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TO ASSESS THE SERUM HOMOCYSTEINE LEVELS AND ITS CORRELATION WITH LIPID PROFILE IN TYPE II DIABETES MELLITUS PATIENTS IN TERTIARY CARE CENTRE - A CASE CONTROL STUDY

Sagar H[1], G B Doddamani[2], Chandrashekhar Karpoor[3], Harish G Bagewadi[4*], Devendrappa B G [5], Shivalee. A[6], Rohini Kallur[7]

[1]Assistant Professor, Department of General Medicine, Gulbarga Institute of Medical Sciences, Kalaburagi, India.
[2]Professor & HOD, Department of General Medicine, Gulbarga Institute of Medical Sciences, Kalaburagi, India.
[3]Professor & HOD, Department of Physiology, Gulbarga Institute of Medical Sciences, Kalaburagi, India.
[4]Associate Professor, Department of Pharmacology, Gulbarga Institute of Medical Sciences, Kalaburagi, India.
[5]Biostatistician, Department of Community Medicine, Gulbarga Institute of Medical Sciences, Kalaburagi, India.
[6]Research Scientist, Multi-Disciplinary Research Unit, GIMS, Kalaburagi, India.
[7]Research Scientist, Multi-Disciplinary Research Unit, GIMS, Kalaburagi, India.

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Corresponding Author: Dr. Harish G Bagewadi, Department of Pharmacology, Gulbarga Institute of Medical Sciences, Kalaburagi.
Email: harish2957@gmail.com

Abstract

Background: Diabetes mellitus is a widely prevalent disease that has apparently become a global epidemic. Hyperhomocysteinemia have a strong association with the onset of atherosclerosis. Elevated homocysteine in type-II DM causes endothelial cell damage by extravagant sulfation of collagen which increases risk of thrombosis and arteriosclerosis. Exploration of newer novel biomarkers in diabetes mellitus is a felt need to halt the disease prognosis and severity. **Materials and Methods:** In the present study, total 80 subjects were recruited. They were grouped into cases (n=40), type II diabetes mellitus patients and apparently healthy controls (n=40). Blood samples were collected for estimation of random blood sugar, HbA1c, serum homocysteine and lipid profile. **Results:** Homocysteine level (Hcy) among diabetic patients was 23.6 ± 11.4 µmol/L which was significantly higher than control group (9.54± 2.64 µmol/L, $p < 0.001$). Serum TG and VLDL were significantly higher among diabetic patients with hyperhomocysteinemia than diabetic patients with normal with serum homocysteine. Positive correlation of homocysteine was observed with RBS and HbA1c (r =0.562 and 0.743 respectively). **Conclusion:** Type 2 diabetes mellitus patients are at risk of having hyperhomocysteinemia which leads to dyslipidemia. There is a strong positive correlation between hyperhomocysteinemia and hyperglycemic state. This can be one of the important casual factor in pathogenesis of coronary heart disease events among diabetes patients.

Keywords: Diabetes mellitus, Lipid profile, Biomarkers, Homocysteine, HbA1c

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Introduction

Diabetes is associated with accelerated atherosclerosis leading to widely distributed vascular lesions including cardiovascular disease, coronary artery disease, cerebrovascular disease and peripheral arterial disease with cardiovascular disease being the major cause of premature death in diabetes.[1] Dyslipidemia amplifies the risk of developing atherosclerosis and subsequently cardiovascular disease in diabetes. Indeed, a significant association was observed between dyslipidemia with high level of total Cholesterol/HDL-C ratio, triglycerides and arterial stiffness leading to the development of atherosclerosis in diabetic patients compared to non-diabetic individuals.[2,3] There are numerous studies which have shown higher prevalence of dyslipidemia with poor glycemic control, increasing plasma levels of glycated hemoglobin (HbA1c) and hypercholesterolemia in diabetic individuals.[4,5] Diabetic individuals are highly prone to coronary artery diseases and hence it is necessary to search for advanced novel biomarkers to assess the coronary artery diseases risk.

Homocysteine (Hcy) is a non-essential sulphur containing amino acid which is produced as an intermediate during conversion of methionine to cysteine. Elevated Homocysteine levels promote insulin resistance and beta cell dysfunction through its adverse metabolic effects, ultimately contributing to the pathogenesis of type 2 diabetes and associated complications.[6] Putative mechanisms of atherothrombosis in hyperhomocysteinemia include endothelial cell injury, endothelial dysfunction, increased vascular smooth muscle cell growth, increased platelet adhesiveness, enhanced LDL oxidation and deposition in the arterial wall and direct activation of the coagulation cascade.[7] Hyperhomocysteinemia can be corrected with vitamin therapy.[7] Insulin resistance and hyperinsulinemia in diabetes mellitus along with increased homocysteine is thought to cause endothelial dysfunction. Dyslipidemia is one of the major risk factors for cardiovascular disease in diabetes mellitus. The lipid changes associated with diabetes mellitus are attributed to increased free fatty acid flux secondary to insulin resistance.[8] Diabetic patients having hyperhomocysteinemia suffer from increased mortality and morbidity from cardiovascular disease events.

