Association between Oxidative Stress, and Risk of Development of Cardiovascular Disease in Diabetic Patients

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Abstract

Objective: A cross sectional study was carried out to find the association between oxidative stress, and risk of the development of cardiovascular disease in diabetic patients

Material and Methods: Study included 60 patients and 30 controls with age 20-45 years. About 30 diabetic patients with duration of diabetes>five year (Group A) and 30 cases of type 2 diabetics with duration of diabetes<one year (Group B) were included. Another 30 subjects with no history of any disease were recruited as controls (Group C). Blood sample of both subjectsand controls was drawn to estimate the levels of serum malondialdehyde, serum catalase, fasting blood sugar, serum catalase, serum cholesterol and serum triglyceride using standard kits.

Results: Male/female ratio was 1:2&1:3 in groups A & B respectively. Majority of middle-aged diabetic of both groups were smokers, professional and having moderately active lifestyle. Nearly all patients were non-obese with positive family history of diabetes. Mean levels of fasting blood sugar, serum MDA, serum cholesterol was high in Group A compared to Group B and controls. The mean level of serum triglycerides was high in Group B compared to Group A& controls. The levels of serum catalase were low in both A & B compared to group C. According to analysis of variance, significant difference was observed in values of fasting blood sugar, serum MDA, serum catalase, serum cholesterol and triglycerides between groupsA, B & C.

Conclusion: Reduced level of catalase and increased values of malondialdehyde cause imbalance of oxidative stress that may increase the risk of cardiovascular disease in both new and known diabetic patients.

Keywords: Oxidative stress, diabetes, cardiovascular disease.

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Introduction:

Diabetes mellitus is an assemblage of metabolic ailments explained primarily by increased blood sugar levels ensuing from impairments in secretion or function of insulin or by the combination of both. Chronic raised levels of blood sugar results in various systemic problems including renal and a vascular diseases, retinopathy etc.[1,2] It has been shown that the start of diabetes type II is associated with metabolic risk factors related with cardiovascular issues like dyslipidemia, high blood pressure, and prothrombotic factors.[3]

The incidence of diabetes is increasing worldwide due to urbanization, population growth, obesity and aging. In Asian countries, the prevalence of diabetes is high in young and middle age people4.In Pakistan, the incidence of diabetes has been estimated tobe 14.62%. The risk factors associated with diabetes, as identified in Pakistani population, include advancing age, the number of diabetic family members, obesity and hypertension.[5]

Hyperglycemia is known to induce oxidative stress-mediated injury of cells. Elevated glucose levels in the blood can increase glucose uptake by cells, leading to an

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increase in the production of reactive oxygen species (ROS). Hyperglycemia-encouraged oxidative stress causes dysfunction of epithelial cells that play the main role in development of micro/macro-vascular ailments. Hyperglycemia also activates formation of diacylglycerol which activates the enzyme protein kinase C & NADPH-oxidase, which in turn, causes the synthesis of reactive oxygen species and increases oxidative stress in ailment of diabetes6. The basic mechanism of such cellular insult is a disparity between free radical formation and cell's ability to eliminate them. Increased free radical production and decreased scavenging by the antioxidant system results in the synthesis of malondialdehyde (MDA) and may affect the function of vascular, renal and retinal tissues in addition of islet of cells. To mitigate oxidative stress in the body, non-enzymatic (ascorbate, tocopherol etc.) and enzymatic antioxidants (catalase, glutathione peroxidase, superoxide dismutase-1 etc.), play important roles. Reduction in their levels increases predisposition to oxidative damage and may result in cardiovascular problems and other complications.[7]

Weak antioxidant defense systems, unresponsive to high production of ROS, cause oxidative stress and are unable to remove this high level of ROS. This accumulation of free radicals leads to increased production of malondialdehyde (MDA) and synthesis of conjugated form of diene which are cytotoxic/mutagenic and may cause bad effect of oxidation on the usual function of vascular, retinal and kidney issues in addition to harmful impact on pancreatic islet cells.[8]

Raised oxidative stress or decreased antioxidant capacity could potentially be the root cause of the complications observed in diabetic patients. Cardiovascular disease is the main reason of death in diabetic patients, which in many situations, appears to be affected by oxidative stress. ROS negatively modulates calcium handling of myocardium leading to the development of arrhythmia, and increasing cardiac remodeling by influencing hypertrophic signals and apoptosis. ROS also promotes the formation of atherosclerotic plaque[9]. Amongst these, catalase is an important antioxidant enzyme and MDA is an oxidative damage product and their imbalance may have a role in the development of oxidative stress induced cardiovascular complications in diabetic patients[10]. Lipids are found to be one of the sole victims of ROS. Changes in the metabolism of lipids (cholesterol and triglycerides), in diabetic patients, suggests that per oxidative injury maybe responsible for the development of diabetic complications including myocardial infarction[11]. Serum malondialdehyde is directly and serum catalase inversely related to oxidative stress and development of cardiovascular disease in diabetic patients. Cardiometabolic issues, including Type-2 diabetes, are growing apprehension worldwide. The incidence of diabetes is rising due to high population growth, aging, urbanization, and obesity. Oxidative stress plays pivotal role in progression and development of diabetes and its complications including cardiovascular disease. The prognostic significance of oxidative stress biomarkers is still poorly understood. Proper knowledge of oxidative imbalance is based on high values of malondialdehyde and reduced values of catalase that may help to understand complications of diabetes. Proper therapies may help to reduce impact of oxidative stress that may be useful to lessen diabetic complications.

