Role of Fetuin-A and Fasting Blood Glucose in Predicting Pre-diabetes in First Degree Male Adolescents of Diabetic People

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Abstract

Objectives: To evaluate the role of high levels of Fetuin-A and fasting blood Glucose in predicting pre-diabetes in first degree adolescents of diabetic people.

Methods: A cross sectional study was conducted in department of Biochemistry and Department of Pathology from January 2019 to December 2019 at Department of Biochemistry, Services Institute of Medical Sciences, Lahore. This study was carried on 35males first degree relatives (FDR)of diabetics and 35 male adolescents with no familial diabetic element. The age range of both groups was 18-30 years. Blood samples for estimation of blood glucose, serum insulin and Fetuin A of all subjects were collected in fasting condition. Insulin resistance was calculated by formulation.

Results: Mean age of adolescents was 19 years with a BMI 24.09. Majority of the first degree relatives of diabetics have sedentary life style using mixed diet along with junk food. Levels of fasting blood sugar, serum insulin, serum Fetuin-A and insulin resistance were increased in male adolescents of diabetics as compared to adolescents of non-diabetics. Significant direct correlation of blood sugar with serum Fetuin-A and weak direct correlation with insulin resistance was observed in first degree relatives of diabetics.

Conclusion: Higher prevalence of impaired Fetuin-A and fasting blood glucose was observed in first degree relatives of diabetics. Significant correlation between fasting blood glucose and serum Fetuin-A suggests the role of Fetuin-A as an early predictor of pre-diabetes in adolescents of diabetics.

Key Words: first degree relatives of diabetics, fasting blood sugar, fetuin-a

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Introduction

Type-II diabetes mellitus is a metabolic complaint characterized by continual hyperglycemia due to lack of synthesis of insulin or resistance of peripheral tissue to insulin. Persistent hypergly be reason of functional and structural co-morbidities and lead to number of complications like diabetic nephropathy, neuropathy, retinopathy, hypertension as well as cardio-vascular problems.[1] Fetuin-A (α-Heremans-Schmid glycoprotein) is a glycoprotein of 64.0 KDa and considered as hepatokine and adipokine. It reversibly binds with insulin receptor tyrosine kinase in peripheral tissues thus block the intracellular signaling mediated by insulin and causing insulin resistance of peripheral tissues as well as insulin receptor auto-phosphorylation and increased risk of type-II diabetes mellitus.[2] Fetuin-A gene is found to be present on chromosome[3] which is associated with type-II diabetes mellitus and cardio-vascular diseases. It is proposed that alteration of gene may have strong effecton blood levels of Fetuin-A and shows the possible fundamental role of Fetuin-A in type 2 diabetes.[3]

Fetuin-A was linked with hyperinsulinemia.[4] It is associated with metabolism of glucose and lipid and insulin resistance via blockage of action of insulin through suppression of GLUT-4 (glucose transporter) and auto-

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phosphorylation of tyrosine kinase (receptor of insulin). Besides Fetuin-A in association with saturated form of fatty acids may stimulate inflammation via TLR4 (Toll-like receptor 4).[5,6] However, some studies showed that there was no relationship of insulin resistance and Fetuin-Ain diabetic patients as well as no link of Fetuin-A with risk of developing diabetes.[7,8]

Prevalence of type 2 diabetes is predicted to increase to 52.0 % from 387.0 million in the year of 2014 to 592.0 million in the year of 2035 particularly in low and middle income.[9] Incidence of impaired fasting blood glucose in Pakistan is 14.4%.[10,11] with a consistent rise which may damage the body organs thus increasing the risk of complications in people who were asympto-matic for many years of their life.[11] It is proposed that high levels of blood glucose persuaded trans-activation of gene of Fetuin-A protein and increases the risk of developing type 2 diabetes.[12]

Thus there is a need to trace altered fasting blood glucose and levels of Fetuin-A in adolescents of diabetics and should be tried to lessen the problem of diabetes mellitus and its complications in the community. This study was therefore designed to evaluate the role of high levels of Fetuin-A and fasting blood Glucose in predicting pre-diabetes in first degree adolescents of diabetic people.