In the literature, some studies have observed a positive correlation between insulin levels or insulin resistance and plasma homocysteine levels.[9] Further, insulin has also been reported to inhibit the conversion of homocysteine into cysteine by the trans-sulfuration pathway.[10] Elevated homocysteine level in blood is said to be associated with increased lipid peroxidation. It is suggested that lipid lowering drugs may be helpful for management of endothelial dysfunction in individuals with hyperhomocysteinemia.[11] Both acute and prolonged exposure to Homocysteine has detrimental effect on beta cell glucose metabolism, insulin secretary responsiveness and cell viability.[12] Homocysteine generates reactive oxygen species in a redox-cycling reaction that explains the decline in viability of insulin secreting cells leading to reduced glucokinase phosphorylating ability, diminished insulin secretory responsiveness and cell death.[13]

Hyperhomocysteinemia has been demonstrated in type-II DM patients in some previous studies, and may be a contributory factor in the development of vascular complications.[14] According to Wijekoon *et al.*,[15] an increase in the plasma level of homocysteine has been identified as a risk factor for many diseases, including cardiovascular disease. According to Abraham *et al.*,[16] the two pathways which metabolize homocysteine are trans-sulfuration and re-methylation. Excess of homocysteine present in the blood circulation leads to formation of a major byproduct, homocysteine thiolactone. This by-product is entrapped by macrophages and later incorporated into foam cells as early atherosclerotic plaques. Within these plaques, homocysteine thiolactone acylates the proteins and modifies the oxidative processes of vessels. This in turn promotes atherothrombosis. Moreover, oxidation of homocysteine results in the formation of superoxide and hydrogen peroxide. Such oxygen-derived

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molecules may contribute to oxidation of LDL, and hence, endothelial dysfunction further promotes proliferation of the smooth muscles of blood vessels. In a previous study done by Ronald *et al.*[17] it is observed that lipid abnormalities are due to resistance to insulin and hyperglycemia.

In previous studies, folic acid and vitamin B12 supplements have been proved to be helpful to decrease homocysteine levels in circulation.[18] The most effective defense against homocysteine buildup is a combination of vitamins B6, B-12 and folic acid, which convert homocysteine into nontoxic substances. Increased serum homocysteine level is a risk factor for accelerated atherosclerosis.[18] Patients with homocysteinuria display early onset of arteriosclerosis and venous thrombosis.[19] High levels of homocysteine are believed to promote the formation of oxidation products such as homocysteine disulfide and homocysteine thiolactone. These oxidation products damage vascular endothelium by causing excessive sulfation of collagen, which in turn promotes thrombosis and arteriosclerosis. In a study conducted by Lentz *et al.*[20] it was demonstrated that serum homocysteine levels are an independent risk factor for cardiovascular disorders in type 2 diabetes patients. In the recent systemic review analysis, it was observed that Metformin administration was not statistically associated with the change of homocysteine levels when compared with the control treatment.[21] Previous studies indicated that the plasma homocysteine levels did not show a significant difference between those in the Metformin and the non-Metformin treated groups in type II diabetes mellitus patients.[22,23] Homocysteine has been recommended as an independent and important predictor of complications in DM, primarily atherothrombotic events.[24] In a study done by Ebru *et al.*[25] it was observed that serum homocysteine is independent risk factors for cardiovascular disease. Hyperhomocysteinemia is defined as a concentration of Homocysteine levels ≥15 μmol/l.[26] Homocysteine levels in the blood have been associated with increased lipid peroxidation. The relationship between serum homocysteine levels and type 2 diabetes is still debated. Future studies needs to be undertaken which can find the association that the diabetic patients have deranged levels of serum homocysteine and their association with dyslipidemia, will give promising leads to develop the scope of primary and secondary preventive measures of cardiovascular disease in those patients. As diabetic individuals are at higher risk of vascular disease, therefore it is required to look for reliable novel biomarkers that can help in predicting prognosis and severity of the disease.

With this background, the present study was conducted to assess the serum homocysteine levels and lipid profile of the patients of type 2 diabetic patients and to correlate serum homocysteine with lipid profile.

