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ORIGINAL ARTICLE

Serum Homocysteine and Its Association with Lipid Profile in Type II Diabetes Mellitus

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ABSTRACT

Introduction: Diabetes mellitus (DM) is a widely prevalent disease that has apparently become a global epidemic. Long-standing diabetes is characterized by development of several complications, including cardiovascular disease (CVD), nephropathy, neuropathy, and retinopathy. These complications share a common etiology of poor glycemic control and endothelial dysfunctions. Any metabolite which is atherosclerotic in nature may contribute to the development of such chronic complications. Dyslipidemia and hyperhomocysteinemia have been recognized as independent markers of atherosclerosis. However, their influence on each other and on insulin metabolism is highly debated. Evaluation of the association of these risk markers may be helpful in decreasing the occurrence of complications and increasing the age of diabetic patients.

Aim: The present study was planned to study the association of homocysteine with the components of lipid profile and glycated hemoglobin in type II diabetic patients. Serum homocysteine and lipid profile levels of diabetic patients were also compared with those of healthy nondiabetic subjects.

Results: Serum homocysteine and lipid profile were observed to have a strong association. Diabetic patients with hyperhomocysteinemia were reported to have higher S. cholesterol and low-density lipoprotein (LDL) levels. S. homocysteine was also found to be elevated in patients with HbA1c levels >8.0%, which indicates a poor glycemic control. On comparing with healthy subjects, S. homocysteine, cholesterol, triglycerides, LDL, and very low-density lipoprotein (VLDL) were also significantly higher in diabetic patients.

Conclusion: Regular screening for serum lipid profile and hyperhomocysteinemia is strongly recommended in patients suffering from type II DM. Proper patient management in terms of controlling lipid levels, hyperhomocysteinemia, and maintenance of a good glycemic control can assist in averting the development of various complications and enhancing the quality of life.

Keywords: Diabetes mellitus, Glycemic control, Homocysteine, Hyperhomocysteinemia, Lipid profile.

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INTRODUCTION

Diabetes mellitus includes a group of metabolic diseases characterized by elevated blood sugar concentrations for prolonged duration.[1] Its worldwide prevalence was reported as 8% in 2011 and is expected to rise to about 10% by the year 2030.[2] India is considered the "Diabetic Capital of the World." According to Wild et al,[3] the prevalence of diabetes is anticipated to increase to as high as 366 million by the year 2030. Further, it is expected that up to 79.4 million of the above-mentioned diabetic individuals shall be from India. Diabetes mellitus occurs due to defects in insulin secretion, insulin action, or both, and is mainly characterized by prolonged hyperglycemia.[4] Type II diabetes, also termed as noninsulin-dependent DM, occurs due to deficiency of insulin, and the insulin that is produced is less effective.

This disorder has a more gradual onset and is more common in age above 40 years. About 90% of diabetics are type II diabetics.[5] Insulin resistance and diabetes are considered to have a strong association with the development of various cardiovascular complications and morbidities. Patients with diabetes are considered to be at a two to three-fold higher risk of coronary artery disease and post myocardial infarction morbidity and also have four times higher mortality following acute myocardial infarction than nondiabetic persons. Premature atherosclerosis is often associated with type II diabetes.[6,7]

Several studies have demonstrated a positive correlation between glucose intolerance and CVD due to factors like obesity, hypertension, polycystic ovaries, smoking, sedentary lifestyle, certain ethnic groups, poorly regulated diabetes, and hyperinsulinemia. However, these factors are not sufficient to justify the strong association of diabetes with premature atherosclerosis.

Homocysteine, a sulfur-containing intermediate amino acid, has gained recognition as a significant risk factor for arteriosclerosis and atherosclerosis. It is produced as an

intermediate during conversion of methionine to cysteine. Hyperhomocysteinemia and homocysteinuria display a strong association with early onset of atherosclerosis and is manifested as arterial and venous thrombosis.[8]

Few studies have suggested that an increased level of homocysteine in type-II DM is related to increased risk of atherosclerosis and CVD, especially with a poor glycemic control. Homocysteine has been recommended as an independent and important predictor of complications in DM, primarily atherothrombotic events.[9]

Diabetic patients diagnosed with macroangiopathy and nephropathy have increased prevalence of elevated homocysteine levels. However, the relationship among macroangiopathy, renal disease, and hyperhomocysteinemia in type-II DM has not been established yet. Presently, the relationship between serum homocysteine levels and type II diabetes is highly debated.

Several studies have observed a positive correlation between insulin levels or insulin resistance and plasma homocysteine levels.[10,11] Further, insulin has also been reported to inhibit the conversion of homocysteine into cysteine by the trans-sulfuration pathway.[12] 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.[13] Evaluation of the association between serum homocysteine levels and various components of lipid profile in patients of type II DM may be helpful in assessing the risk of developing CVD and atherosclerosis. The present study, therefore, proposes to analyze the association of homocysteine and serum lipids in type II diabetic patients.