Material & Methods

A cross sectional study was carried out on two groups (group A and group B). Group A included 35 adolescents (first degree relatives) of diabetics. Group 2 was comprised of 35 adolescents with no familial diabetic element and taken as controls. The age range of both groups (subjects and controls) was 18-30 years. Sample size was calculated by following formula: -

$$n = \frac{\left\{ z_{1\alpha/2}\sqrt{2\bar{P}(1-\bar{P})} + z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)} \right\}^2}{(P_1-P_2)^2}$$

Both subjects and controls were taken from diabetes management center, Lahore. Period of study was January 2019 to December 2019. History of dietary pattern, lifestyle pattern and related problems of both groups was also noted. Letter of consent was taken from both groups. Study was approved by IRB committee Department of Biochemistry, Services Institute of Medical Sciences, Lahore. The purpose of research was clearly explained to each subject. Blood samples for estimation of blood glucose, serum insulin and serum Fetuin-A of all subjects were collected in fasting condition. Blood glucose was estimated by glucose oxidase method using auto-analyzer. Levels of serum insulin and serum Fetuin-A were estimated by technique of ELISA. Insulin resistance was calculated by formulation. Pre-diabetes is a state in which the level of fasting blood sugar is impaired but may not aid to identify the diabetic state. It may be called as altered fasting blood glucose and may be in a range of 100 -125.0 mg/dl and subject with this range may be believed as prediabetic.[13]

Data was analyzed by SPSS 20. Quantitative variable was expressed as mean ± SD. Students 't' test was applied to compare the biochemical variables between adolescents with familial diabetic element and adolescents without familial diabetic element. Correlation of Fetuin-A and Fasting Blood Glucose was calculated using Pearson's correlation coefficient. $P \leq 0.05$ was considered as significant.

Table 1: *Demographic Variables in Male Adolescents*

Variables	Male adolescents (group A) (n=35)	Male adolescents (group B) (n=35)
Age (years)	19.7±2.27	19.00±2.15
BMI (Kg/m^2)	24.9±1.06	24.8±1.06
Life style	32 Sedentary (91.4 %) 03 Active (8.6%)	30 active (85.7 %) 05 sedentary (14.3 %)
Socioeconomic status	Upper class=10 Middle class= 25	Upper class= 09 Middle class= 26
Dietary Pattern	Mixed diet + junk food	Mixed diet + junk food
Present residence	Day scholar 20 Hostilities 15	Day scholar 25 Hostilities 10

Table 2: *Variation in the Level of Fasting Blood Sugar, Serum Insulin and Serum Fetuin-A in Male Adolescents with and Without Familial diabetic element. Values are expressed as mean ± SD*

	Male adolescents (group A) (35)	Male adolescents (group B) (35)
Fasting blood sugar(mg/dl)	100±7.36	84.23±7.37
Serum Insulin(mIU/L)	5.99±2.3	5.80±3.61
Serum Fetuin-A(ng/ml)	137.89 99(78-267)	97.77 115(50-200)
Insulin resistance	0.99	0.56

Table 3: *Correlation of Serum Fetuin-A with Fasting Blood Sugar and insulin resistance in Male Adolescents with Familial diabetic element.*

Variables	Serum Fetuin-A (ng/ml)	
	Correlation coefficient	p value
Fasting blood sugar (mg/dl)	0.5	0.023
Insulin Resistance	0.01	0.065

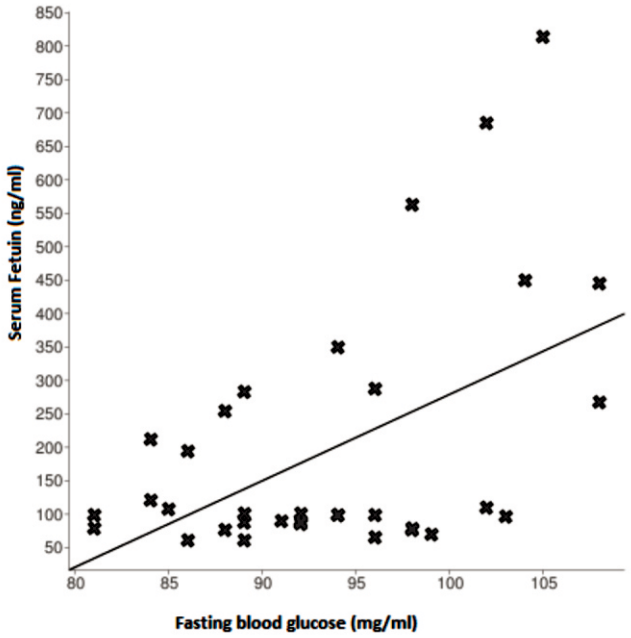

Fig-1: *Correlation of fasting blood sugar with serum Fetuin -A (R=0.50) in male adolescents with familial diabetic background.*

