µg).[14]

Statistical Analysis was done on Microsoft excel.

Data was presented as Mean±SD for continuous variables and frequency with percentage for categorical variables.

Results:

Of the fifty DFI samples 36 were obtained from males and 14 from females. The age range of patients was between 35 - 80 years. Mean age was 53 ± 9.5years.

HbA1c results were above normal limits >7% going upto 14.2% in all except one patient with normal HbA1c 5.1% .

Most patients had grade 2 or grade3 ulcer as shown in Figure 1. Twenty four (48%) patients had grade 2 ulcer while 20 (40%) had grade 3 ulcer.

On culture monomicrobial growth was obtained in 62% while seven specimens yielded no growth Figure 2. Most common isolates were Gram negative organisms Figure 3. The different organisms isolated are shown in Figure 4.

Methicillin resistance in Staphylococcus aureus was 43% (MRSA). Resistance to ciprofloxacin was >93% in Staphylococcus aureus. All MRSA were sensitive to vancomycin and linezolid Table 1.The second most common isolate was Pseudomonas species. Twenty-seven percent Pseudomonas sp. showed resistance to third generation cephalosporins, ceftazidime, while only 1 (09%)showed resistance to imipenem. The Enterbacteriaceae and Acinetobacter species isolated and their sensitivity pattern is shown in Table 2. Resistance to ciprofloxacin was very high 73-100 % in Gram-negative organisms. Antibiotics taken by patients before arriving at DMC are shown in Table 3.

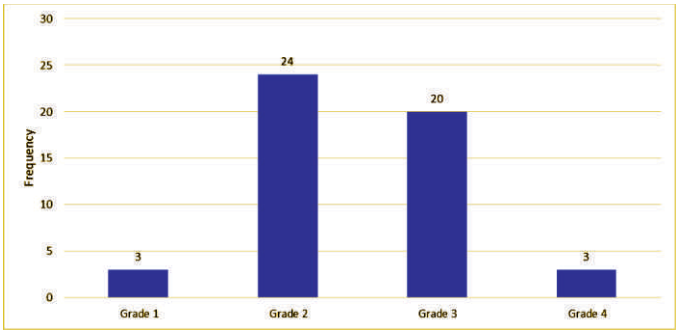


Figure-1: *Grading of Diabetic Foot Ulcer Patients According to Magitt Wegener´s Classification n=50*

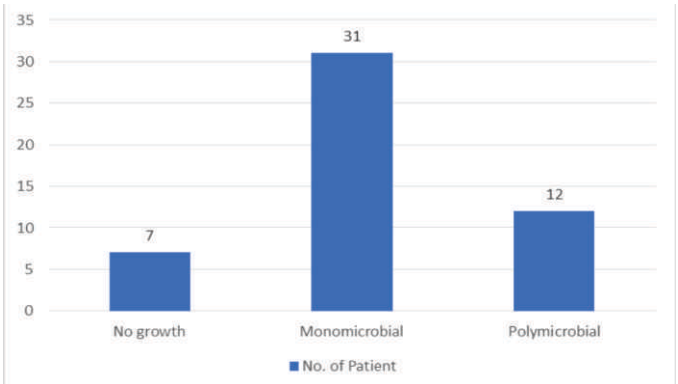


Figure-2: *Frequency of Monomicrobial and Polymicrobial Organisms in Diabetic Foot Ulcer Samples. n=50*

Table 1: *Resistance Pattern of Gram Positive Organisms*

Organism Identified	P	FOX	VA	CN	AK	E	DO	CIP	DA	SXT	LZD
Staph aureus (n=14)	14 (100%)	6 (43%)	0 (0%)	1 (7%)	2 (14%)	7 (50%)	13 (93%)	13 (93%)	7 (50%)	11 (79%)	0 (0%)
Streptococcus spp (n=1)	1 (100%)	1 (100%)	0 (0%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)	0 (0%)

n =15

Table 2: *Resistance Pattern of Gram Negative Organisms*

Enterobac-teriaceae	AMP	AMC	TZP	CTX	CRO	CAZ	IPM	MEM	CN	AK	DO	CIP	SXT	CT
E.coli (n=6)	4 (67%)	6 (100%)	6 (100%)	2 (33%)	1 (17%)	-	2 (33%)	1 (17%)	2 (33%)	0 (0%)	6 (100%)	6 (100%)	6 (100%)	-
Citrobacter spp (n=1)	1 (100%)	1(100%)	0(0%)	0(0%)	0 (0%)	-	0(0%)	0(0%)	0(0%)	0(0%)	1(100%)	0(0%)	0(0%)	-
Klebsiella (n=5)	IR*	0 (0%)	3 (60%)	4 (80%)	4 (80%)	-	1 (20%)	1 (20%)	2 (40%)	2 (40%)	5 (100%)	5 (100%)	5 (100%)	-
Proteus (n=10)	IR*	IR*	1 (10%)	9 (90%)	9 (90%)	-	6 (60%)	5 (50%)	4 (40%)	1 (10%)	IR*	8 (80%)	9 (90%)	-
Non Fermentors														
Pseudomonas (n=11)	IR*	IR*	1 (9%)	IR*	IR*	3 (27%)	1 (9%)	0 (0%)	6 (55%)	5 (45%)	IR*	8 (73%)	IR*	-
Acinetobacter (n=4)	IR*	IR*	4 (100%)	4 (100%	4 (100%)	-	3 (75%)	3 (75%)	2 (50%)	1 (25%)	IR*	4 (100%)	4 (100%)	0 (0%)

n=37
*Intrinsic resistance

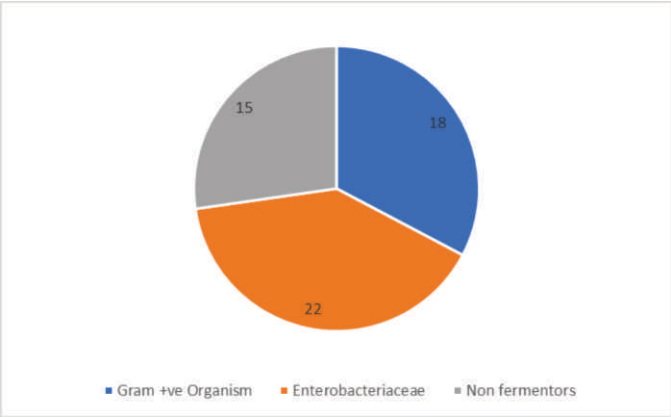
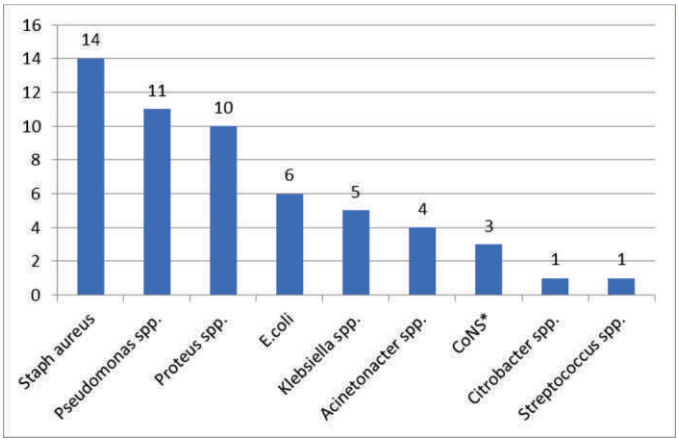


Figure-3: *Most Common Isolates in Diabetic Foot Ulcers*



**Coagulase negative Staphylococcus*

Figure-4: *Frequency of Various Organisms Isolated from Diabetic Foot Infection Patients*

Table 3: *Empiric Therapy Prescribed to Patients*

Antibiotics Received	No. of patients
Augmentin& Moxifloxacin	28
Moxifloxacin	9
Augmentin	7
Linezolid	3
Augmentin , Moxifloxacin & Amikacin	2
Augmentin & Amikacin	1
Total	**50**

Discussion:

Diabetes mellitus and its complications like DFU are increasing and have become leading cause of morbidity and mortality in Pakistan and worldwide.[1,15,16,17] Patients of DFU are predisposed to infections which if not prevented and treated early with appropriate drugs lead to gangrene & amputation. Moreover, due to prolonged use of multiple antibiotics, it often results in development of antibiotic resistance.[7] Present study was conducted to study the organisms causing infections in DFU and their sensitivity to various antibiotics, which will help in formulating appropriate empiric antibiotic therapy.

The majority of patients with diabetic foot infection (DFI) in the present study were males. This is because diabetes mellitus and diabetic foot ulcer are more common in males as compared to females.[4,18,19] Another reason may be due to males involvement in outdoor activities in hot humid environment , lack of appropriate foot care and absence of formal education.[8,20] Other studies carried out on DFU also show preponderance of male patients in Pakistan and the subcontinent.[7,9,10,21]

The age group most affected was 53±9.5. Past studies carried out in Islamabad, Karachi and Peshawar also show a similar age group affected with diabetic foot ulcer and infection.[4,7,10]

The glycemic control of patients was poor as evidenced by HbA1c results; only one patient out of the 50 affected had normal value. This was as expected: poor glycemic control leads to peripheral neuropathy and to peripheral arterial disease which leads to formation of ulcers and infections.[4,8,22] Infected diabetic foot ulcer takes longer to heal in the presence of high HbA1c level; hence, prolonged antibiotic therapy is required with appropriate antibiotics as per culture sensitivity report.[23,24]

Most of the patients had grade 2 or grade 3 ulcer (Figure1) which might be why monomicrobial growth was more common than polymicrobial growth in the present study (Figure 2). It has been observed that as the infection starts to involve deeper layers, multiple organisms are more likely to be isolated, making it polymicrobial.[3] Studies in which patients presented early to hospital were more likely to have monomicrobial growth.[24,8]

Seventy four percent isolates were Gram negative in present study Figure 3. This finding is similar to study carried out by Miyan et al. In this study on 473 samples 76.2% of isolates were Gram negative.[7]

Staphylococcus aureus was the most common Gram positive organism isolated. Of these, 43% were MRSA. All MRSA remained sensitive to vancomycin and linezolid. Resistance to quinolones, ciprofloxacin was 93% (Table 1). Other studies in Pakistan and

the subcontinent also reveal Staphylococcus aureus to be the most common Gram positive causative agent responsible for infections in DFU.[7,3] Different studies carried out in Pakistan showed resistance to ciprofloxacin between 53.68% to 73%.[6,7,10]

Pseudomonas species Figure 4, was the second most common isolate. This is similar to the study carried out in Islamabad by Chadury et al on 50 patients.[25] In present study resistance in Pseudomonas species to carbapenem was 27% and to ciprfloxacin was 73%. In another study in which the number of pseudomonas species isolates was seven, resistance to quinolones was 71.4% and to carbapenem was 28.6% very similar to the present study. In a study carried out in Karachi by Miyan et al ninty three Pseudomonas species were isolated from DFI in which 39.5% were resistant to quinolones and 6.17% resistant to carbapenem.[7,10] The marked variation in the sensitivity pattern in these studies is due to difference in the number of Pseudomonas species isolates.

Proteus species were the most common isolates among the Enterobateriaceae family Table 2. Most other studies reported E.coli to be the most common isolate in Enterobateriaceae family.[6,9,10]

The standard treatment patients were prescribed included Moxifloxacin with Augmentin or as monotherapy (Table 3). As the results of sensitivity of both Gram positive and Gram negative organisms reveals high degree of resistance to quinolones, ciprofloxacin, and augmentin. Thus there is an urgent need to develop new empiric therapy.

Conclusion

Staphylococcus aureus, Pseudomonas species and Proteus species are the most common pathogens responsible for DFI. Most of the Gram positive and Gram negative organisms isolated were resistant to multiple antibiotics. Moreover resistance to quinolones and augmentin, commonly prescribed antibiotics was very high.

