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Original Research Article.

Role of Homocysteine in Development of Cardiovascular Disease in Type 2 Diabetes

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ABSTRACT

Object: Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. DM is a condition in which there is a chronically raised blood glucose concentration. Diabetes mellitus represents an important independent risk factor for the development of and mortality from coronary heart disease, and increases the risk by 2 to 4 times. An increased plasma homocysteine level is an important risk factor for vascular disease, including coronary atherosclerosis, in the general population. However, the role of hyperhomocysteinemia in the development of coronary artery disease (CAD) in patients with type 2 diabetes is unknown. Therefore, present study was conducted to determine the relationship between plasma homocysteine levels and the presence of CAD in patients with type 2 diabetes.

Materials and Methods: Patients of known or newly diagnosed cases of diabetes mellitus type 2 for 8 months duration who came through outdoor patient department (OPD) or indoor patient of Hi-tech hospital and research center, Bhubaneswar. Blood samples were collected in fasting state to analyzed for fasting blood glucose, lipid profile, Plasma homocysteine level.

Results: In DM patients, Homocysteine found to be statistically significant increased ($p < 0.001$) from 11.39 ± 0.91 to 19.19 ± 1.08 µmol/L by 68.48% with respect to control subjects.

Conclusion: The aforementioned observations suggested that elevated level of homocysteine could be responsible for the pathogenesis of CAD. Available evidence indicates that hyperglycemia increases risk for cardiovascular disease in diabetes mellitus.

Key Words: Diabetes Mellitus, Homocysteine, Hyperglycemia, Glycosylated Hemoglobin.

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INTRODUCTION

Diabetes mellitus is one of the common metabolic disease characterized by chronic hyperglycemia together with biochemical alteration in metabolism of carbohydrate, fat, and protein or relative deficiencies in insulin secretion and/or insulin action.[1]

The prevalence of known diabetes in urban areas of Indian subcontinent is>12%. Patients with long standing diabetes are at risk of developing both microvascular and macrovascular complications. Microvascular complications are nephropathy, neuropathy and retinopathy and that of macrovascular are myocardial infarction and stroke.[2]

Homocysteine, a sulfhydryl-containing amino acid, is an intermediate product in the normal biosynthesis of the amino acids methionine and cysteine.[3] It is an amino acid produced via demethylation of dietary methionine, which is abundant in animal protein.[4] Continuously elevated homocysteine level is thought to contribute to plaque formation by damaging arterial walls. High levels may also act on blood platelets and increase the risks of clot formation; however, whether high level of homocysteine actually cause cardiovascular disease has yet to be agreed upon. There are indications that elevated plasma homocysteine can predict early cardiovascular disease or cardiovascular events.[5] However, few prospective studies[6,7] in diabetes have shown an independent association between elevated plasma homocysteine level and all-cause mortality.

Therefore, the aim of the present study was to correlation between hyperhomocysteinemia with cardiovascular and type-2 diabetes that might be helpful for the prevention and management of disease in Indian peoples.

MATERIALS AND METHODS

This study was carried out in Department of Biochemistry and Hi-Tech Medical College & Hospital, Bhubaneswar, Odisha. The study was conducted in 100 human Subjects. Out of which 50 age matched normal healthy volunteers were considered as control Group-I and 50 were type 2 diabetes with cardiovascular complication (Male & Female) Group-II. A detailed history was collected from the patients before starting analysis, the written consent from all subjects were taken. The study was approved by institutional ethical committee and was carried out by keeping all ethical norms in mind. The various parameters which were studied include age of the patients (in years), sex, smoking history, blood pressure (mmHg), BMI (kg/m^2), history of ischemic heart disease (IHD). Blood Sugar levels (FBS, PPBS), plasma homocysteine levels, and glycosylated hemoglobin, were measured in both the cases and controls.

Blood samples were collected in the morning after overnight fasting in EDTA and sodium fluoride oxalate vials. The blood samples were centrifuge for 10min at 3000rpm, the plasma samples were stored at -20^0 C for measuring Hcy and fluoride oxalate sample were analyzed fasting and PP glucose level.