Results

Demographic variables in Male adolescents were tabulated as **(Table-1)**. Mean age of adolescents was 19 years with a BMI 24.09. About 91 % first degree relatives (FDR) of diabetics had sedentary lifestyle. Whereas only 14% of adolescents without familial diabetic element had sedentary lifestyle. Majority of FDR belong to middle socioeconomic class using mixed diet along with junk food and were living in hostels.

Variations in the level of fasting blood sugar, serum insulin and serum Fetuin-A in male adolescents with and without familial diabetic element was tabulated as **(Table 2)** It was observed that the levels of fasting blood sugar, serum insulin and serum Fetuin-A were increased in male adolescents having familial diabetic background as compared to adolescents having no familial diabetic background. Significant difference was only observed in case of serum Fetuin-A. Values of insulin resistance were increased in adolescents having familial diabetic background.

In adolescent boys with familial diabetic background, a significant ($P<0.01$) direct correlation of blood sugar with serum Fetuin-A and weak direct correlation with insulin resistance was observed **(Table 3 & Fig-1)**.

Discussion

According to our study majority of FDR or adolescents of diabetics had sedentary lifestyle with routine use of poor quality diet. We agreed with a study that also observed a higher incidence of sedentary lifestyle and found that age, poor quality of diet along with lack of physical activity may be a good predictor of pre-diabetes among adolescents.[14,15] The reason for sedentary lifestyle is the adaptation of routine activities based on using internet, video games and seeing television for long period of time.[16] According to a study healthy lifestyle may be defined as active lifestyle (exercise, Jim and walk), good quality diet and proper sleep.[17]

We observed a high or impaired fasting blood sugar, serum insulin, serum Fetuin-A and insulin resistance in adolescents having familial diabetic element as compared to adolescents with no familial diabetic element.

Our study is agreed with a study who reported that fasting blood sugar less than 100 mg/dl is considered as normal whereas fasting blood sugar in the range of 100-125 mg/dl was considered as impaired fasting blood glucose level. Study found that individual with impaired fasting blood sugar may have a 20-30 % chance of emerging diabetes in next five to ten years. Study concluded that impaired or altered fasting blood glucose is a known glycemic disarray which typically leads to Dia betes mellitus.[13] We also agreed with a group of workers who observed a direct association of impaired blood sugar in adolescents of diabetics even with normal BMI.[18]

A high value of insulin is observed in our studied adolescents of diabetics. A study proposed that there may be a chance of alteration of the action of insulin along with high or normal fasting blood sugar in adolescents of diabetic and it is due to mutation of insulin receptor or presence of antibodies of anti-insulin receptors.[19]

We also agreed with another study that also found a high insulin resistance in FDR of diabetics and stated that resistance to insulin-motivated blood glucose uptake is a typical finding in diabetic patients and among FDR of diabetics.[20]

We observed significantly high values of Fetuin-A in adolescents of diabetics as compared to adolescents of non-diabetics. Number of studies agreed with our findings. According to a study the high levels of Fetuin-A in individuals may be a functional modulator of role of insulin and insulin resistance in adolescents.[11] Another study reported that the high level of Fetuin-A along with increased values of insulin resistance along the normal glycemic index were very high in diabetics followed by pre-diabetes and were very low in subjects with normal glycemic index.[21] Recently a study also observed that high value of Fetuin-A is accountable for resistance of insulin.[22]

Present study observed a significant ($P\leq0.05$) direct correlation of blood sugar with serum Fetuin-A and

weak direct correlation with insulin resistance was also observed. Same observation was also reported by some studies. A study stated that positive correlation of Fetuin-A with blood glucose suggested that Fetuin-A may be a better predictor of insulin resistance instead of blood glucose as blood glucose is affected by many factors such as diet.[22-24] A study found that every increase in 0.10 g/L (Standard Deviation) of Fetuin-A was related with 19 times more chances of developing diabetes mellitus.[8] Additionally, it is stated that high values of Fetuin-A give an adverse effect on glycemic index. It is therefore suggested that Fetuin-A and fasting plasma glucose may be used as tools to find the susceptibility of a person to become pre-diabetic and finally diabetic.[11]