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Safety and Efficacy of Four Anti-Diabetic Treatment Regimens in Patients with Type 2 Diabetes during Ramadan fasting: A Comparative Study

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Abstract

Objective: To compare the anti-hyperglycaemic effectiveness and safety of different anti-diabetic treatment regimens in fasting type 2 diabetic subjects during Ramadan.

Methods: This was a prospective four-week study of 161 subjects with type 2 diabetes (HbA1c 6.5-8.5%) during Ramadan, at the Department of Endocrinology & Metabolism, Services Hospital, Lahore, Pakistan. Study participants were randomized into four treatment groups: lifestyle modification only (group 1: lifestyle), metformin monotherapy (group 2: Metformin), metformin and sulfonylurea (group 3: Met/SU) and metformin and DPP4 inhibitor (group 4: Met/Sita). Anthropometric and biochemical evaluation were done one week before onset of Ramadan and in the last week of Ramadan. 134 patients completed the study protocol and repeated measures ANOVA was used to compare the groupsfor change inclinical and laboratory parameters from pre-Ramadan baseline.

Results: There was a significant decrease in mean blood glucose (mg/dL) and fructosamine(µmol/L)levels post-Ramadan in all treatment groups, with the greatest reduction seen in Met/Sita treatment group [(fructosamine -35.9, $p < 0.01$), mean blood glucose (-23.6, $p < 0.05$)]. In the safety analysis, Met/Sita group also showed improvement in several metabolic parameters including lipid profile (cholesterol -12.4 mg/dL, $p < 0.05$; LDL -8.6mg/dL, $p < 0.05$; triglycerides -41.9mg/dL, $p < 0.05$) and transaminases. Only one patient among the study population reported a hypoglycaemic event (Met/SU group).

Conclusion: During Ramadan fasting, combination treatment with metformin-sitagliptinin type 2 diabetic subjects resulted in the greatest improvement in glycaemic control without causing hypoglycaemia, and was associated with improvement in lipid profile and hepatic transaminases.

Key words: Metformin, sitagliptin, fasting, Ramadan, type 2 diabetes, glucose control

Introduction:

Islam is the second largest world religion with an estimated 1.8 billion followers.[1] Ramadan fasting is obligatory for all adult Muslims; however, exemption is granted in certain situations including any form of ill-health likely to be severely affected by fasting.[2] Despite this laxity, Muslims are keen to fulfill this obligation irrespective of their illness, diabetic patients being no exception. An estimated 40-50 million diabetic Muslims fast during Ramadan[3]. As reported by the large multi-centric Epidemiology of Diabetes and Ramadan study (EPIDIAR), 79% of type 2 diabetic subjects and 43% of type 1 observe Ramadan fasting annually.[4] Many of the Muslim majority countries have the highest percentage of diabetic patients, including Pakistan, which has a reported diabetes prevalence of ~12%, in a population of 220million,ranking 6th among world nations[5].

Ramadan is a lunar-based month and the length and timing of fasting vary each year according to the seasons and geographical location. Fasting during this month requires abstinence from food, fluids and medicines from daybreak to dusk daily[6]. As this is opposed to the conventional dietary pattern recommended in diabetes, fasting can be expected to

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cause erratic glycaemic control and metabolic derangements even in well-controlled diabetic patients.As the frequency of self-monitoring of blood glucose during fasting is also reduced, these glycaemic swings generally go undetected. Dehydration and stroke from prolonged fasting in summer months are also potential risks. Consequently, the first International Congress on Health and Ramadan, recommended that patients suffering from severe co-morbid conditions should avoid fasting[7].

Current recommendations have clearly defined categories of diabetic patients at varying degrees of risk from fasting[8]. The epidemiological evidence available on the impact of Ramadan fasting on diabetes control concludes that fasting is well-tolerated in stable type 2 diabetic patients treated either with diet alone or combined diet and oral hypoglycaemic agents (OHA)[9]. The International Diabetes Federation has issued comprehensive guidelines on diabetes management during Ramadan in collaboration with Diabetes and Ramadan International Alliance[10].

For the fasting type 2 diabetic patient, the aim of treatment is to minimize the frequency of hypoglycamia and maintain euglycaemia taking into consideration religious constraints. The recent years have seen an increase in therapeutic options for glucose control in diabetes. Studies have been done on the safety and efficacy of OHAs during Ramadan targeting specific treatment modalities including sulfonylureas, metformin, biphasic insulin and DPP-IV inhibitors, however, no consensus exists about the superiority in terms of safety and efficacy of any one regimen[11].

This study compared different anti-diabetic treatment regimens in terms of their anti-hyperglycaemic effectiveness and safety profile during Ramadan fasting in type 2 diabetic patients.

Methods

This was an open-label, single-centre, interventional study conducted in Department of Endocrinology & Metabolism, Services Hospital, Lahore during the month of Ramadan. The duration of fasting on average was more than 15 hours and ambient temperatures approximately 38 C. The study was designed in accordance with Declaration of Helsinki and the protocol was reviewed and approved by the Institutional Review Board.

Subject recruitment was done in three phases from among the diabetic patients registered with the Department: In the first phase about three months before start of Ramadan, 252 type 2 diabetic subjects intending to fast throughout Ramadan and willing to participate in the study were enrolled and their written informed consent obtained. All subjects were reminded about the specific exemption from fasting in disease states and the potential risks of acute complications. In the second phase, screening was done for underlying complications and their glycaemic control was assessed to confirm eligibility. Final screening was carried out one month prior to Ramadan onset.

The eligibility criteria were type 2 diabetes, age more than 18 years, on either diet alone or ≤ 2 oral anti-diabetic agents with good to moderate control (HbA1c 6.5-8.5%), in the three months preceding Ramadan. Exclusion criteria included any contraindications either to fasting or to any of the trial medication (metformin, sufonylurea or sitagliptin), pregnancy, clinical or biochemical evidence of co-morbid conditions, advanced diabetes complications, frequent hypoglycaemic episodes, or on SGLT2 inhibitors.

One week prior to start of Ramadan, the enrolled 161 participants were called to the clinic in fasting state for baseline clinical assessment and anthropometry. Fasting capillary glucose levels were checked by point-of-care device (OptiumXceed®, Abbott Diabetes Care). Venous whole blood samples were collected for CBC and HbA1c, and serum was separated and stored at -20C for assays forliver and renal function tests, RFTs, serum amylase, lipid profile and serum fructosamine.

The enrolled subjects were then assigned to 1 of 4 intervention groups based on the treatment regimen they were already taking: Group 1: lifestyle modification alone (n=37); Group 2: Metformin monotherapy (n=37); Group 3 Metformin/ Glimepiride combination (n=47); Group 4:Metformin/ Sitagliptin combination (n=40). Pre-Ramadan dose adjustment was done in accordance with standard Ramadan guidelines for achieving optimal glycaemic control.

Participants were provided with a standardized 1200 calorie diet chart and a food diary, to record the type

and amount of food and beverages taken at pre-dawn and sunset meal throughout Ramadan. Participants were advised to shift their exercise (30 minutes walk) schedule to after the post-sunset meal. A capillary blood glucose monitoring device (Optium Xceed®, Abbott Diabetes Care) and adequate glucose strips were provided to each participant for glucose monitoring three times daily during Ramadan: half hour before pre-dawn meal, at mid-day and 1 hour before sunset meal with additional monitoring in case of suspected hypoglycaemia. Participants were given handouts on hypoglycaemia recognition, with instructions to break the fast in case of hypoglycaemia (BSL< 70mg/dl).

During the follow-up visit (which was done just before the end of Ramadan, to avoid a clash with the Eid festival, which immediately follows Ramadan) the food diaries, blood glucose charts and adverse event charts were collected. The total number of days fasted by each participant was also noted. Re-estimation of body weight, height and waist circumference was done and venous samples in fasting state were collected.

The primary outcome measure was change in glycaemic profile (measured by serum fructosamine and mean blood glucose (MBG) during Ramadan fasting, by measuring. The secondary outcomes were change in body weight and BMI, and safety parameters (fasting lipid profile, liver and renal function)after Ramadan fasting.

Statistical Analysis:

Data were analyzed using SPSS for Windows version 11.0 (SPSS Inc., Chicago, IL, USA) and presented as means ± SD. Repeated measures ANOVA was done to compare the change from baseline among the different treatment groups. $p<0.05$ was considered statistically significant.

Results

The sequence of study enrollment, randomization and follow-up is depicted in Figure 1. The final study population included 161 subjects out of which 134 subjects completed the four-week study per protocol with small difference in retention in each group. 27 subjects failed to complete the study with 22 being lost to follow-up and 5 compelled to interrupt fasting due to acute inter-current illness. All treatment regimens were well-tolerated by the patients. The baseline characteristics of the participants in different treatment were comparable, except mean body weight, which was higher in group 4 participants (Table 1).

Primary outcome measures

The changes in clinical and metabolic parameters between the four treatment after 4 week period of Ramadan fasting were compared by ANOVA. Glycaemic measures, including serum fructosamine (µmol/L)and mean blood glucose (MBG) levels (mg/dL) pre and post-Ramadan reflected a decline in all four treatment groups, however, Group 3 showed a significant reduction in serum fructosamine (-26.2, $p< 0.01$), while in Group 4, there was a significant reduction in both serum fructosamine (-35.9, $p <0.01$) and MBG (-23.6, $p< 0.05$) from baseline values.(Fig 2a and 2b)

Secondary outcome measures

Baseline body weight (kg) and BMI were similar between treatment groups 1-3 (mean 72.6) but higher in treatment group 4(mean 83.8). All treatment groups from 1-4 showed a significant reduction in body weight and BMI post-Ramadan: group 1 (-4.7, $p < 0.01$); group 2 (-1.6, $p < 0.05$); group 3 (-0.3, $p < 0.01$); group 4 (-0.2, $p < 0.05$) (Fig 3).

Safety parameters included tests for hepatic and renal function, serum amylase and lipid profile. At 4 weeks, there was significant reduction in serum triglycerides, cholesterol and LDL levels in treatment group 4 (cholesterol -12.4 $p < 0.05$; LDL -8.6 $p <0.05$; triglycerides -41.9 $p <0.05$) but not in the other three treatment groups. Over a four week period of fasting, there was a significant improvement in transaminases in all treatment groups.(Fig 4a and 4b).

The changes in clinical and metabolic parameters between the four treatment groups after Ramadan fasting are summarized in Table 2.

No adverse events either secondary to diabetes or treatment regimens were reported in any subjects who dropped out of the study. Only one case of hypoglycaemia was reported(in group 3 (Met/SU)).

Discussion

The present study aims to add to the slowly-growing and much-needed evidence-based safe and effective management of type 2 diabetes in Ramadan by comparing the efficacy and safety of the most commonly prescribed OHAs. A majority of studies done on diabetes management during Ramadan have targeted specific treatment modalities studying the safety and efficacy of individual hypoglycaemic regimens[14]; studies comparing different classes of oral hypoglycaemic agents in this respect are lacking.

The primary objective of this study was to determine which if any anti-diabetic treatment group is superior in terms of improving glycaemic control and other metabolic parameters during Ramadan fasting. Keeping in view the limited time span of the study, we selected fructosamine levels and mean blood glucose among glycaemic parameters, over HbA1c, which was less likely to reflect change in glycaemic control over the period of one month. The results showed that the metformin-sitagliptin combination was superior to other treatment regimens in improving both glycaemic control and other clinical and metabolic parameters including body weight, lipid profile and hepatic transaminases. There was no significant difference between the treatment groups in the incidence of hypoglycemic episodes.