The analysis of Plasma Hcy method used a solid phase immunoassay system, which measures total homocysteine in plasma or serum (BioRad) and principal based on Protein bound homocysteine was reduced to free homocysteine and enzymatically converted to S-adenosyl- L-homocysteine (SAH) in a separate procedure prior to the immunoassay[8] and blood glucose (F and PP) was estimated using Trinder's method (GOD-POD, end point)[9], Glycosylated Hemoglobin was measured by Ion - exchange resin.[10,11]

Statistical Analysis

Statistical evaluation was performed using the statistical Package for the Social Sciences 16.0 (SPSS) software. Data obtained from the study groups were compared use the Student-t test. The results were expressed as mean ± standard deviation and p< 0.001 value was considered statistically significant.

Table 1: Defining characteristics of individuals participating in the study

Parameters	Group-I	Group-II
Total number of subjects (n=100)	50	50
Mean age (years)±SD	46.39 ± 10.25	48.96 ± 12.52
Male/ Female	31/19	30/20
Smoking (%)	27	28
Alcohols intake (%)	21	28

Values are given as mean ± SD from 50 subjects in each group.

Table 2: Comparison of all parameters between study groups

Parameters	Group	
	Group-I	Group-II
Blood Glucose (Fasting)	86.98 ± 10.94	154.73 ± 12.55**
Blood Glucose (Post prandial)	109.71 ± 16.28	227.92 ± 18.82**
HbA1c	5.4±0.30	9.44±2.31**
Homocysteine	11.39 ± 0.91	19.19 ± 1.08**

Values are given as mean ± SD from 50 subjects in each group.

***Shows the statistical significance between the patient group-II and control group-I (p < 0.001 highly significant)*

Table 3: Spearman's correlation between all study parameters in group-II (Type-2 DM with cardiovascular disease) subjects. (n=50)

Parameters	Blood Glucose (F)	Blood Glucose (PP)	HbA1c	Homocysteine
Blood Glucose (F)	--	0.914**	.818**	0.040
Blood Glucose (PP)	0.914**	--	0.860**	-0.153
HbA1c	0.818**	0.860**	--	0.035
Homocysteine	0.040	-0.153	0.035	--

***Correlation is significant at the P<0.01 level (2-tailed)*

Figure 01: Changes in Glucose (Fasting & PP) levels in Group I & II

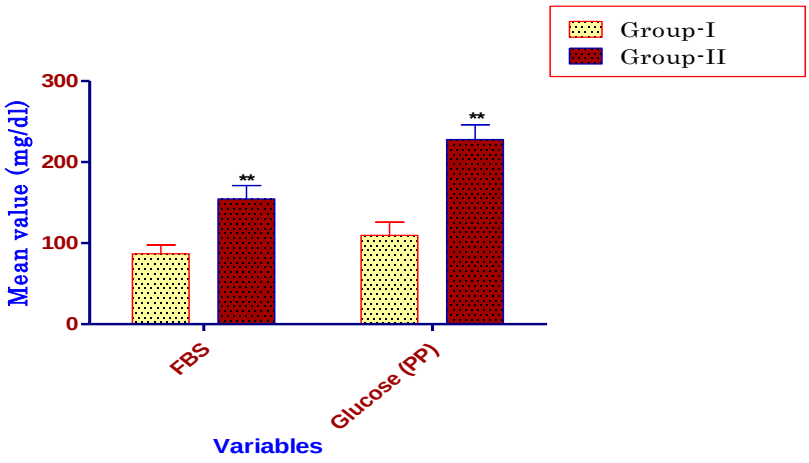

Figure no. 01- Changes in Glucose (Fasting and PP) lavel in Group -I (n=50) and Group-II(n=50) value are expressed as mean ± SD. statistical significance - **p< 0.001 significant.