Materials and Methods

Stdy included 60 patients and 30 controls. Duration of study was October 2022 to November 2023. Study was carried out at CMH Lahore Medical College & Institute of Dentistry, Lahore The study was approved by the ethics committees and written consent was taken from each patient according to the principles of the Declaration of Helsinki. Participants were recruited from the general population of Lahore city using non-probability purposive sampling. Patients with age 20-45 years, with uncontrolled diabetes (HbA1c>6.5% along with FBS >126 mg/dl) were included in the study. Subjects with type 1 diabetes, BMI>27 Kg/m^2, diagnosed hypertension, usage of anti-oxidant, anaemia were excluded from the study. A total of 30 type 2 diabetes mellitus patients with duration of diabetes > five year (Group A) and 30 cases of type 2 diabetics with duration of diabetes<one year (Group B) were included in the study. Group A taken as known diabetic and group B as newly diabetics. Another 30 subjects with no history of any disease were recruited as controls (Group C). Sample size was calculated using the sample size calculator software available online (https:// riskcalc.org/samplesize) for continuous outcomes at confidence level of 95% and power of 80%. The sample size was calculated using the formula:

$$n_1 = \left(1 + \frac{1}{k}\right)\sigma^2\left(\frac{z_{1-\alpha/2} + z_{1-\beta}}{\mu_0 - \mu_1}\right)^2 ; n_0 = kn_1$$

where μ_0 and μ_1 are the means of the end-points in group one and group two, n_1 is the sample size in group one,

n_2 is the sample size in group two, $k = n_1/n_2$ is the ratio of two sample sizes, and σ^2 is the variance of the two samples (assumed common). After a 12-hour fast, BMI of all subjects wasassessed. Blood sample of both subjects and controls was drawn to estimate the level of serum malondialdehyde, serum catalase, fasting blood sugar, serum catalase, serum cholesterol and serum triglyceride using standard kits. Fasting blood sugar was estimated by Auto Analyzer using glucose oxidase kit method. Serum Catalase was estimated using hydrogen peroxide. Serum Malondialdehyde will be measured by using thiobarbituric acid method. A study-specific questionnaire was used to collect data. Data was analyzed by SPSS 23.Qualitative variables were expressed as frequency and relative frequency. Quantitative variables were expressed as mean ± Standard deviation, Study variables (subject to normal distribution) were compared by One-way Anova. $P<0.05$ was considered as significant.

Results

Demographic characteristics of diabetic group (A & B) and controls showed that in Group A (diabetes with>5 yrs.), male /female ratio was 1:2. Mean age of majority was<40 years followed by middle age (41-50 years) and age>50 years. In this group 60% were former smokers and 40% were regular smoker. All diabetics of this age groups were professionally active. Their lifestyle was based on their exercise and walking. It is observed that active lifestyle was observed in majority (33-40%) and about 27% were formally active. Family history was observed in nearly all diabetics with BMI<25 Kg/m^2. **(Table-1)**. Demographic characteristics of diabetic group (A & B) and controls showed that in Group B (diabetes<1 yrs.), male /female ratio was 1:3. Mean age of majority was<40 years followed by age>50 years and middle age (41-50 years). In this group majority was former/non-smokers. All diabetics of this age group were professionally active. Their lifestyle was based on exercise and walking. Active lifestyle was observed in majority (60%) and about 23% were formerly active and 16% had no physical activity. Family history was observed in nearly all diabetics with BMI<25 Kg/m^2 **(Table-1)**. Mean levels of fasting blood sugar, serum MDA, serum cholesterol was high in Group A compared to Group B and controls. Whereas the mean level of serum triglycerides was high in Group B compared to Group A& controls. On the other hand the level of serum catalase was low in both A & B compared to Group C **(Table-2)**. Analysis of variance (one way) of biochemical parameters was carried out between groups and within groups of diabetic subjects (Group A & B) and controls. According to analysis significant ($P<0.001$) difference was observed in values of fasting blood sugar, serum MDA, serum catalase, serum cholesterol and triglycerides between groups **(Table-3)**.