Dawn to dusk fasting daily throughout Ramadan involves alteration in diet, sleep and activity patterns; however, whether this has an impact on glycaemic and other metabolic variables is controversial. A recent meta-analysis of clinical trials on the over-all effect of Ramadan fasting in diabetic patients noted many conflicting results[15]. These discrepancies in study findings may be explained by variation in fasting duration, dietary norms and medication regimen between different study populations. Several studies have reported no change in serum HbA1c and fructosamine levels during Ramadan fasting while others have reported a decrease in both values during Ramadan[16].

In our study, the Met/Sita Group showed a significant reduction in blood glucose levels over the 4-week period of Ramadan. A number of studies have assessed the role of DPPIV inhibitors in fasting type 2 diabetic patients. VECTOR, a UK-based comparative study in type 2 diabetic patients fasting during Ramadan proved that subjects on vildagliptin-metformin combination had significantly improved HbA1c post Ramadan, better tolerability and treatment adherence and reduced incidence of hypoglycaemic episodes compared to a sulphonylurea-metformin treatment. Sifri et al in a large multi-centre study concluded that switching to a sitagliptin-based regimen reduced the risk of hypoglycaemia in comparison to a gliclazide-based regimen. In the VIRTUE study, vildagliptin therapy was associated with fewer hypoglycameic episodes compared to SU-based regimen in a large cohort study[17].

Clinical parameters of body weight and BMI showed a significant decrease across all four groups at the end of Ramadan, which can be explained by the overall calorie reduction during Ramadan as participants across the four groups were provided with standardized calorie restricted diet chart appropriate for their BMI. Most studies have reported similar results of reduction in body weight and BMI in response to Ramadan fasting. In healthy, non-diabetic subjects, Salehi et al reported a significant decrease in body weight and BMI following complete fasting in Ramadan[18]. An Algerian study by Khaled and Belbarouton 276 type 2 diabetic females fasting in Ramadan reported significant weight loss (-3.12 kg; $p < 0.01$) together with a decrease in meal frequency and energy consumption[19]. A study on 137 healthy Jordanian adults grouped into overweight, normal and under-weight reported significant weight reduction across all groups.

In our study, the serum levels of triglycerides, total cholesterol and LDL were similar in all participants at baseline. The metformin-sitagliptin treatment group showed a significant decrease in all lipid fractions post-Ramadan; whereas the change was not significant inany of the other three groups. This result cannot be explained by the significant reduction in body weight alone which was observed in all four treatment groups. The effect of Ramadan fasting on lipid profile has also been the topic of a number of studies with variable results depending on the nature and amount of food consumption. Some studies have correlated this change with the change in body weight due to altered dietary regimen during Ramadan, decreased activity and cultural parameters[20]. Similar results were reported by Adlouni et al. in Morocco

with a significant reduction in total cholesterol and triglyceride levels; on the other hand, a Kuwait study showed no significant change in lipid parameters[21,22].

An additional finding was a significant drop in hepatic transaminases, blood urea and creatinine after a four-week fasting period observed in treatment group 4. The role of metformin in reversing amino-transferase abnormalities is established in obese insulin-resistant mice with fatty liver disease[23]. Human trials with metformin have shown mixed results with several pilot studies on subjects with NASH treated with metformin reporting significant reduction in mean transaminase concentrations than dietary treatment alone[24]. Various small studies have also demonstrated the efficacy of sitagliptin in type 2 diabetes with NAFLD in improving hepatic trans-aminases[25].

The EPIDIAR study reported a 5-fold and 7.5-fold increase in incidence of hyperglycaemia and hypo-glycaemia respectively in fasting type 2 diabetic subjects[4]. In our study, only one case of hypoglycaemia occurred in group 3 (metformin/glimepiride). This findingmay be explained by the dietary guidelines provided to the patient, which prescribed slow absor-bing complex carbohydrates in the pre-dawn meal, and exclusion of high-risk diabetic subjects with brittle control or those prone to hypoglycaemic episodes.

Our study had certain limitations. Our treatment groups were defined by the pre-existing therapy, and this precluded blinding of either the participants or the investigators. The very low incidence of hypogly-caemia seen could have been due to failure on the part of the participants to check blood glucose at the appropriate times. We recommend that future studies may use continuous glucose monitoring to get a better picture of hypoglycaemia during a fast.

Conclusion

Type 2 diabetic subjects with moderately well-controlled diabetes can fast safely in Ramadan, with appropriate modification of medication regimen tailored for each patient. In our study, metformin-sitagliptin combination was a safe and effective thera-peutic option in type 2 diabetes in terms of effective-ness in achieving glycaemic control compared to other treatment groups. There is a need for more research on the comparative effectiveness of various therapeutic options, in fasting diabetic patients.

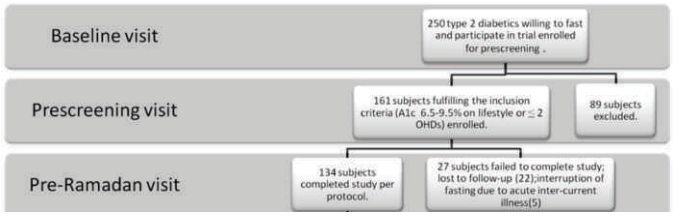


Figure 1: *Consort Diagram:*

Total number of participants was 161. The groups are 1: Lifestyle modification; 2: Metformin monotherapy; 3. Metformin/ Sulfonylurea combination; 4: Metformin/ DPP4 combination. Values reflect change from baseline. BMI: Body mass index. MBG: mean blood glucose. ALT: Alanine amino-transferase. AST: Aspartate aminotransferase

Table 1: *Baseline characteristics of the study population:*

Baseline Characteristics (Mean)	Group 1	Group 2	Group 3	Group 4	Sig.
n	37	37	47	40	
Weight	72.1	72.1	74.3	83.9	.000*
BMI	28.05	28.68	28.58	31.22	.011*
Bilirubin(mg/dl)	0.47	0.48	0.43	0.50	.631
ALT(IU/L)	42.00	39.44	31.80	42.91	.237
AST (IU/L)	30.05	32.16	26.00	32.47	.266
Urea (mg/dl)	27.05	31.32	29.02	31.71	.385
Creatinine (mg/dl)	.78	.78	.81	.85	.678
Cholesterol(mg/dl)	189.74	186.76	194.09	186.06	.844
Triglyceride(mg/dl)	164.74	168.12	203.69	229.79	.251
HDL (mg/dl)	39.95	42.08	40.40	39.74	.858
LDL (mg/dl)	112.47	107.48	111.73	99.91	.460
Amylase (U/L)	79.13	67.40	62.98	67.24	.314
Fructosamine (µmol/L)	282.61	285.04	298.38	307.40	.293
HbA1c(%)	7.01	7.36	7.18	7.58	.355

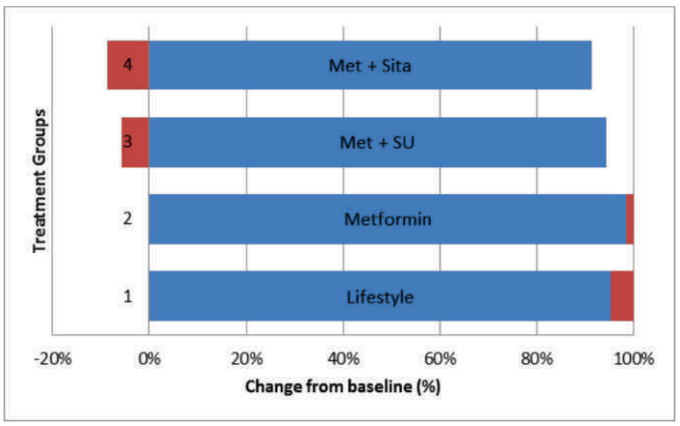


Fig 2: *Change in glycaemic parameters from*

baseline after Ramadan fasting in different treatment groups: The groups are 1: Lifestyle modification; 2: Metformin monotherapy; 3. Metformin/ Sulfonylurea combination; 4: Metformin/ DPP4 combination; Blue: baseline; Red: change from baseline

2a. mean blood glucose

2 b. serum fructosamine

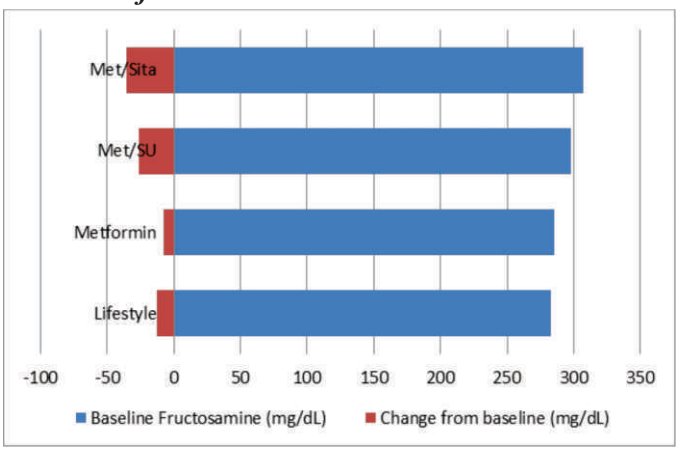


Fig.3: *Change in weight from baseline after Ramadan fasting in different treatment groups: The groups are 1: Lifestyle modification; 2: Metformin monotherapy; 3. Metformin/ Sulfonylurea combination; 4: Metformin/ DPP4 combination; Blue: baseline; Red: change from baseline*

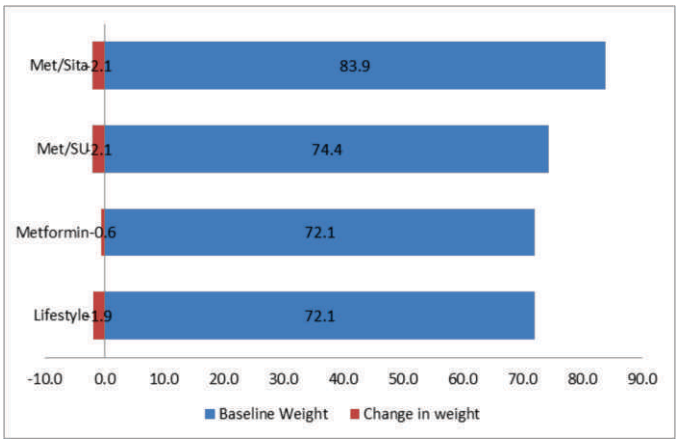
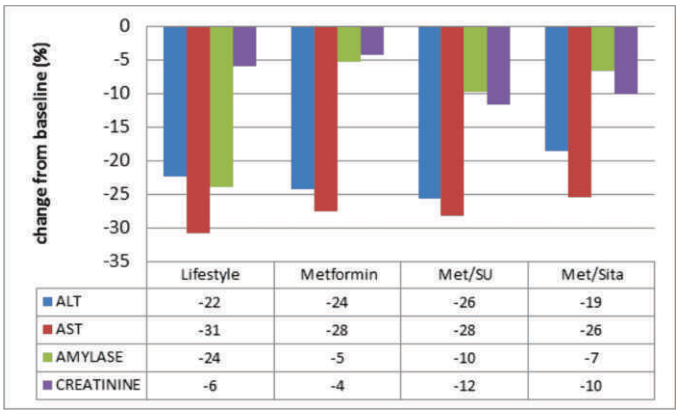


Fig 4: *Safety of different treatment groups during Ramadan fasting. Percentage change from baseline after Ramadan fasting in: a. metabolic parameters; b. lipid profile*

The groups are 1: Lifestyle modification; 2: Metformin monotherapy; 3. Metformin/ Sulfonylurea combination; 4: Metformin/ DPP4 combination



