ORIGINAL ARTICLE

Role of Circulating Homocysteine and Fibrinogen, in increasing the risk of Cardiovascular diseases in patients with uncontrolled diabetes

KIRAN NAMOOS[1], HALEEMA SAJID[2], MUDASSAR ZIA[3], IMRAN ALI ZAIDI[4], AFSHAN ZAREEN BILAL[5], WAQASSHABBIR[7],
[1]Assistant Professor Biochemistry, Shalamar Medical & Dental College, Lahore, Pakistan
[2,3]Assistant Professor Biochemistry, Ameer-ud-din Medical College, Lahore, Pakistan.
[4]Assistant Professor Biochemistry, FMH College of Medicine & Dentistry, Lahore, Pakistan.
[5]Associate Professor Biochemistry, Rahbar Medical and Dental College, Lahore, Pakistan
[6]Assistant Professor Gastroenterology, PGMI/LGH, Lahore
Correspondence to Dr. Kiran Namoos, E-mail: knamoos@hotmail.com, Cell: 03234739904

ABSTRACT

Aim: To compare the serum level of homocysteine and fibrinogen in patients with controlled and uncontrolled type 2 diabetes mellitus
Methods: It was a cross sectional study. Total 120 consented patients with age range 35-45 years were involved in this study. Patients were taken from LGH, Lahore General Hospital from 2016 August to January 2017. Grouping of patients was done on the values of HbA1c i.e. Group I included controlled diabetes with HbA1c <7 and Group II included uncontrolled diabetes with HbA1c >7. Level of blood HbA1c, fibrinogen and homocysteine were estimated by immunoturbidimetric, Clauss method and ELISA technique respectively
Results: Mean age of group I and II was 44 and 46 with BMI 25 and 27 kg /m^2 respectively. Chronicity of DM in group I was 24 months and in group II was 49 months. Percentages of HbA1c was 6.25 in group I and 8.65 in group II. Level of fibrinogen and homocysteine was significantly high in group II as compared to group I.
Conclusions: High level of fibrinogen along with homocysteine may be useful predictor of cardiovascular risk in uncontrolled diabetic people.
Keywords: Cardiovascular disease, Diabetes, fibrinogen, homocysteine.

INTRODUCTION

Diabetes Mellitus (DM) is a chronic disease that arises due to insufficient insulin production. It may be described in two classes on the basis of levels of HbA1c i.e. controlled diabetes in individuals with HbA1c ≤6.5% and un-controlled diabetes with HbA1c greater than 6.5%. The incidence of controlled /uncontrolled type 2 DM in Pakistan was 13.5%, and 86.5% respectively[1].

Uncontrolled diabetes may results complications on long-term basis and increases the risk of mortality. Probable complications of uncontrolled diabetes are cardiovascular problems, cataracts, glaucoma, kidney failure, loss of vision, infection in genital tract in female etc. However, in patients with controlled diabetes the risk factors may be obesity, sedentary life style and hypertension in-spite of taking regular medicine. In controlled diabetics altered glucose tolerance is typified by resistance of insulin and atherosclerosis[2].

Women having diabetes with age of 35 to 45 years may experience menopausal signs and termed as premature or early menopause. Knowledge of regarding the relationship of diabetes with reproductive aging in not well understood. It is proposed that menopause accompanied by diabetes indicate a collaborative effect and may increase the riskof heart disease and other disease[3].

Morbidity and mortality may increase in diabetes due to the impaired haemostatic pathogenesis in small and large vessels. High level of circulating fibrinogen may be a predictor of complications of vessels and death in diabetic patients[4]. It is proposed that diabetic patients have a chance of developing arterial thrombosis and altered fibrinolysis results in early formation of plaque and delayed cardiovascular complications.

Increased level of homocysteine is also a main determinant of the many cardiovascular diseases.[5]Ithas been proved that high level of homocysteine is related with high resistance of insulin. A positive association between hyper-homocystinemia and resistance of insulin may be due to insulin governed to decrease the function of enzymes which take part in the pathway of remethylation or maintain the pathway of transsulfuration[6]. Though the link of insulin resistance with hyperhomocystinemia in not clear. Various studies found that increased level of homocysteine promote resistance of insulin and type 2 diabetes.

Hyperhomocysteinemia is a good marker of mortality in diabetics in comparison with non-diabetics. It may show the association of microalbuminuria with high risk of cardiovascular problems. It is found that good glycaemic management is found in hyperhomocysteinemia[7].

METHODS

A cross sectional study was carried out to compare the serum homocysteine and fibrinogen level in controlled and uncontrolled DM Type 2. 120 consented patients having age range 35-45 years were involved in the study. Patients were taken from LGH, Lahore Patents were taken from LGH, Lahore General Hospital from 2016 August to January 2017. Grouping of the patients was done on the

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level of HbA1c i.e. Group I included controlled diabetes with HbA1c less than 7 and Group II included uncontrolled diabetes with HbA1c greater than 7. Patients with history of stroke or CAD, chronic infection were not included in current study. Level of blood HbA1c, fibrinogen and homocysteine were estimated by immunoturbidimetric, Clauss method and ELISA technique respectively.This study was approved by Ethics Committee (No: 126-16/11-05-2016) PGMI/AMC.

Statistical Analysis: Data of study was analyzed by SPSS 20. Variables were given as mean±standard deviation. Independent sample t-test was applied to compare the variables with significant value < 0.05.