Table 1: *Demographic Characteristics of Diabetic Groups (A&B) and Controls Presented by Frequency and Percentages.*

Variables	Diabetic Group A (>5yrs)	Diabetic Group B (<1 yrs.)	Controls (Group C)
Gender (n%)			
Male	10 (33.33%)	07 (23.33%)	14 (46.66%)
Female	20 (66.66%)	23 (76.66%)	16 (53.33%)
Age distribution			
<40 years	15 (50%)	22 (73.33%)	20 (66.66%)
41-50 yrs	10 (33.33%)	02 (6.66%)	04 (13.33%)
>50 yrs	05 (16.66%)	06 (20%)	01(3.33%)
Smoking			
Never /Former smokers	18 (60%)	25 (83.33%)	23 (76.66%)
Regular smoker	12 (40%)	05 (16.66%)	07 (23.33%)
Profession (n%)			
Employ	16 (53.33%)	23 (76.66%)	28 (93.33%)
Others	14(46.66%)	07 (23.33%)	02(6.66%)
Life Style/physical activity (n%)			
Never /Rare	08 (26.66%)	05 (16.66%)	26 (86.66%)
1-2 times weekly	12 (40%)	18 (60%)	02(6.66%)
3-6 times weekly	10 (33.33%)	07 (23.33%)	02 (6.66%)
Family history of diabetes			
No	01 (3.33%)	28 (93.33%)	30 (100%)
Yes	29 (96.67%)	02 (6.66%)	-
Obesity(BMI= 30- 34 Kg/m^2)			
Yes	01 (96.67%)	01 (96.67%)	-
NO	29 (3.33%)	29 (3.33%)	30 (100%)

Table 2: *Mean and Standard Deviation in Diabetics Groups (A & B) and Controls*

Parameters	Group A	Group B	Controls
Fasting blood sugar (mg/dl)	202.16±34.20	186.55±28.21	97.67±13.95
Serum MDA (mMol)	1.41±0.6	1.33± 0.44	0.88±0.27
Serum Catalase (mg/dl)	1.83±0.22	1.95±0.16	5.4±0.48
Serum cholesterol (mg/dl)	257.4±78.71	212.60±18.28	173.3±35.76
Serum Triglycerides(mg/dl)	286.6±115.85	290.1±97.36	137.6±35.76

Table 3: *Analysis of Variance (One Way) of Biochemical Parameters In Groups (Group A &B) and Controls*

Serum Malondialdehyde				
Sources	**Sum Squares**	**Mean Square**	**F-Statistic**	**P-value**
Between Groups	2.86	1.43	6.63	0.002
Within Groups	12.10	0.21		
Serum Catalase				
Between Groups	9.8	4.9	133.99	0.00
Within Groups	2.2	0.03		
Serum Cholesterol				
Between Groups	37609.80	18804.9	7.48	0.002
Within Groups	67875.32	2513.90		
Serum Triglycerides				
Between Groups	151565	75782.5	9.40	0.00
Within Groups	217601.6	8059.31		
Fasting blood sugar				
Between Groups	199615.87	99807.9	66.17	0.000
Within Groups	90498.60	1508.31		

Discussion

Male/female ratio showed that femalesare more prone to develop diabetes than males. The incidence of diabetes was high with a period less than one year as compared to duration of diabetes>5.0 years. A study also found increased incidence of type 2 in females. The reason may be diversities in environment and lifestyle with difference in economic status. In addition, sex steroid hormones may have a significant effect on metabolism giving energy, composition of body, functions related with vascular system. Thus, imbalance of hormones may increase the risk of cardiovascular issues especially in diabetic females.[12] However, a survey that included eleven studies comprising 96,581 diabetic patients found that males were more prone to develop diabetes than females.[13]

According to our study majority of middle-aged diabetic of both groups were smokers, professionals and having moderately active lifestyle. Nearly all patients were non-obese with positive family history of diabetes. A study also found that incidence of diabetes is more in middle-aged and the risk due to ageing was increased in these diabetics. It is demonstrated that type 2 diabetes may worsen the process of ageing and gradually predisposediabetics to complications like retinopathy, renal impairment, and cardiovascular issues. It is proposed that type 2 diabetes encourages immature senescence in different cells like endothelial cells, β-cells, and cardiomyocytes due to high BMI,inactive lifestyle and positive family history which may increase the risk of progression of cardiovascular issues even with less duration of diabetes.[14]