Aims and Objectives

1. To estimate the serum levels of Homocysteine.
2. To estimate the serum levels of serum cholesterol, triglycerides, HDL, LDL, VLDL cholesterol.
3. To study the association of homocysteine with the components of lipid profile and glycated hemoglobin in type II diabetic patients.

Materials and methods

This was a hospital based case control study. The study participants were recruited from OPD and IPD of department of General medicine. The study was done from May 2023 to July 2024. Institutional Ethics Committee permission was taken before the conduct of the study. Written informed consent was obtained from all the subjects before their participation.

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Inclusion criteria- Individuals aged 30-65 years, diagnosed with diabetes mellitus with patient with random plasma glucose of 200 mg/dl were recruited. Apparently healthy controls aged between 30-65 years inclusive of both sexes were matched and included in the study.
Exclusion criteria- Patients with history of liver disease, thyroid disorders, type I diabetes mellitus, females on oral contraceptives, pregnant and lactating mothers because of the associated hormonal changes which affect body metabolism. Patients on anti-epileptic and anti-cancer drugs were also excluded from the study since these patients show false high levels of homocysteine. Patients on lipid lowering drugs, multivitamins supplementation were excluded from the study.
In the present study, total 80 subjects were recruited. Type II diabetes mellitus patients (n=40) and apparently healthy controls (n=40) aged between 30-65 years inclusive of both sexes were matched. Calculations were done by the Epi Info software, a program developed by the centres for disease control and prevention, available at www.cdc.gov/epiinfo. The study measurable parameters had 6% margin of error, with 10% as the prevalence rate of diabetes in a previous study done by Mathur *et al.*[27] With the % of controls exposed is 70%, odds ratio of 10, ratio of controls to cases is 1 and with a power of 80% and 95% confidence interval, By substituting the values, we calculated a sample size of 40 cases and 40 controls. Total sample size = 80.
Our calculated sample size and sampling methods are in accordance with previous studies done by Dharmesh G, *et al.*[28] and Saurabh B, *et al.*[29] General information such as age, gender, occupation, literacy status, smoking status and socio-economic status were collected. Biochemical measurements: The blood sample (5ml) was withdrawn from all subjects by vein puncture. 2ml of the blood was placed in EDTA tubes and stored at (2-8 c) for HbA1c measurement. The remaining 3 ml of the blood was placed in plane tubes. The blood sample was centrifuged (at 3000 rpm for 10 minutes). The serum was isolated and stored at 2 to 8 degrees Celsius and analyzed for random blood glucose, HbA1c, lipid profile and homocysteine levels. Determination of random blood glucose and HbA1c, lipid profile- was done by automatic biochemistry analyzer. The serum homocysteine level was determined using a commercially available ELISA kit.

Statistical Analysis
The quantitative variables were expressed as Mean ± Standard Deviation. The qualitative variables were expressed as counts and percentages. Values of diabetic and control group were compared by applying unpaired student's t-test. Pearsons correlation regression test was applied. p value ≤ 0.05 was considered as statistically significant. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 16.

Results
Table 1. Shows the comparison of socio demographic profile and laboratory parameter between cases and control group. Both groups were comparable for age and gender distribution. The glycemic parameters (RBS, HbA1c) were significantly higher in diabetic patients as compared to control group. Lipid profile parameter such as TG, VLDL was high significantly among diabetics than non-diabetic patients. Whereas Cholesterol, HDL and LDL were higher among diabetic than non-diabetic patients but not statistically significant.
Table 1: Comparison of socio demographic profile and laboratory parameters between cases and control group.

Parameter	Control group (n = 40)	Diabetic group (n= 40)	p-value
Age (years)	47.7±9.49	47.8±9.28	0.989

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Male: Female	17: 23	22: 18	-
Smoker	2 (5.0%)	04 (10.0%)	-
BMI	21.9 ± 2.31	26.6 ± 1.85†	< 0.01
RBS (mg/dL)	126± 37.85	351±101.6†	< 0.01
HbA1c (%)	6.27± .458	11.6 ± 1.94†	< 0.01
S. Hcy (µmol/L)	9.54± 2.64	23.6± 11.4†	< 0.01
S. Cholesterol (mg/dL)	190± 37.4	208± 57.6	0.119
S. TG (mg/dL)	223± 11.5	298± 33.5	< 0.01
S. LDL (mg/dL)	104± 3.58	115± 4.01	0.196
S. HDL (mg/dL)	45.6± 8.89	43.1± 7.25	0.150
S. VLDL (mg/dL)	44.5± 2.33	60± 4.33†	< 0.01

†p<0.01 versus control group

From figure- 1 and table 1, it was observed that serum homocysteine level (Hcy) among diabetic patients was 23.6± 11.4 µmol/L which was significantly higher than control group (9.54± 2.64 µmol/L, p < 0.01).