In addition, a study suggested the probable role of Fetuin-A in regulation of metabolism of glucose and is associated with inheritance as gene of Fetuin-A is present on chromosome 3q 27, the same susceptibility gene or locus for metabolic syndrome including insulin resistance. Thus Fetuin-A may be a good predictor for evaluating the diabetic status of a person.[25] Recently it is thought that Fetuin-A encourages insulin resistance by the inhibition of receptor of insulin as well as by mediating the inflammatory signals of free fatty acids that in-turn mediate inflammation of the pancreatic β-cells and help in developing insulin resistance.[22]

Our research paper has some limitations. The study subjects are only male adolescents. So our results may not apply to female relatives of diabetics. Study should also be carried out on second degree relatives of diabetics as well.

Conclusion

Higher incidence of impaired Fetuin A and fasting blood glucose was observed in adolescents of diabetics. Significant correlation between fasting blood glucose and serum Fetuin-A suggests the role of Fetuin-A as an early predictor of developing diabetes in adolescents of diabetics. It is therefore a need for prompt screening and intervention like lifestyle modification of such subjects that can prevent occurrence of diabetes in future as well as this will decrease national diabetic burden.

Conflict of Interest

None

Reference

1. Chawla A, Chawla R, Jaggi S. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? Indian J EndocrinolMetab. 2016; 20(4): 546-551. doi:10.4103/2230-8210.183480
2. Ward K, Mulder E, Frings-Meuthen P, O'Gorman DJ and Cooper D. Fetuin-A as a Potential Biomarker of Metabolic Variability Following 60 Days of Bed Rest. Front. Physiol. 2020;11:573581. doi: 10.3389/ fphys. 2020.573581
3. Jensen MK, Jensen RA, Mukamal KJ, Guo X, Yao J, Sun Q et al. Detection of genetic loci associated with plasma fetuin-A: a meta-analysis of genome-wide association studies from the CHARGE Consortium. Hum Mol Genet. 2017 Jun 1;26(11):2156-2163. doi: 10.1093/hmg/ddx091
4. Liu S, Hu W, He Y, Li L, Liu H, Gao L, Yang G, Liao X. Serum Fetuin-A levels are increased and associated with insulin resistance in women with polycystic ovary syndrome. BMC Endocrine Disorders. 2020 Dec; 20: 1-7.
5. Sujana C, Huth C, Zierer A, Meesters S, Sudduth-Klinger J, Koenig W, Herder C, Peters A, Thorand B. Association of fetuin-A with incident type 2 diabetes: results from the MONICA/KORA Augsburg study and a systematic meta-analysis. J Eur J Endocrinol. 2018; 178:389–98.
6. Jialal I, Pahwa R. Fetuin-A is also an adipokine. Lipids Health Dis. 2019;18:73
7. Song A, Xu M, Bi Y, Xu Y, Huang Y, Li M, Wang T, Wu Y, Liu Y, Li X, Chen Y. Serum fetuin-A associates with type 2 diabetes and insulin resistance in Chinese adults. PLoS One. 2011 Apr 27;6(4):e19228.
8. Jensen MK, Bartz TM, Djoussé L, Kizer JR, Zieman SJ, Rimm EB, Siscovick DS, Psaty BM, Ix JH, Mukamal KJ. Genetically elevated fetuin-A levels, fasting glucose levels, and risk of type 2 diabetes: the cardiovascular health study. Diabetes Care. 2013 Oct 1;36(10):3121-7.
9. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res ClinPract. 2014 Feb;103(2):137-49. doi: 10. 1016/ j.diabres.2013.11.002.
10. Basit A, Fawad A, Qureshi H, Shera AS.NDSP Members. Prevalence of diabetes, pre diabetes and associated risk factors: second national diabetes survey of Pakistan (NDSP) 2016-2017. BMJ Open. 2018;8:e020961. doi: 10.1136/bmj open-2017-020961
11. Kaur S and Mahajan M. Fetuin A: A Newer Marker for Pre Diabetes.British Journal of Medicine & Medical Research 2016;17(1): 1-7 DOI: 10.9734/BJMMR/ 2016/26644
12. Khadir, A., Kavalakatt, S., Madhu, D. Hammad M, Devarajan S, Tumelitho J. Fetuin-A levels are increased in the adipose tissue of diabetic obese humans but not in circulation. Lipids Health Dis 2018;17, 291 doi.org/ 10.1186/s12944-018-0919-x
13. Ali A, Taj A, Ahmed MU, Tabrez E. Frequency of impaired fasting glucose in first degree relatives of Type-II diabetic patients and its association with Body Mass Index. Pak J Med Sci. 2020;36(3):407-411. doi: 10. 12669/ pjms.36.3.57