Relationship between normal/low BMI was less studied. It is thought non-obese diabetic havea changed genetic vulnerability to diabetes and is related to severe & progressive diabetes. A study was conductedon 5339 obese and lean type 2 diabetics in China to find out the association of type 2 diabetes withgenetic variants. Results showed that the genotype risk score was more related with the risk or issue for slim type 2 diabetics than for obese ones. Alsodys function of beta cells and low levels of insulin was noted in non-obese diabetics.[15] A review of study reported that incidence of type 2 diabetes was usually higher in less developed countries and the highest increase in incidence of diabetes is assumed in coming lifetime. Conversely, pathological/ physiological characteristics and issues, that increase the risk of developing type 2 diabetes in non-obese individuals is much discussed.[16]

A study of about 15.40% regular smokers, 4.80% former smokers and 79.80% non-smokers in which patients were middle-aged diabetics was carried out. It is found that regular /heavy smokers showed a higher risk of developing cardiovascular issues as compared to former smokers and non-smokers.The exact mechanism of impact of smoking on diabetes is not known. It is proposed that smoking along with diabetes may help to develop cardiovascular issues via increased oxidative stress and injury of endothelial cells resulting in the formation of plaques of atheroma.[17]

One of the risk factors i.e. sedentary/in-activelifestyle and increased complications of diabetes is widely studied. It is proposed that regular exercise and walk boosts the antioxidant defense of the body. However, exercise without guidance engulfs defenses causing damage due to free radicals. Thus individual who only exercise vigorously on weekends only may experience more harm than benefit. It is proposed that injuries due to moderate to high-intensity exercise with short-duration causes increased production of ROS that damages many tissues of body like skeletal muscle.[18] A data based on about 1990 diabetic and 1930 non-diabetics was conducted on Spanish people. Study tried to compare relationship of health to quality of life (physical &mental) and limitation of activities in both groups and found its impact on cardiovascular issues. It is concluded that low quality of life may increase the risk of cardiovascular problems, even in diabetics.[19]

Mean levels of fasting blood sugar, serum MDA, serum

cholesterol was high in diabetics with duration of diabetes >5 years compared to diabetics with duration <one year. Dyslipidemia is known in type 2 diabetes affecting 73% to 86% patients characterized by hypertriglyceridemia (HTG) and hyperglycemia. HTG appears due to increased synthesis, low clearance with known dyslipidemia in diabetics[20]. We agreed with a study, carried out in 60 diabetics. Among these 30 diabetics are newly diagnosed and 30 were known. Their blood levels of fasting blood sugar, cholesterol, triglycerides and MDA was estimated. Study found high values of fasting blood sugar, cholesterol, triglycerides and MDA in diabetics of large duration compared to recent diabetics. It is suggested that duration of diabetes is independently related with raised values of lipid peroxidation due to chronic oxidative stress due to excess of free radicals. These free radicals cause complications of diabetes including cardiomyopathy, neuropathy and retinopathy[21]. According to studies the key risk issue for process of dyslipidemia in diabetics are aging, hypertension, inactive lifestyle, high BMI and prolonged duration of diabetes.[22,23]

We observed, however, increased values of serum triglycerides in newly diagnosed diabetics compared to known diabetics. Most of the studies found high levels of serum triglycerides in known diabetics compared to newly diagnosed. It is proposed that high levels of triglycerides are related to micro-vascular complications due to endothelial dysfunction and lipid peroxidation. It is suggested that estimation of triglyceride may be helpful to monitor the metabolic position in clinical situations.[24]

Low levels of serum catalase was observed in both new and known diabetic. first_page

Study observed low levels of catalase in both new and known diabetics. A study tried to elucidate the association of diabetes with antioxidant defense. Study included 102 middle aged diabetics and investigated the levels of superoxide dismutase, catalase and status of vitamin D and A. An inverse activity of catalase and superoxide dismutase was related with risk of type 2 diabetes. The probable influences are lifestyle, triglyceride and cholesterol that may mediate the link of superoxide dismutase and catalase with risk of type 2 diabetes[24]. Number of studies proposed the association of low value of catalase and risk of developing the type 2 diabetes. One of the studies proposed that low catalase causes failure of function of pancreatic beta cells and damage by reactive oxygen species. Besides, hyperglycemia is one of the factors to down regulate the expression of catalase.[25]

Conclusion

Reduced levels of catalase and increased values of malondialdehyde cause imbalance of oxidative stress that may increase the risk of cardiovascular disease in both new and known diabetic patients. However, more studies are needed to find the gender specific risk issues, intensity/duration of exercise, emphasis on oxidative/anti-oxidative enzyme, dyslipidemia and reason of non-obese diabetes. Sex-dimorphouspatho-physiological devices of type 2 diabetes and its complications may help to additional personalized care of diabetes in coming years and give more perception in gender related risk issues.

Conflict of interest : None

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Authors Contribution

HA: Conceptualization of Project
SIAS: Data Collection
RK: Literature Search
HA: Statistical Analysis
SIAS: Drafting, Revision
RK: Writing of Manuscript