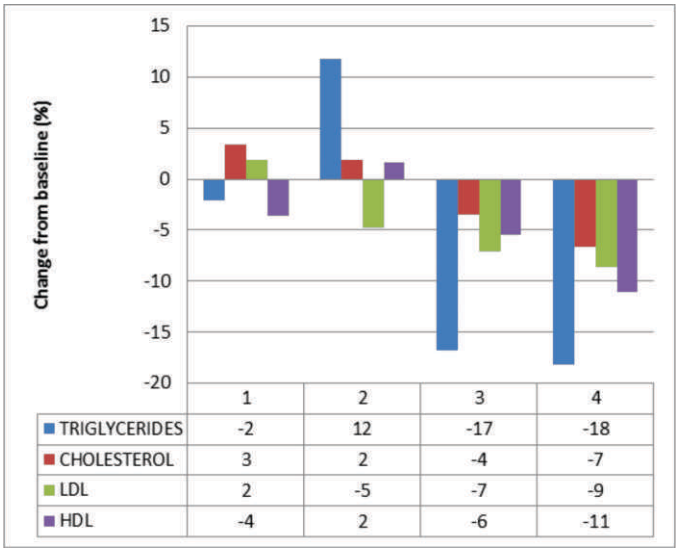


Fig 4a:

Table 2: *Table 2: ANOVA showing in clinical and metabolic parameters from baseline after Ramadan fasting in different treatment groups:*

Parameter (Mean change from baseline)	Group 1	Group 2	Group 3	Group 4	Sig.
Weight (Kg)	-1.40	-0.40	-1.60	-1.77	0.051
BMI	-0.47	-0.16	-0.35	-0.18	0.056
Bilirubin(mg/dl)	0.07	0.05	0.08	0.01	0.670
ALT (IU/L)	-9.37	-9.67	-8.16	-7.97	0.974
AST (IU/L)	-9.26	-8.96	-7.36	-8.29	0.923
Urea (mg/dl)	-2.16	-2.63	-1.91	-3.70	0.788
Creatinine (mg/dl)	-0.05	-0.03	-0.10	-0.09	0.271
Cholesterol (mg/dl)	6.47	3.50	-6.87	-12.38	0.144
Triglyceride (mg/dl)	-3.42	19.79	-34.22	-41.88	0.147
HDL (mg/dl)	-1.42	0.71	-2.31	-4.41	0.207
LDL (mg/dl)	2.16	-5.13	-8.00	-8.61	0.396
Amylase (U/L)	-18.97	-3.54	-6.60	-4.50	0.087
Fructosamine(µmol/L)	-12.67	-8.17	-26.20	-35.97	0.025*
MBG(mg/dl)	+7.23	+2.97	-11.27	-23.56	0.045*

Fig 4b:

*The groups are 1: Lifestyle modification; 2: Metformin monotherapy; 3. Metformin/ Sulfonylurea combination; 4: Metformin/ DPP4 combination. Values reflect change from baseline. BMI: Body mass index. MBG: mean blood glucose. ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. * indicates level of significance p<0.05.*

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Adaptation Of Oral Hygiene Habits In Dental Professionals: A Kap Study

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Abstract

Objective: The present survey was carried out to assess the practice and perception of dental professionals towards their own dental care.

Methods: This cross-sectional study was carried from May 2019 to April 2020, in Altamash Institute of Dental Medicine, Karachi. Ethical approval was obtained from institutional review board. A self-administered questionnaire was developed comprising of 20 questions among the dental personnel (Staff and BDS students) of Altamash Institute of Dental Medicine Karachi, Pakistan, to assess their practice and care, regarding their own oral hygiene. Responses were collected through both, the hard copy and an online google form link. Data was evaluated for 176 complete forms. For all the asked questions, a comparison was also made between male and female candidates, and between their academic levels. For all the variable as categorical values, percentages were tabulated using SPSS 21.

Results: The results indicated that not all the dental professionals had their same practice to maintain oral hygiene. Not all of them were following the proper theoretical knowledge. From their choices of toothpastes to their habits of flossing and using additional aids for maintaining oral hygiene, majority factors varied individually in spite of the fact that there is well-awareness of consequences of negligence.

Conclusion: It was found that not all the dental practitioners follow the proper guidelines to maintain oral hygiene, and not all of them follow the instructions they give to their patients.

Key Words: Oral Hygiene, Dental Professionals, Tooth Paste, Mouth Wash, Dentistry, Oral Hygiene Maintenance, Dental practitioners.

Introduction

The negative effects of abysmal oral health conditions on health and quality of life, cannot be ignored.[1] There can be multiple consequences of poor oral hygiene, the most common of which is bad odor from mouth or Halitosis. Poor oral hygiene can be a major cause for it, which includes, dental plaque and caries, gingivitis, periodontitis, malignancies, dry mouth on the other hand may or may not be a contributing factor, etc.[2-6] The purpose of dentistry is to respond to the patients need and desires so as to restore the patient's oral health to normal contour, function, comfort, esthetics & speech.[7,8] Dentists with proper knowledge and oral health methods can contribute to the oral education and act as role models for the general community.[9] For transferring proper knowledge and awareness to the patient, a dental practitioner should first practice himself on all the suggestions before he advises to patients.

Due to professional knowledge of the prevention of oral diseases, dentists hold a key position in providing a positive role for oral self-care and to instruct and encourage their patients to maintain good oral health behavior.[10]

It was hypothesized that dentists with better orientation and greater knowledge of preventive care would have better oral hygiene behavior and dental service utilization. When talking about the preventive orientation in dentistry, it is determined by the state-

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ment that "Preventive training and practice should be increased both in undergraduate education and in dental practice".[11] Education contributes to improve knowledge, and as a level of education increases there is improvement in the level of oral health, awareness, attitude and behavior.[12]

Dentistry as a profession is known to be stressful both physically and mentally thus demanding more responsibility by dentists for their own general and oral health well-being.[10] Health related knowledge, attitudes and beliefs acquired through professional education could therefore be the most significant individual level factors influencing their intermediate and final oral health outcome. In any society, dental professional should thus be a model group regarding oral health.[11]

Thus, the present study was designed and executed among dental practitioners in a dental institute to assess their own oral hygiene awareness, practice and maintenance, with the main objective that whether they put the same efforts in maintaining their oral health or not as they advise their patients.

Methods

The current cross-sectional study was conducted with informed consent, from March 2019 to February 2020. Ethical approval was obtained from institutional review board. A self-administered questionnaire was developed comprising of 20 questions among the dental personnel of Altamash Institute of Dental Medicine Karachi, Pakistan, to assess their practice and care, regarding their own oral hygiene. Responses were collected through both, the hard copy and an online google form link. Around 200 questionnaires were distributed to get the responses and data was evaluated for 176 completed forms with appropriate answers.

STATISTICS: The statistical analysis was done through SPSS version 21. Descriptive analysis was done and Percentages were calculated for all the variables. Chi-square was applied for all the question for comparison between male and females, and also for academic qualifications. The p-value of 0.05 or less was considered significant.

Results:

The total number of dental personnel targeted were 200, out of which 37.5% were male and 62.5% were female. For age 60.2 % patients were in 18-24-year age limit, 32.4 % patients were 25-34 years age group whereas 7.4 % patients were above 34 year of age. For academic levels, 40.3 % patients were undergrads, 44.3% patients were graduates whereas 15.3 %. Married patients were 15.9% whereas unmarried were 84.1%. 65.3% were the ones who brush twice a day as per recommended by American Dental Association. Only 36.4% said that they brush their teeth before going to bed and after breakfast. Among all the participants, 56.3% brush their teeth for a recommended time of 2 mins and 62.5% used soft tooth brushes. 95.5% of the candidates used tooth brush and toothpaste to maintain their oral hygiene, among which 75% used fluoridated tooth pastes. 25% were the ones who used pea sized quantity of toothpaste. 50.6% used mouth wash and 26.1% used dental floss as an additional aid to clean their teeth. It concludes that 43.2% dental professionals were aware of the right time to change their toothbrush and 40.3% of the dental professionals practice the correct method of brushing. To remove the food debris from the teeth 46.6% of our participants used dental floss.

It was indicated that, 80.7% of the participants believed that oral health is overall health. Taking para-functional habits into view, 20.5% said that they possess para-functional habits, 59.7% said that they do not and 8.5% quit. 34.7% complained of bleeding gums occasionally, 5.7% had bleeding gums while brushing and 52.8% never experienced bleeding gums. 60.8% dental professionals did not have halitosis at all, 27.8% had it occasionally whereas 3.4% had it always.

Considering the eating and drinking habits of our participants, 45.5% were the one who ate sweet products anytime of the day whereas 35.8% had them once a week. 48.9% were the ones who had carbonated drinks once a week and 29.5% had them anytime of the day. 25.6% get their teeth professionally cleaned every 6 months and 40.3% get them cleaned once a year. 60% dentists claimed that they take care of their own oral hygiene as they instruct their patients and 11.4% did not take care in the same way. As shown in Table No.1

When comparison was made using between the male

and female and the academic level for all the comparison all of the variables either showed nonsignificant results or chi-square test was not applicable due to decrease cell count. As shown in Table No. 2

Discussion

Today, it is well-known that abysmal oral health conditions have a negative effect on overall health and quality of life in people.[3] The purpose of dentistry is to respond to the patients' needs and desires i.e. to restore the patient's oral health to normal contour, function, comfort, esthetics & speech.[9,10] Oral hygiene is the practice of keeping the mouth clean by brushing and flossing to halt tooth and gum diseases. Good oral hygiene has shown to contribute immensely to the prevention of oral diseases.[15]

According to our research carried out among the dental professionals, 65.3% of the participants were the ones who brushed twice daily. Similar results were found out in a research carried out in 2002 by A. Merchant et al, which demonstrated that 70% of the participants brushed twice daily.[16] In a study carried out among the Mongolian dentists in 2004, it was concluded that 81% of the practitioners brushed twice a day and 62% used fluoridated toothpastes whereas in our study the fluorinated tooth paste utilization is 75%.[13]

Table 1: *Participants Characteristics and Oral Hhygiene Details (N=176)*

variable	Options	Percentage	variable	Options	Percentage	variable	Options	Percentage
Gender	Male	36.9%	**Hygiene Methods**	Tooth Brush + Tooth Paste	95.5%	**Oral Health is Overall Health**	Yes	80.7%
	Female	63.1%		Manjun	2.8%		No	10.2%
Age	18-24	60.2%		Miswak	1.1%		May be	6.3%
	15-34	32.4%		Tooth Brush + Miswak	0.6%		Don't Know	2.8%
	>34	7.4%	**Kind of Toothpaste**	Fluoridated	75%	**Para-functional Habits**	Yes	20.5%
Academic Level	Undergraduate	40.3%		Non-fluoridated	5.1%		No	59.7%
	Graduate	44.3%		Herbal	11.4%		Quit	8.5%
	Post-Graduate	15.3%		Don't Know	8.5%		Never Noticed	11.4%
Marital Status	Married	15.9%	**Quality of Toothpaste**	Full length of Bristles	34.7%	**Bleeding Gums**	On brushing	5.7%
	Unmarried	83%		Half -length of Bristles	38.1%		Occasionally	34.7%
Frequency of Brushing per day	Once	23.9%		Pea Sized	25%		Not at all	52.8%
	Twice	65.3%		Just Peck	2.3%		Never Noticed	6.8%
	Thrice	9.7%	**Additional Aids**	Mouth Wash	50.6%	**Halitosis**	Always	3.4%
	More	1.1.%		Floss	26.1%		Occasionally	27.8%
Preferred time of Brushing	Before Bed + After Breakfast	36.4%		None	16.5%		Not at all	60.8%
	Before Bed + Before Breakfast	44.9%		Other	6.8%		Never Noticed	8%
	After Every Meal	10.2%	**Time to Change Brush**	Every Month	13.1%	**Frequency of Eating Sweets**	Anytime	45.5%
	After Breakfast	8.5%		Every 2 Months	34.7%		Frequent intervals	10.2%
Time Duration to Brush	< 1 min	24.4%		Every 3 Months	43.2%		After Dinner	8.5%
	2 min	56.3%		Until Bristles Wear out	9.1%		Once a week	35.8%
	3 min	16.5%	**Direction of Brushing**	Vertical	9.1%	**Use of Carbonated Drinks**	Anytime	29.5%
	>3 min	2.8%		Horizontal	11.4%		Frequent intervals	9.1%
Type of Brush	Soft	62.5%		Circular	40.3%		Once a day	12.5%
	Hard	4.5%		Combination	39.2%		Once a week	48.9%
	Medium	29%	**Food Debris Removal**	Floss	46.6%	**Professional Cleaning**	Every 4 Months	9.15
	Don't Know	4.2%		Tooth-Pick	25%		Every 6 Months	25.6%