Figure 02: Changes in HbA1c & Homocysteine levels in Group I & II

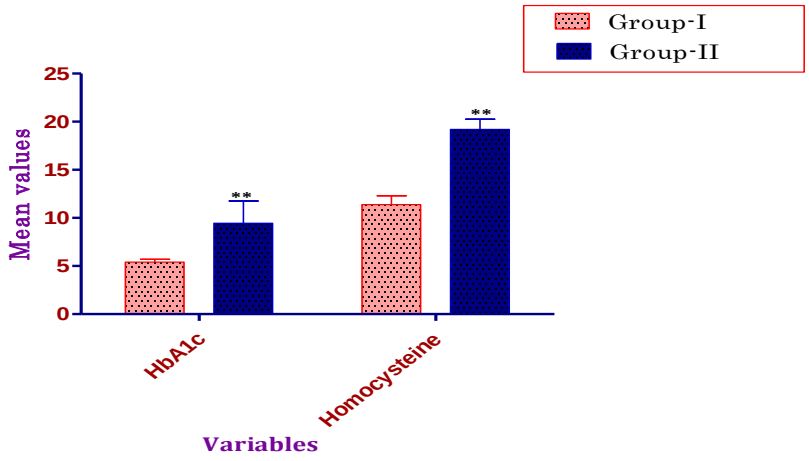

Figure no. 02- Changes inHbAc and Homocysteine lavel in Group -I (n=50) and Group-II(n=50) value are expressed as mean ± SD. statistical significance **p< 0.001 significant.

RESULTS

In the present study, Homocysteine level was estimated in 50 Type-2 diabetes mellitus subjects and 50 age and sex matched controls. Homocysteine levels were correlated with FBG, PPBG and glycosylated Hemoglobin (HbA1c). Table-1 shows some demographic characteristics of the study population. The mean age in the cases and Controls was 48.96±12.52 and 46.39±10.25 years respectively, with no significant difference in mean age (Table 1). The youngest age was 33 years. Among 50 patients studied 60% were male and 40 % were female (Table 1). In this study M:F ratio is 1.5:1. There were no difference between groups with respect to age and sex.

The mean Plasma fasting blood glucose level in Type-2 diabetic patients (Group-1) was 86.20±8.28 mg/dl. The mean Plasma fasting blood glucose level in Control was 167.70±59.80mg/dl (Table2). Group-1 had a higher plasma fasting blood glucose level when compared to Control and normal range (70-100mg/dl) and it was statistically significant (p<0.001). The mean plasma PPBS values of control are 107.20±19.11 and that of patients is 238.30±81.31. This increase in the PPBS value in patients compared to shows statistically very large effect (p<0.001).

The mean HbA1c level in Type-2 diabetic patients (Group-II) was 19.19±1.08. The mean HbA1c level in Controls was 11.39±0.91. Group-1 had a higher HbA1c level when compared to Control and normal range (4-6%) and it was statistically highly significant (p<0.001). the mean HbA1c value indicates poor metabolic control among the diabetics.

Table 2 and Figure 3 shows the result of Homocysteine found to be statistically significant increased (p<0.001) from 11.39 ± 0.91 to 19.19 ± 1.08 µmol/L by 68.48% with respect to control subjects.

DISCUSSION

In the present study diabetic had higher homocysteine level than controls signifying increased cardio-vascular risk. The possible mechanism by which homocysteine increases cardiovascular risks are not fully understood.

Homocysteine is a by-product formed in the biological transmethylation reactions and detoxified with the methionine

synthetase, which is the enzyme depending on vitamin B12, B6, and folate as coenzymes for proper functioning S-adenosylmethionine and methylation.[12,13] The increase in homocysteine levels might induce atherothrombosis via the formation of homocysteine thiolactate, a byproduct of oxidation of homocysteine. Homocysteine thiolactate combines with low density lipoprotein (LDL) to form LDL- homocysteine thiolactone aggregates. These are taken up by macrophages and subsequently incorporated into foam cells in early atherosclerotic plaques.[14,15] Homocysteine thiolactate could also impair the oxidative phosphoryation and enhancement of the proliferation and fibrosis of smooth muscle cells.[16]

In our cross sectional study, we studied the different blood parameters in patients of type 2 diabetics and compared the results with the non-diabetic healthy population. We found significantly higher levels of fasting blood glucose, post-prandial blood glucose and glycosylated haemoglobin (HbA1c) in the diabetic population (group II); also, the homocysteine were significantly higher in diabetics in comparison to normal healthy volunteers. The results from our study showed homocysteine to be significantly higher in diabetic patients than the control and it is consistent with the study of Poodeh et al also shows that high serum Hcy level in type-2 DM with Atherosclerosis Patients.[17]