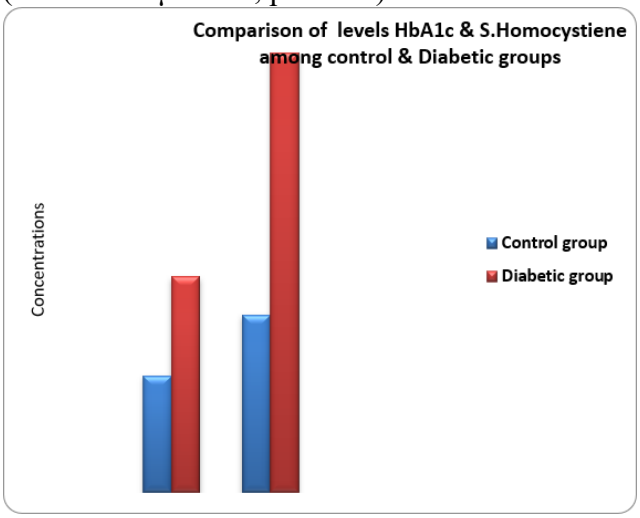

Figure 1: Shows the comparison of levels of HbA1c and serum homocysteine.

Table 2: The diabetic patients were divided into two groups according to serum homocysteine levels. A serum (Hcy) level of ≥ 15.0 µmol/L is considered as hyperhomocysteinemia. Total 34 patients had hyperhomocysteinemia and 06 diabetic patients had homocysteine level ≤ 15.0 µmol/L.

Variables	S. Hcy ≤ 15 µmol/L (n = 6)	S. Hcy ≥ 15 µmol/L (n = 34)	p-value
RBS (mg/dL)	294± 131	415± 99.9*	.044
HbA1c (%)	9.32 ± .445	13.7± 2.16††	.004
S. Cholesterol (mg/dL)	195± 27.1	271± 67.0†	.010
S. TG (mg/dL)	239 ± 66.7	407 ± 213*	.049
S. HDL (mg/dL)	104± 19.5	158± 36.2††	.001
S. LDL (mg/dL)	42.5± 4.76	46.0 ± 8.88	.321
S. VLDL (mg/dL)	47.8 ± 13.2	81.5± 42.6*	.049

*p<0.05, †p<0.01, ††p<0.001 versus S. Hcy ≤ 15 µmol/L group

From figure 2 and table 2, it was observed that serum TG, VLDL levels were high in diabetic patients with hyperhomocysteinemia than diabetic patients with serum homocysteine ≤ 15

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µmol/L which was statistically significant (<0.01). Where as serum cholesterol, LDL, HDL, levels were high among diabetic hyperhomocysteinemia with diabetic patients homocysteine level <15.0 µmol/L but were not statistically significant.

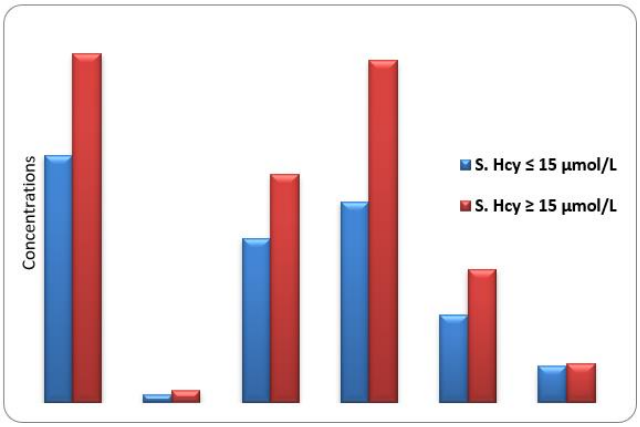

Figure 2: Shows the comparison of RBS, HbA1c and lipid profile among varied homocysteine groups.

Table 3: Shows the correlation between serum homocysteine and other parameters.

Correlation	r- value	p-value
Hcy and RBS	0.562	< 0.001
Hcy and HbA1c	0.743	< 0.001
Hcy and S. Cholesterol	0.0925	0 .432
Hcy and S. TG	0.0015	< 0.05
Hcy and S. HDL	0.121	< 0.05
Hcy and S. LDL	0.0103	< 0.05
Hcy and S. VLDL	0.0015	< 0.05

In table 3, it was observed that there was positive correlation of homocysteine with and RBS, HbA1c, TG, HDL, LDL, VLDL which was statistically significant <0.05. The positive correlation of homocysteine was not statistically significant with serum cholesterol.