Another study by V. Gopinath in 2010 showed that, 55.9% respondents brushed twice a day and 55.1% of the practitioners used fluoridated toothpastes and 19.6% followed the recommended instructions to maintain oral hygiene, whereas in our research, 75% people used fluoridated toothpastes and 60.2%

Table 2: *Comparison of Male and Female and Academic Levels for all the Variables (N=176)*

Toothpaste and Brushing Details	Options	Male n=66	Female n=110	p-value	U/grad n=71	Grad n=78	Post/grad n=27	p-value
Frequency of brushing	Once	23	19	NA	14	18	10	NA
	Twice	33	82		52	51	12	
	Thrice	8	9		5	8	4	
	More	2	0		0	1	1	
Preferred Time to Brush	Before Bed + After Breakfast	22	42	0.54	26	29	9	NA
	Before Bed + Before Breakfast	28	51		35	33	11	
	After Every Meal	9	9		4	11	3	
	After Breakfast	7	8		6	5	4	
Time Duration to Brush	< 1 min	9	34	NA	19	17	7	NA
	2 min	47	52		45	41	13	
	3 min	9	20		6	17	6	
	>3 min	1	4		1	3	1	
Type of Toothbrush	Soft	40	70	NA	50	47	13	NA
	Hard	2	6		3	4	1	
	Medium	20	31		16	24	11	
	Don't know	4	3		2	3	2	
Kind of Toothpaste	Fluoridated	48	84	NA	54	58	20	NA
	Non-fluoridated	2	7		2	5	2	
	Herbal	10	10		9	8	3	
	Don't Know	6	9		6	7	2	
Quantity of Toothpaste	Full length of Bristles	24	37	NA	23	27	11	NA
	Half -length of Bristles	23	44		31	27	9	
	Pea Sized	15	29		17	23	4	
	Just Peck	4	0		0	1	3	
Time to Change Brush	Every Month	11	12	0.087	11	8	4	NA
	Every 2 Months	20	41		22	30	9	
	Every 3 Months	25	51		32	33	11	
	Until Bristles Wear out	10	6		6	7	3	
Direction of Brushing	Vertical	10	6	0.065	5	6	5	NA
	Horizontal	10	10		7	10	3	
	Circular	25	46		29	30	12	
	Combination	21	48		30	32	7	
Duration between Meal and Brushing	5 min	6	9	0.086	7	5	3	NA
	10 min	14	17		11	15	5	
	15 min	24	26		20	23	7	
	I don't brush after meals	22	58		33	35	12	
Food Debris Removal	Floss	29	53	NA	30	43	9	NA
	Tooth-Pick	15	29		21	14	9	
	Nothing	14	23		14	16	7	
	Others	8	5		6	5	2	
Hygiene Methods	Tooth Brush + Tooth Paste	59	109	NA	70	75	23	NA
	Manjun	4	1		1	1	3	
	Miswak	2	0		0	2	0	
	Tooth Brush + Miswak	1	0		0	0	1	
Additional Aids	Mouth Wash	27	62	NA	35	36	18	NA

Chi square test applied, * statistically significant difference, NA=chi square not applicable due to decreased cell count

followed the recommended instructions.[17]

Mechanical methods of plaque control e.g. the effective way of using a toothbrush and dental floss can aid oral health and decrease the incidence of dental discomforts and abnormalities.[18-20] Comparing the genders, in a research carried out in 2019 showed that females were more active in flossing their teeth than men, just like our research showing females to be more proficient in taking extra steps for oral care.[21] A research carried out in 2019 signified that 70% of their participants brushed their teeth only once a day, leading to dental issues. Our research had results in accordance to a study conducted in India in 2014, which stated that their participants had a habit of brushing two times a day.[22,23]

In a study carried out in Brazil and four Asian countries, it was concluded that majority of the candidates brushed once a day which was dissimilar to our study.[24] Our research revealed that 45.5% of the practitioners could take sugar products anytime of the day unlike the members of the study in 2004, where 52% of the practitioners consumed sugar containing foods for less than once a day.[13]

Taking additional aids for oral hygiene into consideration, 50.6% and 26.1% of our practitioners used mouth wash and dental floss, whereas according to a study in 2002 by A. Merchant et al. 56.3% of their

Table 3: *Comparison of Male and Female and Academic Levels for all the Variables (contd)*

Health and Habits	Options	Male n=66	Female n=110	p-value	U/grad n=71	Grad n=78	Post/grad n=27	p-value
Oral Health is Overall Health	Yes	52	90	NA	56	66	20	NA
	No	8	10		8	5	5	
	May be	4	7		6	5	0	
	Don't Know	2	3		1	2	2	
Bleeding from Gums	On Every Brushing	7	3	NA	4	2	4	NA
	Occasionally	17	44		26	26	9	
	Not at all	35	58		35	47	11	
	Never Noticed	7	5		6	3	3	
Para-functional Habits	Yes	13	23	0.143	15	16	5	NA
	No	34	71		37	51	17	
	Quit	8	7		8	5	2	
	Never Noticed	11	9		11	6	3	
Halitosis	Always	4	2	NA	3	1	2	NA
	Occasionally	18	31		18	23	8	
	Not at all	36	71		46	48	13	
	Never Noticed	8	6		4	6	4	
Frequency of eating sweets	Anytime	34	46	0.600	37	31	12	NA
	Frequent Intervals	5	13		6	10	2	
	After Dinner	5	10		7	3	5	
	Once a week	22	41		21	34	8	
Use of Carbonated Drinks	Anytime	22	30	0.341	23	16	13	NA
	Frequent Intervals	6	10		8	6	2	
	Once a day	11	11		10	8	4	
	Once a week	27	59		30	48	8	
Professional Cleaning	Every 4 Months	8	8	0.374	6	3	7	NA
	Every 6 Months	13	32		19	23	3	
	Once a Year	26	45		24	34	13	
	Never	19	25		22	18	4	
Oral Care as Instructed	Yes	41	65	0.174	38	51	17	0.650
	No	9	11		11	7	2	
	Occasionally	11	31		18	18	6	
	Never Noticed	5	3		4	2	2	

Chi square test applied, * statistically significant difference, NA=chi square not applicable due to decreased cell count

participants used dental floss on a regular basis.[16] Contrary to this, in a study in 2012 by Baseer et al, less than 50% of the candidates used dental floss and mouth wash and less than 10% used Miswak and toothpick for their oral hygiene.[25] In the same manner our research indicates least use of additional aids i.e. 1.1% of our candidates used Miswak and 0.6% used toothbrush + Miswak, though 25% were using toothpick as part of their routine oral hygiene.

A research published in 2008 concluded that 79.6% of their participants brushed twice out of which 73.8% brushed in circular motion. On the other hand, our survey showed that 40.3% were the ones brushing in circular motions.[26] An analytical study in Saudi Arabia in 2020 declared that 57% of the women were doing brush in circular motion just like our study where majority of the women were doing the correct strokes of toothbrush. It's a well-known fact to use a brush with soft bristles for normal healthy teeth, 54% of the male candidates for this study expressed that they used soft type of toothbrush, unlike the study we conducted where more females used soft type of tooth brushes.[27]

Para-functional habit can be one of the major causes of poor oral conditions. A prevalence of these habits in a study in Rehman College of Dentistry, Peshawar, showed that 30% of the undergraduates had and 70% of them had no para-functional habits, similar to our survey where majority of the undergraduates had no such habits.[28] Another research held 2017 in Lahore revealed that 38.3% of the undergraduates consumed carbonated drinks on daily basis, whereas 5.28% (10 out of 176) of the undergraduates in our study unveiled that they consumed carbonated drinks at least once a day. [29]

The current research we carried out clearly states that not all the dental professionals take proper measures to maintain a better oral hygiene, regardless the amount of knowledge they have through their theoretical and clinical experiences. This research was carried out on a limited number of candidates and in a limited environment. Further researches can be done on a vast majority of people giving more data about the title.

Conclusion

There is lack of practice towards oral hygiene maintenance by dental practitioners and it is found that not all of them follow proper guidelines and instructions as given to their patients. Further research would be needed for assessment. Also, there is need of improvement in practitioner's knowledge, behavior and attitude towards prevention to enable them to provide their patients and reinforce positive attitude for the same.

Author's Contribution

HW: Idea, Research Work
DM: Data Collection, write up
RA: Supervision, proof reading the manuscript
SW: Data evaluation, statistical work of study

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Safety and Efficacy of Four Anti-Diabetic Treatment Regimens in Patients with Type 2 Diabetes during Ramadan fasting: A Comparative Study

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Abstract

Objective: To compare the anti-hyperglycaemic effectiveness and safety of different anti-diabetic treatment regimens in fasting type 2 diabetic subjects during Ramadan.

Methods: This was a prospective four-week study of 161 subjects with type 2 diabetes (HbA1c 6.5-8.5%) during Ramadan, at the Department of Endocrinology & Metabolism, Services Hospital, Lahore, Pakistan. Study participants were randomized into four treatment groups: lifestyle modification only (group 1: lifestyle), metformin monotherapy (group 2: Metformin), metformin and sulfonylurea (group 3: Met/SU) and metformin and DPP4 inhibitor (group 4: Met/Sita). Anthropometric and biochemical evaluation were done one week before onset of Ramadan and in the last week of Ramadan. 134 patients completed the study protocol and repeated measures ANOVA was used to compare the groupsfor change inclinical and laboratory parameters from pre-Ramadan baseline.

Results: There was a significant decrease in mean blood glucose (mg/dL) and fructosamine(µmol/L)levels post-Ramadan in all treatment groups, with the greatest reduction seen in Met/Sita treatment group [(fructosamine -35.9, $p < 0.01$), mean blood glucose (-23.6, $p < 0.05$)]. In the safety analysis, Met/Sita group also showed improvement in several metabolic parameters including lipid profile (cholesterol -12.4 mg/dL, $p < 0.05$; LDL -8.6mg/dL, $p < 0.05$; triglycerides -41.9mg/dL, $p < 0.05$) and transaminases. Only one patient among the study population reported a hypoglycaemic event (Met/SU group).

Conclusion: During Ramadan fasting, combination treatment with metformin-sitagliptinin type 2 diabetic subjects resulted in the greatest improvement in glycaemic control without causing hypoglycaemia, and was associated with improvement in lipid profile and hepatic transaminases.

Key words: Metformin, sitagliptin, fasting, Ramadan, type 2 diabetes, glucose control

Introduction:

Islam is the second largest world religion with an estimated 1.8 billion followers.[1] Ramadan fasting is obligatory for all adult Muslims; however, exemption is granted in certain situations including any form of ill-health likely to be severely affected by fasting.[2] Despite this laxity, Muslims are keen to fulfill this obligation irrespective of their illness, diabetic patients being no exception. An estimated 40-50 million diabetic Muslims fast during Ramadan[3]. As reported by the large multi-centric Epidemiology of Diabetes and Ramadan study (EPIDIAR), 79% of type 2 diabetic subjects and 43% of type 1 observe Ramadan fasting annually.[4] Many of the Muslim majority countries have the highest percentage of diabetic patients, including Pakistan, which has a reported diabetes prevalence of ~12%, in a population of 220million,ranking 6th among world nations[5].