A S Bembde found homocysteine to be higher in diabetic patients than the control. Increase in plasma concentration of homocysteine, associated with the increased incidences of atherosclerosis and other cardiovascular disease.[18,19] In 1969, Mc Cully made the first correlation between high plasma homocysteine and vascular disease.[20]

Drzewoski et al reported in their studies that elevated blood levels of homocysteine is strongly related to an increased risk for atherosclerosis and cardiovascular disease.[21] High plasma homocysteine level has been also reported as an independent risk factor for atherosclerosis, cardiovascular disease, and venous thrombosis.[22-24]

Our study showed homocysteine to be significantly associated with the glycosylated hemoglobin (Figure- 2). Homocysteine level increased as the value of HbA1c become higher. Homocysteine is also a marker of altered physiology in diabetes. A study by Drzewoski showed that diabetic subject had increased level of homocysteine and there was highly significant correlation between serum Hcy and HbA1c.[25]

The result of various studies about impact of glycemic control on plasma homocysteine is in consistent. Some previous studies suggested there no significant correlation between serum homocysteine and glycemic control. Sheikh et al report there is no significant association between serum homocysteine and HbA1c concentration.[26] In another study Aghamohammadi et al suggested there is no statistically significant correlation between homocysteine and glycemic control.[27]

Available evidence indicates that hyperglycemia increases risk for cardiovascular disease in diabetes mellitus.

CONCLUSION

Diabetes Mellitus is a common metabolic disorder associated mainly with disturbance in carbohydrate, lipid and protein metabolism. Diabetes Mellitus represents an important independent risk factor for development of mortality from cardiovascular disease.

Homocysteine (Hcy) contribute significantly to the risk of coronary artery disease and increases thrombotic risk. In conclusion, the aforementioned observations suggested that elevated levels of homocysteine could be responsible for the pathogenesis of CAD. Plasma homocysteine level could be used as possible predicting risk factor for premature cardio vascular event in type-2 diabetes mellitus.

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REFERENCES

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care, 2005; 28(1): 537-42.

2. Neil HA, Gatling W, Mather HM, Thompson AV, Thorogood M, Fowler GH, Hill RD, Mann JI. The Oxford Community Diabetes Study: evidence for an increase in the prevalence of known diabetes in Great Britain. Diabet. Med., 1987 Nov-Dec; 4(6): 539–43.

3. Owoaje EE, Rotimi CN, Kaufman JS, Tracy J, Cooper RS. Prevalence of adult diabetes in Ibadan, Nigeria. E. Afr. Med. J., 1997 May; 74(5): 299–302.

4. UK Prospective Diabetes Study Group Prospective Diabetes Study IV. Characteristics of newly presenting type 2 diabetic patients: male preponderance and obesity at different ages - Multicenter Study. Diabetic Medicine. 1988; 5: 154–159.

5. Ebesunun MO, Agbedana EO, Taylor GOL, Oladapo OO. Plasma lipoprotein (a), homocysteine and other cardiovascular disease(CVD) risk factors in Nigerians with established CVD. Appl. Physiol. Nutr. Metab., 2008; 33: 282–289.

6. Soinio M, Marniemi J, Laakso M, Lehto S, Rönnemaa T. Elevated plasma homocysteine level is an independent predictor of coronary heart disease events in patients with type 2 diabetes mellitus. Ann. Intern. Med., 2004 Jan 20; 140(2): 94–100.

7. Nygard O, Voiliset SE, Refsum H, Stenvoid L, Tverdal A, Nordnehang JE. Total homocysteine and cardiovascular risk profile–the Hordland homocysteinestudy.JAMA1995;274:1526-33.

8. Homocysteine by Enzyme Immunoassay. BIORAD- (Company Manual) 1997.

9. Trinder P. Determination of glucose in blood using glucose oxidase with an alternative oxygen receptor. Ann. Clin. Biochem. 1969; 6: 24–27.