14. Sami W, Ansari T, Butt NS, Hamid MRA. Effect of diet on type 2 diabetes mellitus: A review. Int J Health Sci (Qassim). 2017;11(2):65-71.
15. Chaabane, S., Chaabna, K., Abraham, A. et al. Physical activity and sedentary behaviour in the Middle East and North Africa: An overview of systematic reviews and meta-analysis. Sci Rep 2020; 10: 9363doi.org/ 10. 1038/s41598-020-66163-x
16. Huard Pelletier V, Lessard A, Piché F, Tétreau C, Descarreaux M. Video games and their associations with physical health: a scoping review. BMJ Open Sport & Exercise Medicine 2020;0: e000832. doi:10.1136/ bmjsem-2020-000832
17. Oftedal S, Vandelanotte C, Duncan MJ. Patterns of Diet, Physical Activity, Sitting and Sleep Are Associated with Socio-Demographic, Behavioural, and Health-Risk Indicators in Adults. Int J Environ Res Public Health. 2019;16(13):2375. doi: 10.3390/ ijerph 16132375
18. Rodríguez-Moran M, Guerrero-Romero F, Aradillas-García C, Violante R, Simental-Mendia LE, Monreal-Escalante E, Mendoza Ede L. Obesity and family history of diabetes as risk factors of impaired fasting glucose: implications for the early detection of prediabetes. Pediatr Diabetes. 2010 Aug;11(5):331-6. doi: 10.1111/ j.1399-5448.2009.00590.x. PMID: 19895410.
19. Tagi VM, Giannini C and Chiarelli F. Insulin Resistance in Children. Front. Endocrinol 2019; 10:342. doi: 10. 3389/ fendo.2019.00342
20. Sonuga OO, Abbiyesuku FM, Adedapo KS, Sonuga AA. Insulin Resistance Index and Proatherogenic Lipid Indices in the Offspring of People with Diabetes. Int J Diabetes Metab 2019; 25: 11–18 doi.org/ 10.1159/ 000497079
21. Ou HY, Yang YC, Wu HT, Wu JS, Lu FH, Chang CJ. Serum Fetuin A levels are elevated in subjects with impaired glucose tolerance and newly diagnosed type 2 diabetes. ClinEndocrinol. 2011;75:450- 455.
22. El-Messallamy FA, AbdoSoliman JS, SaeedShalaby SM, Abdel-Rahman H, Abdel-Rahman K. Fetuin-A as a Marker of Insulin Resistance in Type 2 Diabetic Patients in Zagazig University.The Egyp J HospMed 2020; 79: 462-468.
23. Shadman Z, Khoshniat M, Poorsoltan N, Akhoundan M, Omidvar M, larijani B, Hosein S. Association of high carbohydrateversus high fat diet with glycosylated haemoglobin in high calorie consuming type 2 diabetes. Journal of Diabetes and Metabolic Disorders. 2013;12:27. DOI: 10.1186/2251-6581-12-27 23.
24. Zhou ZW, Ju HX, Sun MZ, Chen H, Fi Q, Jiang D. Serum Fetuin-A levels in obese and non-obese subjects with and without type 2 diabetes mellitus. ClinChimActa 2018; 476:98-102.
25. Bourebaba L, Marycz K. Pathophysiological Implication of Fetuin-A Glycoprotein in the Development of Metabolic Disorders: A Concise Review. J Clin Med. 2019;8(12):2033. Published 2019 Nov 21. doi: 10.3390/jcm8122033.

Authors Contribution

SN, AI: Conceptualization of Project

SN: Data Collection

AR, AR, RMA: Literature Search

KR: Statistical Analysis