RESULTS

The comparison of nonclinical descriptive variables & clinical variables between Group I and Group II are tabulated in Table 1. and Table 2. respectively. Mean age of group I and II was 44.7 and 46.1 with BMI 24.9 and 27.5 kg /m^2 respectively. Diabetes duration of group I was 24 months and in group B was 44.4 months. Percentages of HbA1c was 6.19 in group I and 8.9 in group II. Level of fibrinogen and homocysteine was significantly high ($p<0.001$) in group II in comparison with group I.

Table 1: Independent samples t-test showing comparison of nonclinical variables

Variables	Group I	Group II	p value
Age (yrs)	44.75±5.85	46.18±5.95	0.153
BMI (kg/ m^2)	24.95 ±2.79	27.55±3.42	<0.001*
Diabetes duration (months)	24.01±17.55	44.40±19.97	<0.001*

*p < 0.05 Statistically significant

Table 2: Independent samples t-test showing comparison between clinical markers

Marker	Group I	Group II	p value
HbA1c (%)	6.19± 0.52	8.94±1.33	0.000*
Fibrinogen (mg/dl	290.70±66.39	408.92±108.40	0.000*
Homocysteine (µmol/L)	9.78± 2.06	13.00±3.88	0.000*

*p < 0.05 Statistically significant

DISCUSSION

Many factors are related with impaired glucose level like busy schedule of working, lack of balance diet, lack of active life style and usage of medication in time may help in controlling diabetes[8]. In our country of Pakistan about 76 % of patients have uncontrolled diabetes with associated factors like increase body weight, lack of exercise, hypertension and family history of diabetes.

Results of present study found the mean age of group I and II was 44.7 and 46.1 with BMI 24.9 and 27.5 kg /m^2 respectively. Diabetes duration in group I was 24 months and in group II was 44.4 months. According to a study conducted in Ethiopia showed that people in age of 41-50 years fail to manage their blood sugar levels in comparison with other groups[9] This poor management of glucose increases the risk of various complication which may increase mortality rate in these individuals. A study by Aamir AH et al, showed that 39% of middle-aged patients had uncontrolled form of diabetes having longer period of diabetes[10]. Study also observed that longer period of disease and high BMI are directly related with the status of uncontrolled diabetes. A study by Hussain S, Sattar U and Azhar MA stated same results[11]. However, a study found insignificant dissimilarity between impairs glycemic control and BMI[12].

In present study a high percentage of HbA1c was detected in patients with uncontrolled diabetes in comparison with patients who had controlled diabetes. We agreed with work of a group who also found a high percentage of HbA1c and stated that increase values of HbA1c is a good predictor of risk of cardiovascular problem in uncontrolled diabetics in both gender[13,14].

Our study agreed with local study done by Memoona R and group who found raised fibrinogen levels in patients with uncontrolled diabetes and predicted an increase chances of developing cardiovascular problems. According to a study high level of fibrinogen in diabetics is due to increase production of fibrinogen.[15]This high level of fibrinogen is related with deficiency of insulin and impairs glycaemic control. Study found that fibrinopeptide that convert fibrinogen in fibrin is direly associated with circulating glucose. It is suggested that high values of blood fibrinogen results in hyperglycaemia mediated active coagulation[16]. Thus, poor impaired glycaemic control results in thrombophilia lead to raises the threat of cardiovascular diseases in diabetics. A study by Zaidi I A et al indicated similar results and proved that elevated levels of fibrinogen are positively correlated with HbA1c and blood fasting sugar.[17]In our study the high levels of fibrinogen and homocysteine are found in patients without any complications so it would be helpful to estimate these biochemical markers in patients having high HbA1c levels to prevent future complications in diabetics.

High values of homocysteine were significantly high in uncontrolled diabetes revealed that impaired glycaemic control is related with harmful effects on the blood vessels.[18] It causes stimulation of impaired vasomotion, raises inflammatory responses, high oxidative stress, and widespread pro-coagulant state[19].

It is demonstrated that high values of homocysteine may suppress the signalling of insulin via an increase oxidative stress. Additionally, insulin resistance is independently link to high values of homocysteine in diabetic patients.[20] It is proposed that high level of homocysteine promote the synthesis and activation of IL-6 results in high values of insulin and insulin resistance, promote the production of inflammatory cytokine and make possible infiltration of macrophages results in reduction in sensitivity of insulin[21,22]. A study reported high values of homocysteine (HHcy) block the production of anti-oxidant glutathione and increase oxidative stress related with diabetes. Hence, hyperhomocystinemia may have a role to encourage hyperglycaemia moderately via oxidative stress[23].

A study reported the possible link of homocysteine with fibrinogen enhance the threat of cardiovascular problems. Study proposed that thioacetones of homocysteine is reacted with fibrinogen to form Hcys-fibrinogen and study found that both of these form clots consist of thin and tightly pack fibers as compare to human fibrinogens and highly opposed fibrinolysis[24,25].

Limitations of the study: Small sample size and limited to only one city of Pakistan. To confirm the relation of high level of fibrinogen and homocysteine further studies on both controlled and uncontrolled diabetic patients are needed.

CONCLUSION

It is concluded that besides the estimation of glycated haemoglobin as a predictor of harmful consequences of hyperglycaemia, the high level of fibrinogen along with homocysteine may be useful predictor of cardiovascular risk in uncontrolled diabetic people. It is therefore a need to screen especially uncontrolled diabetic people for finding their circulating levels of fibrinogen and homocysteine to lessen the chances of cardiovascular diseases.

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Authors Contribution*:*
KN: Conceived the idea, did practical work, and responsible and accountable for the accuracy or integrity of the work
HS: Literature search and referencing,
MZ: Data collection and manuscript writing
IAZ: Manuscript editing and proofreading.
AZB: Statistical Analysis
WS: data collection and write up.

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