Ramadan is a lunar-based month and the length and timing of fasting vary each year according to the seasons and geographical location. Fasting during this month requires abstinence from food, fluids and medicines from daybreak to dusk daily[6]. As this is opposed to the conventional dietary pattern recommended in diabetes, fasting can be expected to

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cause erratic glycaemic control and metabolic derangements even in well-controlled diabetic patients.As the frequency of self-monitoring of blood glucose during fasting is also reduced, these glycaemic swings generally go undetected. Dehydration and stroke from prolonged fasting in summer months are also potential risks. Consequently, the first International Congress on Health and Ramadan, recommended that patients suffering from severe co-morbid conditions should avoid fasting[7].

Current recommendations have clearly defined categories of diabetic patients at varying degrees of risk from fasting[8]. The epidemiological evidence available on the impact of Ramadan fasting on diabetes control concludes that fasting is well-tolerated in stable type 2 diabetic patients treated either with diet alone or combined diet and oral hypoglycaemic agents (OHA)[9]. The International Diabetes Federation has issued comprehensive guidelines on diabetes management during Ramadan in collaboration with Diabetes and Ramadan International Alliance[10].

For the fasting type 2 diabetic patient, the aim of treatment is to minimize the frequency of hypoglycamia and maintain euglycaemia taking into consideration religious constraints. The recent years have seen an increase in therapeutic options for glucose control in diabetes. Studies have been done on the safety and efficacy of OHAs during Ramadan targeting specific treatment modalities including sulfonylureas, metformin, biphasic insulin and DPP-IV inhibitors, however, no consensus exists about the superiority in terms of safety and efficacy of any one regimen[11].

This study compared different anti-diabetic treatment regimens in terms of their anti-hyperglycaemic effectiveness and safety profile during Ramadan fasting in type 2 diabetic patients.

Methods

This was an open-label, single-centre, interventional study conducted in Department of Endocrinology & Metabolism, Services Hospital, Lahore during the month of Ramadan. The duration of fasting on average was more than 15 hours and ambient temperatures approximately 38 C. The study was designed in accordance with Declaration of Helsinki and the protocol was reviewed and approved by the Institutional Review Board.

Subject recruitment was done in three phases from among the diabetic patients registered with the Department: In the first phase about three months before start of Ramadan, 252 type 2 diabetic subjects intending to fast throughout Ramadan and willing to participate in the study were enrolled and their written informed consent obtained. All subjects were reminded about the specific exemption from fasting in disease states and the potential risks of acute complications. In the second phase, screening was done for underlying complications and their glycaemic control was assessed to confirm eligibility. Final screening was carried out one month prior to Ramadan onset.

The eligibility criteria were type 2 diabetes, age more than 18 years, on either diet alone or ≤ 2 oral anti-diabetic agents with good to moderate control (HbA1c 6.5-8.5%), in the three months preceding Ramadan. Exclusion criteria included any contraindications either to fasting or to any of the trial medication (metformin, sufonylurea or sitagliptin), pregnancy, clinical or biochemical evidence of co-morbid conditions, advanced diabetes complications, frequent hypoglycaemic episodes, or on SGLT2 inhibitors.

One week prior to start of Ramadan, the enrolled 161 participants were called to the clinic in fasting state for baseline clinical assessment and anthropometry. Fasting capillary glucose levels were checked by point-of-care device (OptiumXceed®, Abbott Diabetes Care). Venous whole blood samples were collected for CBC and HbA1c, and serum was separated and stored at -20C for assays forliver and renal function tests, RFTs, serum amylase, lipid profile and serum fructosamine.

The enrolled subjects were then assigned to 1 of 4 intervention groups based on the treatment regimen they were already taking: Group 1: lifestyle modification alone (n=37); Group 2: Metformin monotherapy (n=37); Group 3 Metformin/ Glimepiride combination (n=47); Group 4:Metformin/ Sitagliptin combination (n=40). Pre-Ramadan dose adjustment was done in accordance with standard Ramadan guidelines for achieving optimal glycaemic control.

Participants were provided with a standardized 1200 calorie diet chart and a food diary, to record the type

and amount of food and beverages taken at pre-dawn and sunset meal throughout Ramadan. Participants were advised to shift their exercise (30 minutes walk) schedule to after the post-sunset meal. A capillary blood glucose monitoring device (Optium Xceed®, Abbott Diabetes Care) and adequate glucose strips were provided to each participant for glucose monitoring three times daily during Ramadan: half hour before pre-dawn meal, at mid-day and 1 hour before sunset meal with additional monitoring in case of suspected hypoglycaemia. Participants were given handouts on hypoglycaemia recognition, with instructions to break the fast in case of hypoglycaemia (BSL< 70mg/dl).

During the follow-up visit (which was done just before the end of Ramadan, to avoid a clash with the Eid festival, which immediately follows Ramadan) the food diaries, blood glucose charts and adverse event charts were collected. The total number of days fasted by each participant was also noted. Re-estimation of body weight, height and waist circumference was done and venous samples in fasting state were collected.

The primary outcome measure was change in glycaemic profile (measured by serum fructosamine and mean blood glucose (MBG) during Ramadan fasting, by measuring. The secondary outcomes were change in body weight and BMI, and safety parameters (fasting lipid profile, liver and renal function)after Ramadan fasting.

Statistical Analysis:

Data were analyzed using SPSS for Windows version 11.0 (SPSS Inc., Chicago, IL, USA) and presented as means ± SD. Repeated measures ANOVA was done to compare the change from baseline among the different treatment groups. $p<0.05$ was considered statistically significant.

Results

The sequence of study enrollment, randomization and follow-up is depicted in Figure 1. The final study population included 161 subjects out of which 134 subjects completed the four-week study per protocol with small difference in retention in each group. 27 subjects failed to complete the study with 22 being lost to follow-up and 5 compelled to interrupt fasting due to acute inter-current illness. All treatment regimens were well-tolerated by the patients. The baseline characteristics of the participants in different treatment were comparable, except mean body weight, which was higher in group 4 participants (Table 1).

Primary outcome measures

The changes in clinical and metabolic parameters between the four treatment after 4 week period of Ramadan fasting were compared by ANOVA. Glycaemic measures, including serum fructosamine (µmol/L)and mean blood glucose (MBG) levels (mg/dL) pre and post-Ramadan reflected a decline in all four treatment groups, however, Group 3 showed a significant reduction in serum fructosamine (-26.2, $p< 0.01$), while in Group 4, there was a significant reduction in both serum fructosamine (-35.9, $p <0.01$) and MBG (-23.6, $p< 0.05$) from baseline values.(Fig 2a and 2b)

Secondary outcome measures

Baseline body weight (kg) and BMI were similar between treatment groups 1-3 (mean 72.6) but higher in treatment group 4(mean 83.8). All treatment groups from 1-4 showed a significant reduction in body weight and BMI post-Ramadan: group 1 (-4.7, $p < 0.01$); group 2 (-1.6, $p < 0.05$); group 3 (-0.3, $p < 0.01$); group 4 (-0.2, $p < 0.05$) (Fig 3).

Safety parameters included tests for hepatic and renal function, serum amylase and lipid profile. At 4 weeks, there was significant reduction in serum triglycerides, cholesterol and LDL levels in treatment group 4 (cholesterol -12.4 $p < 0.05$; LDL -8.6 $p <0.05$; triglycerides -41.9 $p <0.05$) but not in the other three treatment groups. Over a four week period of fasting, there was a significant improvement in transaminases in all treatment groups.(Fig 4a and 4b).

The changes in clinical and metabolic parameters between the four treatment groups after Ramadan fasting are summarized in Table 2.

No adverse events either secondary to diabetes or treatment regimens were reported in any subjects who dropped out of the study. Only one case of hypoglycaemia was reported(in group 3 (Met/SU)).

Discussion

The present study aims to add to the slowly-growing and much-needed evidence-based safe and effective management of type 2 diabetes in Ramadan by comparing the efficacy and safety of the most commonly prescribed OHAs. A majority of studies done on diabetes management during Ramadan have targeted specific treatment modalities studying the safety and efficacy of individual hypoglycaemic regimens[14]; studies comparing different classes of oral hypoglycaemic agents in this respect are lacking.

The primary objective of this study was to determine which if any anti-diabetic treatment group is superior in terms of improving glycaemic control and other metabolic parameters during Ramadan fasting. Keeping in view the limited time span of the study, we selected fructosamine levels and mean blood glucose among glycaemic parameters, over HbA1c, which was less likely to reflect change in glycaemic control over the period of one month. The results showed that the metformin-sitagliptin combination was superior to other treatment regimens in improving both glycaemic control and other clinical and metabolic parameters including body weight, lipid profile and hepatic transaminases. There was no significant difference between the treatment groups in the incidence of hypoglycemic episodes.

Dawn to dusk fasting daily throughout Ramadan involves alteration in diet, sleep and activity patterns; however, whether this has an impact on glycaemic and other metabolic variables is controversial. A recent meta-analysis of clinical trials on the over-all effect of Ramadan fasting in diabetic patients noted many conflicting results[15]. These discrepancies in study findings may be explained by variation in fasting duration, dietary norms and medication regimen between different study populations. Several studies have reported no change in serum HbA1c and fructosamine levels during Ramadan fasting while others have reported a decrease in both values during Ramadan[16].

In our study, the Met/Sita Group showed a significant reduction in blood glucose levels over the 4-week period of Ramadan. A number of studies have assessed the role of DPPIV inhibitors in fasting type 2 diabetic patients. VECTOR, a UK-based comparative study in type 2 diabetic patients fasting during Ramadan proved that subjects on vildagliptin-metformin combination had significantly improved HbA1c post Ramadan, better tolerability and treatment adherence and reduced incidence of hypoglycaemic episodes compared to a sulphonylurea-metformin treatment. Sifri et al in a large multi-centre study concluded that switching to a sitagliptin-based regimen reduced the risk of hypoglycaemia in comparison to a gliclazide-based regimen. In the VIRTUE study, vildagliptin therapy was associated with fewer hypoglycameic episodes compared to SU-based regimen in a large cohort study[17].

Clinical parameters of body weight and BMI showed a significant decrease across all four groups at the end of Ramadan, which can be explained by the overall calorie reduction during Ramadan as participants across the four groups were provided with standardized calorie restricted diet chart appropriate for their BMI. Most studies have reported similar results of reduction in body weight and BMI in response to Ramadan fasting. In healthy, non-diabetic subjects, Salehi et al reported a significant decrease in body weight and BMI following complete fasting in Ramadan[18]. An Algerian study by Khaled and Belbarouton 276 type 2 diabetic females fasting in Ramadan reported significant weight loss (-3.12 kg; $p < 0.01$) together with a decrease in meal frequency and energy consumption[19]. A study on 137 healthy Jordanian adults grouped into overweight, normal and under-weight reported significant weight reduction across all groups.

In our study, the serum levels of triglycerides, total cholesterol and LDL were similar in all participants at baseline. The metformin-sitagliptin treatment group showed a significant decrease in all lipid fractions post-Ramadan; whereas the change was not significant inany of the other three groups. This result cannot be explained by the significant reduction in body weight alone which was observed in all four treatment groups. The effect of Ramadan fasting on lipid profile has also been the topic of a number of studies with variable results depending on the nature and amount of food consumption. Some studies have correlated this change with the change in body weight due to altered dietary regimen during Ramadan, decreased activity and cultural parameters[20]. Similar results were reported by Adlouni et al. in Morocco

with a significant reduction in total cholesterol and triglyceride levels; on the other hand, a Kuwait study showed no significant change in lipid parameters[21,22].