Discussion

The present study was planned to evaluate the association of homocysteine and components of lipid profile in diabetic patients. In the present study, 85% of the diabetic subjects had serum Hcy≥15 µmol/L. Serum Hcy level among diabetic patients (23.6± 11.4 µmol/L) was higher than control group (9.54± 2.64 µmol/L, p < 0.01). Our study findings are in accordance with previous studies done by Mujumder M *et al.*[30] and Chico *et al.*[31]

According to Puri *et al.*[32] the mean level of homocysteine in diabetes patients was nearly double that of controls. Homocysteine levels >18 mol/L were found in 72.5% of patients, but in only 26.7 % of controls. On the contrary, Wollesen *et al.*[33] found that serum Hcy levels in type 2 diabetic patients (10.6 µmol/L) were insignificant (p>0.05) when compared to control (11.1 µmol/L). Hyperhomocysteinemia has been demonstrated in type-II DM in previous studies and may be a contributory factor in the development of vascular complications.[34] According to Wijekoon *et al.*,[35] an increase in the plasma level of homocysteine has been identified as a risk factor for many diseases, including CVD. In type II diabetes, betaine homocysteine methyl transferase enzyme was observed to play a major role in the increased catabolism of homocysteine in addition to the trans-sulfuration enzymes. In previous studies on diabetic patients, the association between increased plasma homocysteine levels and

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occurrence of CHD has been strong in case–control as well as cross-sectional studies.[36-38] The explanation of significance of hyperhomocysteinemia in type II diabetes is complex. Multiple ways of considering impaired renal function either decreased creatinine clearance or albuminuria or both may be complicated.[39] According to Nickolas *et al.*,[40] atherosclerosis in diabetes mellitus is a persistent low-grade inflammatory condition. Hyperhomocysteinemia is a substantial risk factor for atherosclerosis in both diabetic and non-diabetic people. It has the potential to cause chronic vascular complications.[41] Despite numerous studies, the association between hyperhomocysteinemia and cardiovascular risk is still unknown.

In the present study, components of lipid profile namely cholesterol, TG, LDL, and VLDL were significantly higher in the diabetic group in comparison to the control group. The LDL levels were higher among diabetic hyperhomocysteinemia with diabetic patients homocysteine level <15.0 μmol/L but not statistically significant. Balu *et al.*[42] found significant difference in serum Hcy, serum cholesterol, LDL and HDL levels when compared to controls. The relationship of high Hcy with high cholesterol levels observed in this study indicates causal relationship between plasma Hcy and cholesterol. According to Li *et al.*,[43] high serum Hcy has a

positive effect on the hydroxyl methyl glutaryl CoA synthase enzyme and resulting hypercholesterolaemia. Furthermore, they suggested that high Hcy increases cholesterol accumulation in the endothelial cells. In a similar study by Sniderman *et al.*,[44] hypertriglyceridemia along with increased numbers of small dense LDL particles and low levels of HDL cholesterol were reported. Insulin resistance and hyperglycemia leads lipid abnormalities. The aetiology of this dyslipidemia could be due to increased secretion of TGs rich in VLDL from the liver and their poor clearance.[45] Increased lipid peroxidation is also linked to elevated blood Hcy levels, which predisposes to atherosclerosis. According to Hoogeveen *et al.*[46], hyperhomocysteinemia raised the risk of cardiovascular disease by 1.6 times in type 2 diabetes mellitus patients compared to non-diabetic people.

In the present study, significant positive correlation of homocysteine was observed with and RBS and HbA1c (r = 0.562 and 0.743 respectively). Bansal S *et al.*[47] also observed positive correlation of Hcy with FBS (0.631) and HbA1c (0.416). HbA1c levels were also considerably greater in T2DM patients with hyperhomocysteinemia compared to patients with normal homocysteine levels, according to O A Ala *et al.*[48] The findings suggest that metabolic regulation may have an impact on Hcy levels.[49]

Conclusion

According to the findings of the present study, type 2 diabetes individuals are at risk of having hyperhomocysteinemia which leads to dyslipidemia and vice versa. While homocysteine is a marker of endothelial dysfunction, dyslipidemia is suggestive of cardiovascular complications. Assessment of these risk markers can, therefore, be helpful in early identification of patients at risk of developing such complications. As a result, serum Hcy is an novel biomarker marker that can be used to detect cardiovascular risk events in diabetes mellitus patients and can prevent further complications.

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Conflict of Interest- None.

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