10. Trivelli, L.A., Ranney, P.H and Lai, H.T. Hemoglobin components in patients with diabetes mellitus. N. Eng. J. Med., 1971 Feb 18; 284(7): 353-7.

11. Gonen B., Rubenstein, A.A. Haemoglobin A1 and diabetes mellitus. Diabetalogia, 1978 Jul; 15(1): 1-8.

12. Coral K, Angayarkanni N, Gomathy N, Bharathselvi M, Pukhraj R, Rupak R. Homocysteine levels in the vitreous of proliferative diabetic retinopathy and rhegmatogenous retinal detachment: its modulating role on lysyl oxidase. Invest. Ophthalmol. Vis. Sci., 2009; 50: 3607–12.

13. Chiang PK, Gordon RK, Tal J, Zeng GC, Doctor BP, Pardhasaradhi K, McCann PP. S-Adenosylmethionine and methylation. FASEB J., 1996; 10: 471-80.

14. Ernst E. Fibrinogen as a cardiovascular risk factor Interrelationship with infections and inflammation. Eur. Heart J., 1993; 14: 82K-87K.

15. Angeline T, Aruna RM, Ramadevi K, Mohan G, Jeyaraj N. Homocysteine status and acute myocardial infarction among Tamilians. Ind. J. Clin. Biochem., 2005; 20: 18-20.
16. Miller AL. Cardiovascular disease-Towards a unified approach. Alt. Med. Rev., 1996; 3: 132-147.
17. Poodeh BM, Ghanaat K, Kenari SA,Kashi Z, Izadi J, Tarsi AK. The relationship between serum homocysteine and incidence of atherosclerosis in patients with type-2 diabetes mellitus. J. Mazandaran Univ. Med. Sci., 2015; 25(121): 21-30.
18. Kuldip S, Amandeep S. Changes in plasma fibrinogen, homocysteine and lipid profile in coronary artery disease patients of north Indian (Punjab) population. Biomed. Res., 2008; 19 (2): 125-128 .
19. Mutus B, Rabini RA, Staffolani R, ricciotti R, Fumelli P, Moretti N, Martarelli D, Mazzanti L. Homocyateine induced inhibition of nitric oxide production in platelets; a study on healthy and diabetic subjects. Diabetologia 2001; 44: 979-982.
20. Mc Cully, K.S. Vascular pathology of homocysteine: Implications for the pathogenesis of arteriosclerosis. Am. J. Pathol., 1969; 56: 111-128.
21. Drzewoski J, Czupryniak L, Chwatko G, Bald E. hyperhomocysteinemia in poorly controlled type 2 diabetes patients. Diabetes Nutr. Metab., 2000; 13: 319–24.
22. Angeline T, Aruna RM, Ramadevi K, Mohan G, Jeyaraj N. Homocysteine status and acute myocardial infarction among Tamilians. Ind. J. Clin. Biochem., 2005; 20(1): 18-20
23. Miller AL. Cardiovascular disease-Towards a unified approach. Alt. Med. Rev., 1996; 3: 132-147.
24. McCully KS, Wilson RB. Homocysteine theory of arteriosclerosis. Arteriosclerosis, 1975; 22: 215-227.
25. Drzewoski J, Czupryniak L, Chwatko G, Bald E. Total plasma homocysteinemia and insulin level in type 2 diabetes patients with secondary failure to oral agents. Diabetes Care, 1999; 22(12): 2097-2099.
26. Sheikh MK, Devrajani BR, Shaikh A, Shah SZA, Shaikh S Singh D. Plasma homocysteine level in patients with diabetes mellitus. World Appl. Sci. J. 2012; 16(9): 1269-73.
27. Aghamohammadi V, Pourghassem Gb, Aliasgharzadeh A. Evaluation of the level of plasma homocysteine in patients with type-2 diabetes mellitus under metformin treatment and its correlation with serum total antioxidant capacity, malondialdehyde, creatinine, insulin resistance and glycemic control. J. Zanjan Univ. Med. Sci. 2011; 19(76): 1-11.

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