An additional finding was a significant drop in hepatic transaminases, blood urea and creatinine after a four-week fasting period observed in treatment group 4. The role of metformin in reversing amino-transferase abnormalities is established in obese insulin-resistant mice with fatty liver disease[23]. Human trials with metformin have shown mixed results with several pilot studies on subjects with NASH treated with metformin reporting significant reduction in mean transaminase concentrations than dietary treatment alone[24]. Various small studies have also demonstrated the efficacy of sitagliptin in type 2 diabetes with NAFLD in improving hepatic trans-aminases[25].

The EPIDIAR study reported a 5-fold and 7.5-fold increase in incidence of hyperglycaemia and hypo-glycaemia respectively in fasting type 2 diabetic subjects[4]. In our study, only one case of hypoglycaemia occurred in group 3 (metformin/glimepiride). This findingmay be explained by the dietary guidelines provided to the patient, which prescribed slow absor-bing complex carbohydrates in the pre-dawn meal, and exclusion of high-risk diabetic subjects with brittle control or those prone to hypoglycaemic episodes.

Our study had certain limitations. Our treatment groups were defined by the pre-existing therapy, and this precluded blinding of either the participants or the investigators. The very low incidence of hypogly-caemia seen could have been due to failure on the part of the participants to check blood glucose at the appropriate times. We recommend that future studies may use continuous glucose monitoring to get a better picture of hypoglycaemia during a fast.

Conclusion

Type 2 diabetic subjects with moderately well-controlled diabetes can fast safely in Ramadan, with appropriate modification of medication regimen tailored for each patient. In our study, metformin-sitagliptin combination was a safe and effective thera-peutic option in type 2 diabetes in terms of effective-ness in achieving glycaemic control compared to other treatment groups. There is a need for more research on the comparative effectiveness of various therapeutic options, in fasting diabetic patients.

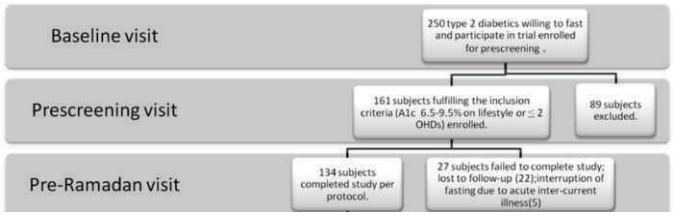


Figure 1: *Consort Diagram:*

Total number of participants was 161. The groups are 1: Lifestyle modification; 2: Metformin monotherapy; 3. Metformin/ Sulfonylurea combination; 4: Metformin/ DPP4 combination. Values reflect change from baseline. BMI: Body mass index. MBG: mean blood glucose. ALT: Alanine amino-transferase. AST: Aspartate aminotransferase

Table 1: *Baseline characteristics of the study population:*

Baseline Characteristics (Mean)	Group 1	Group 2	Group 3	Group 4	Sig.
n	37	37	47	40	
Weight	72.1	72.1	74.3	83.9	.000*
BMI	28.05	28.68	28.58	31.22	.011*
Bilirubin(mg/dl)	0.47	0.48	0.43	0.50	.631
ALT(IU/L)	42.00	39.44	31.80	42.91	.237
AST (IU/L)	30.05	32.16	26.00	32.47	.266
Urea (mg/dl)	27.05	31.32	29.02	31.71	.385
Creatinine (mg/dl)	.78	.78	.81	.85	.678
Cholesterol(mg/dl)	189.74	186.76	194.09	186.06	.844
Triglyceride(mg/dl)	164.74	168.12	203.69	229.79	.251
HDL (mg/dl)	39.95	42.08	40.40	39.74	.858
LDL (mg/dl)	112.47	107.48	111.73	99.91	.460
Amylase (U/L)	79.13	67.40	62.98	67.24	.314
Fructosamine (µmol/L)	282.61	285.04	298.38	307.40	.293
HbA1c(%)	7.01	7.36	7.18	7.58	.355

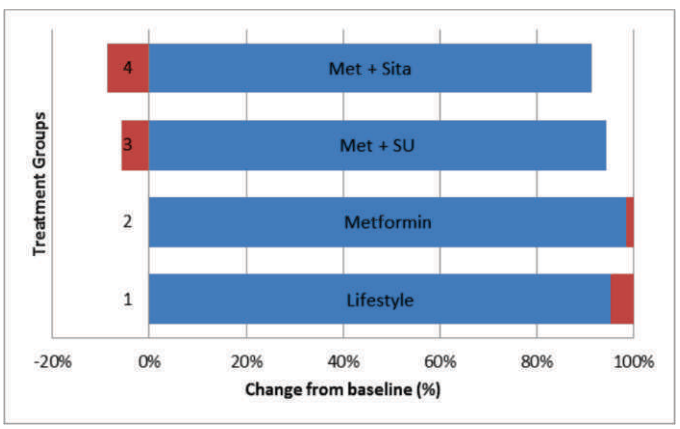


Fig 2: *Change in glycaemic parameters from*

baseline after Ramadan fasting in different treatment groups: The groups are 1: Lifestyle modification; 2: Metformin monotherapy; 3. Metformin/ Sulfonylurea combination; 4: Metformin/ DPP4 combination; Blue: baseline; Red: change from baseline

2a. mean blood glucose

2 b. serum fructosamine

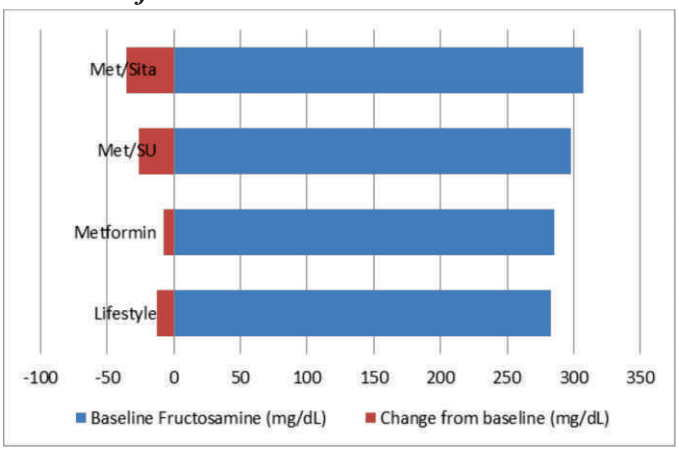


Fig.3: *Change in weight from baseline after Ramadan fasting in different treatment groups: The groups are 1: Lifestyle modification; 2: Metformin monotherapy; 3. Metformin/ Sulfonylurea combination; 4: Metformin/ DPP4 combination; Blue: baseline; Red: change from baseline*

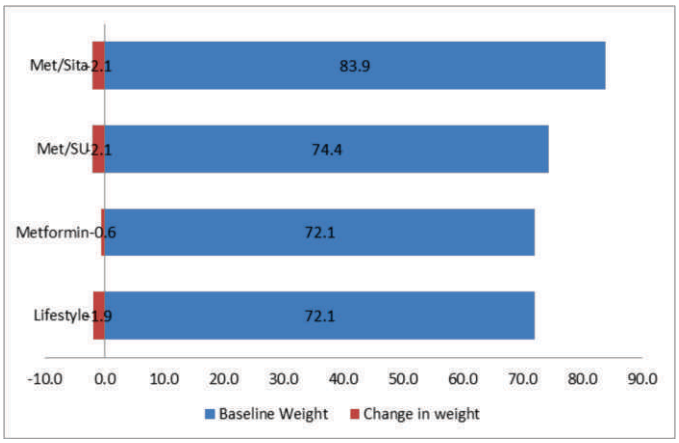
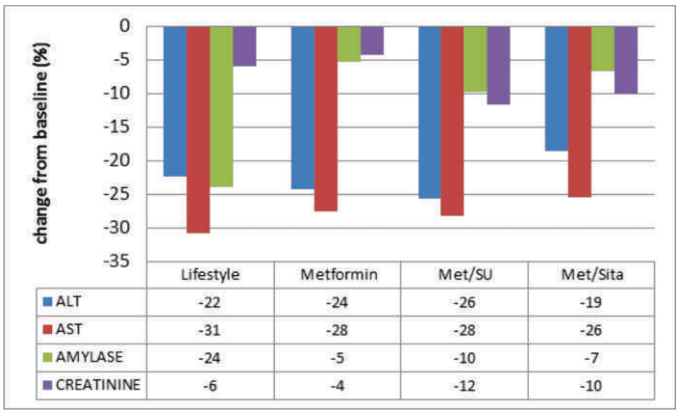


Fig 4: *Safety of different treatment groups during Ramadan fasting. Percentage change from baseline after Ramadan fasting in: a. metabolic parameters; b. lipid profile*

The groups are 1: Lifestyle modification; 2: Metformin monotherapy; 3. Metformin/ Sulfonylurea combination; 4: Metformin/ DPP4 combination



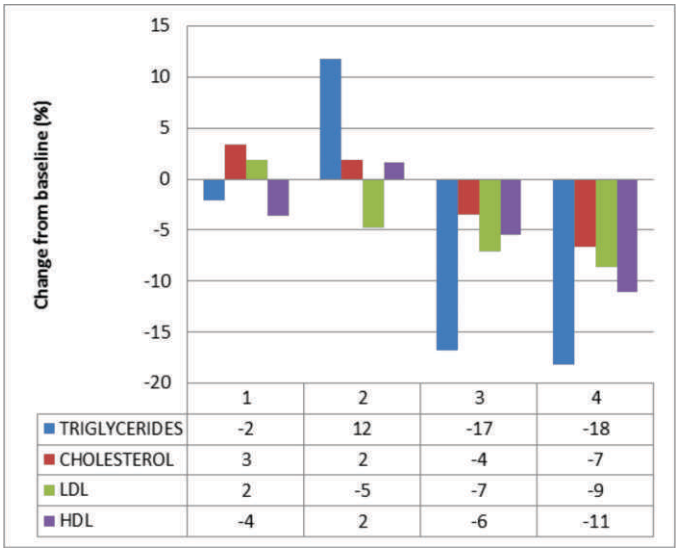


Fig 4a:

Table 2: *Table 2: ANOVA showing in clinical and metabolic parameters from baseline after Ramadan fasting in different treatment groups:*

Parameter (Mean change from baseline)	Group 1	Group 2	Group 3	Group 4	Sig.
Weight (Kg)	-1.40	-0.40	-1.60	-1.77	0.051
BMI	-0.47	-0.16	-0.35	-0.18	0.056
Bilirubin(mg/dl)	0.07	0.05	0.08	0.01	0.670
ALT (IU/L)	-9.37	-9.67	-8.16	-7.97	0.974
AST (IU/L)	-9.26	-8.96	-7.36	-8.29	0.923
Urea (mg/dl)	-2.16	-2.63	-1.91	-3.70	0.788
Creatinine (mg/dl)	-0.05	-0.03	-0.10	-0.09	0.271
Cholesterol (mg/dl)	6.47	3.50	-6.87	-12.38	0.144
Triglyceride (mg/dl)	-3.42	19.79	-34.22	-41.88	0.147
HDL (mg/dl)	-1.42	0.71	-2.31	-4.41	0.207
LDL (mg/dl)	2.16	-5.13	-8.00	-8.61	0.396
Amylase (U/L)	-18.97	-3.54	-6.60	-4.50	0.087
Fructosamine(µmol/L)	-12.67	-8.17	-26.20	-35.97	0.025*
MBG(mg/dl)	+7.23	+2.97	-11.27	-23.56	0.045*

Fig 4b:

*The groups are 1: Lifestyle modification; 2: Metformin monotherapy; 3. Metformin/ Sulfonylurea combination; 4: Metformin/ DPP4 combination. Values reflect change from baseline. BMI: Body mass index. MBG: mean blood glucose. ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. * indicates level of significance p<0.05.*

Author's Contribution

SB: Concept, Design, Writing
KIK: Concept, Design, Data Analysis, Study Conduct
AF: Data Analysis, Writing, Review
AA: Trial Protocol Implementation
FM: Deign, Concept, Clinical Analysis

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AIDS-Associated Disseminated Kaposi's Sarcoma : A Rare Entity

Ayesha Anwar, Ahmad Salman, Saelah Batool, Ashba Nasir Cheema

Abstract

Kaposi's sarcoma (KS) is the most common malignancy among patients with acquired immune deficiency syndrome(AIDS) but disseminated KS is a rare entity.Due to its rapid and progressive nature, early diagnosis and institution of highly active antiretroviral therapy (HAART) is critical to have a better outlook.

We report a case of disseminated KS in an HIV-1 positive patient, who presented with five months history of multiple violaceous macules, patches, papules, plaques and nodules all over the body with involvement of oral cavity and gentalia, pleural effusion and bilateral pulmonary infiltrates.This case is being reported due to the paucity of KS in the literature, especially the disseminated type and to highlight its aggressive clinical course.

Keywords: AIDS, Disseminated, HAART, Kaposi sarcoma.

Introduction

KS was first described in 1872 by the Hungarian dermatologist, Moritz Kaposi. KS is a spindle-cell tumor of endothelial origin. It carries a variable clinical course ranging from minimal mucocutaneous disease to extensive organ involvement. Kaposi sarcoma can be primarily categorized into 4 types: Epidemic AIDS-related KS, Immunocompromised KS, Classic KS, or sporadic/ Endemic (African) KS.[1]

AIDS associated KS is the most common neoplasm in untreated HIV-infected individuals 30 per 1000 patient-years (pre-HAART) to 0.3 per 1000 patient-years (post-HAART). It has male predominance particularly homosexuals & seen usually between 20-40 years of age. Upto 40% of homosexual men with AIDS (pre-HAART) has KS.[2]

Case report

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A 32-year-old HIV-positive male was referred to us from a cardiologist for the evaluation of widespread violaceous macules, papules, plaques and nodules on the skin. Initially he noticed the plaques on the dorsum of his left big toe 5 months back which gradually increased in number to involve other parts of the body over a period of next few months. He complained of fever, malaise and decreased appetite for the past 3 months. He lost 11 Kg weight during this period. History of swelling of bilateral lower limbs, scrotum and penis was present since 2 months. He developed periorbital puffiness, redness of eyes, shortness of breath and abdominal pain from last 15 days.

He had H/O appendicectomy 10 years back. No history of blood transfusion, I/V drug use or unprotected sexual exposure. He had been detected to be seropositive for HIV-1 infection 1month earlier but did not take antiretroviral treatment.

Cutaneous Examination

There were multiple discrete to grouped violaceous papules, plaques and nodules of variable sizes on the face, scalp, trunk and extremities. Similar lesions were present on the genitalia and in the oral cavity predominantly on hard palate. Lesions on rigtht hand were associated with swelling and pain in the little finger.

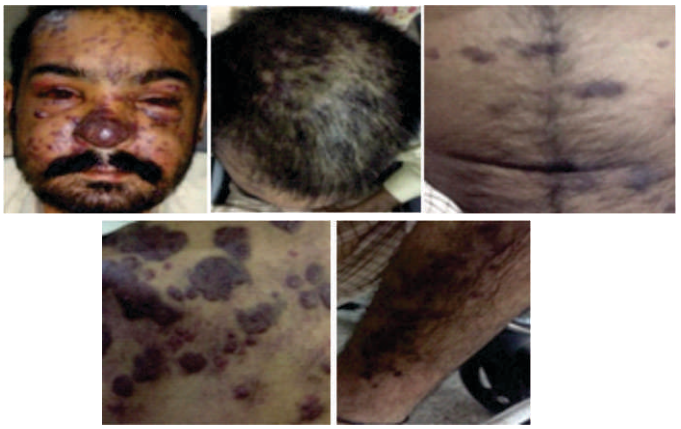

Figure 1: *Discrete to Grouped Violaceous Papules, Plaques, Nodules on Face, Scalp, Trunk and Extremeties*

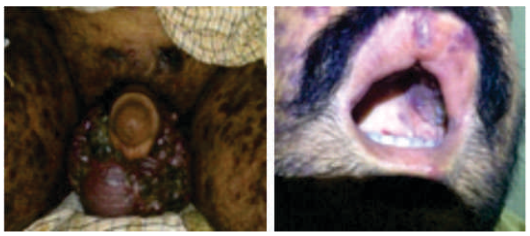

Figure 2: *Violaceous Papules, Plaques and Nodules on the Genitals & in the Oral Cavity*

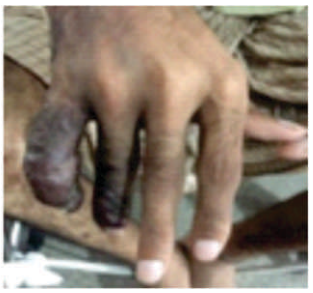

Figure 3: *Violaceous Plaques on Right Hand Along with Swelling of Little Finger*

General & Systemic Examination

Patient had pallor, periorbital puffiness, conjunctival congestion, bilateral pedal edema, and generalized lymphadenopathy: axillary, cervical and inguinal lymph nodes were enlarged (1.5–2.5 cm). They were firm, mobile, non-tender and non-matted. Liver was also enlarged.

On investigations

He had low hemoglogin (7.8 mg/dl), TLC 10,000 with lymphocyte count of 15% and serum biochemistry were unremarkable. Enzyme-linked immunosorbent assay (ELISA) for HIV-1 was positive and the CD4 count was 200 cells/mm.Venereal disease research laboratory (VDRL), hepatitis B surface antigen and anti-hepatitis C virus antibody tests were negative.

Biopsy of a plaque on the trunk showed proliferation of endothelial cells with slit like vascular spaces surrounded by plump spindle cells proliferation throughout the dermis, present individually as well as in groups with extravasation of erythrocytes. The "promontory sign" was noted. The cells stained positively with immunohistochemical stains CD31 and CD34, confirming their vascular lineage and diagnosis of Kaposi's sarcoma.

Ultrasound of abdomen and chest showed mild hepatomegaly and left sided pleural effusion. ECG showed sinus tachycardia and echocardiography revealed normal biventricular systolic function with EF 60% , mild pericardial effusion and mild pulmonary arterial hypertension . A computed tomography (CT) scan of the chest and abdomen showed bilateral moderate pleural effusion with fibronodular infiltrates in both lungs suggesting pulmonary involvement. Mild hepatomegaly and multiple enlarged mesenteric lymph nodes were also noticed.

Fine needle aspiration of an inguinal lymph node showed reactive lymphoid hyperplasia. Endoscopy of the upper and lower gastrointestinal tracts did not show any abnormalities. A final diagnosis of AIDS-related disseminated Kaposi's sarcoma (cutaneous and pulmonary involvement) was made.

Discussion

KS can be the first sign of occult HIV infection. It is the most common neoplastic disease associated with HIV-1. It is a multicentric angioproliferative neoplasm, primarily affecting mucocutaneous tissues, but may affect viscera as well. The oncogenic human herpes virus type 8 (HHV-8) is considered an aetiological agent of Kaposi's scarcoma. Co-infection of HHV-8 with HIV promotes the oncogenic capability of HHV-8, leading to development of KS.[3]

AIDS-associated Kaposi's sarcoma differ from classical form because of its rapid clinical course and widespread dissemination.[4] The incidence of KS is higher in males compared to females.

Clinically, cutaneous Kaposi's sarcoma presents as discrete erythematous or violaceous macules,

patches, plaques and nodules most commonly on the lower extremities. Lymphoedema of the involved areas is common. Common extracutaneous sites are the oral cavity, lungs, liver, Iintestines and lymph nodes.[5]

Our patient presented with violaceous patches, plaques and nodules all over the body along with involvement of genitalia and oral cavity. Oral mucosal involvement is more common in AIDS-related KS. About 22% of HIV seropositive patients with KS have oral involvement as initial manifestation. The presence of oral lesions not only points towards undiagnosed HIV infection but also its association with dissemination of the disease (KS). About 71% of AIDS-related KS patients have oral involvement with cutaneous and visceral lesions.[6]

Lung involvement in KS occurs in 20% of the patients and is associated with poor prognosis of the disease. Patient can present with progressive dyspnea, non-productive cough, fever, chest pain and pleural effusion. Our patient developed shortness of breath due to pleural effusion. Lymph nodes involvement does not effect prognosis.

Our patient had reactive mesenteric lymphadenopathy and mild hepatomegaly (fatty changes).[7] Other rare sites include the pancreas, spleen, heart, testes, kidneys, adrenals, urinary bladder and thyroid.[6]

Pericardial effusion is a known complication of HIV infection. However, the incidence has declined dramatically since the application of ART. Some studies suggest that KS is responsible for 5–7% of HIV-associated pericardial effusions. Other causes of pericardial effusion in HIV patients include mycobacterial, bacterial, fungal, and viral infections, and lymphoma.

KS-related pericardial effusion can be a life-threatening emergency and should be considered in HIV/AIDS patients who present with signs and symptoms of pericardial effusion. The importance of diagnosing and differentiating KS-related pericardial effusion from other causes of pericardial effusion lies in the differences in the treatment. Our patient had pulmonary hypertension and mild pericardial effusion as a complication of HIV infection .[7]

Kaposi sarcoma should be considered in differential diagnosis while dealing with an HIV-seropositive case with violaceous lesions anywhere on the body. Main differentials of KS are bacillary angiomatosis, pseudo-kaposi, lichen planus, pyogenic granuloma and hemangiomas.[8]

Immunohistochemical staining with HHV-8 helps in the diagnosis of KS but we failed to perform the test in our patient.

The clinical course of Kaposi's sarcoma ranges from indolent disease restricted to the skin to rapidly-progressive extensive skin disease with visceral involvement. Our patient had both cutaneous and visceral involvement (lungs).

Management of HIV-associated Kaposi's sarcoma is aimed at reduction of intensive skin and oral lesions, control of pain and symptomatic visceral disease. Management involves the use of HAART and multiple other treatment modalities: surgical resection, cryotherapy, sclerotherapy, laser, intralesional chemotherapeutic agents, radiotherapy and chemotherapy. HAART cause reduction of HIV viral load, restoration of the host immune system (elevation of CD4 count) and regression of Kaposi's sarcoma lesions. Radiotherapy is suitable for treatment of limited skin disease whilst palliative chemotherapy is reserved for extensive skin disease and visceral involvement.[1] HIV-infected patients with Kaposi's sarcoma may develop a fatal reaction after initiating HAART due to immune reconstitution inflammatory syndrome (IRIS). In a study conducted in Mozambique, 11.6% of patients on HAART with Kaposi's sarcoma developed immune reconstitution inflammatory syndrome-associated with Kaposi's sarcoma (IRIS-KS).[5] IRIS is observed in patients who demonstrate a good virologic and immunologic response to HAART but experience a paradoxical clinical worsening. The majority of fatalities are due to pulmonary involvement.[5,9]

Conclusion

- Kaposi's sarcoma is asymptomatic, patients should have a thorough examination before starting HAART and they should be warned of deterioration in the lesions during first 12 weeks of treatment.
- Pulmonary Kaposi's sarcoma is fatal and

requires timeous management.

- Early diagnosis & referral of patient for treatment of HIV will be possible if general physicians are taught to identify HIV-related skin conditions.

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