MATERIALS AND METHODS

One hundred newly diagnosed type II DM patients, age up to 65 years visiting the Outpatient Department of Mahatma Gandhi Medical College Hospital, Jaipur were enrolled for the present study. Fifty healthy individuals of similar age and either sex were enrolled for the study as control group. The study was conducted after seeking approval from Institutional Ethics Committee.

Patients more than 65 years of age, suffering from any significant renal or liver disease, or on lipid lowering drugs were excluded from the study. A written consent was taken from all subjects of case and control groups. Complete history of the subjects was taken and thorough physical examination was performed. Blood samples were collected following an overnight fast by venipuncture using standard aseptic techniques.

The samples were analyzed for fasting blood glucose, serum homocysteine, and serum lipid profile including serum cholesterol, triglycerides (TG), high-density lipoprotein (HDL), LDL and VLDL. All chemical assays were performed using ortho-clinical diagnostics reagents on dry chemistry analyzer VITROS 4600. The data obtained for each analyte were presented as mean ± SD. Values of diabetic and control group were compared by applying Student's t-test.

The diabetic group was further categorized based on the homocysteine levels as normal and hyperhomocysteinemia. Components of lipid profile were compared among these subgroups.

RESULTS

The present study was conducted on 100 patients suffering from type II DM and 50 normal healthy controls. The subjects included in the control group were asymptomatic persons free from any abnormality on routine examination. Mean age of subjects in control and diabetic group was comparable as shown in Table 1. The mean age of control group is 54.22 ± 11.64 years, whereas the mean age of diabetic group is 53.7 ± 15.1 years (Table 1).

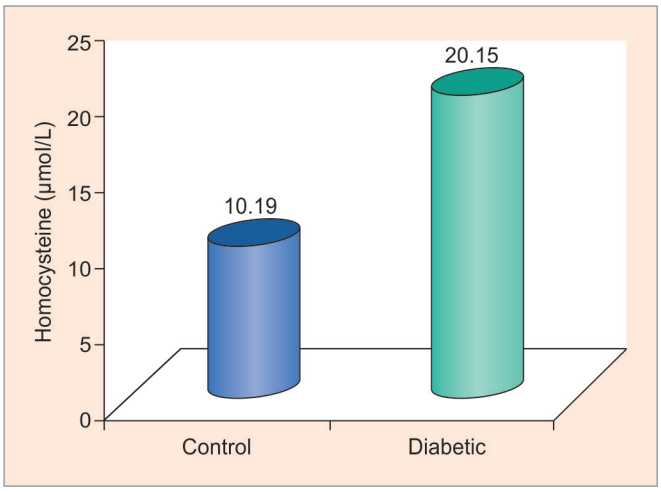
Mean fasting blood glucose level was observed to be significantly higher in the diabetic group (p = 0.000). The mean serum homocysteine concentration of diabetic group was 20.15 ± 7.13 µmol/L, which was significantly higher as compared to that of the control group, i.e., 10.19 ± 3.07 µmol/L (Table 1 and Graph 1). Variables of lipid profile were also compared between the two groups (Table 1 and Graph 2). In the present study, mean serum total cholesterol concentration was 151.24 ± 28.23 mg/dL in control group, whereas in the diabetic patients group, the mean serum total cholesterol was significantly higher (p = 0.000), the value being 172.5 ± 43.8 mg/dL.

Serum TG level was also significantly increased in the diabetic group as compared to control group (p = 0.000). Serum LDL and VLDL-cholesterol were calculated using Friedwald's equation. Both LDL and VLDL showed a

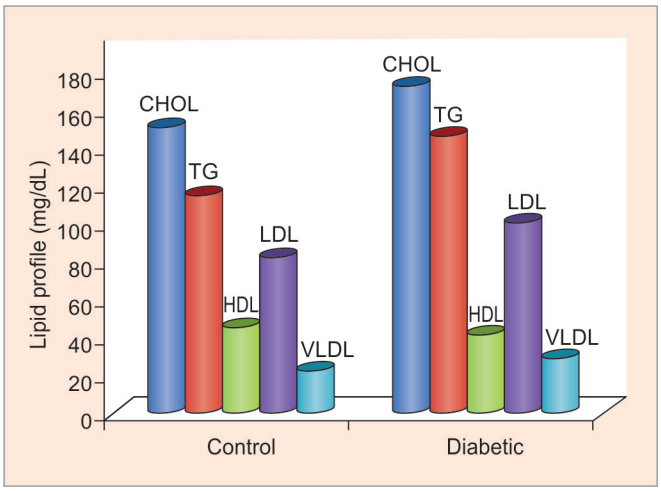
Table 1: Distribution of variables between diabetic patients and control group

Variables	*Diabetic patients (n = 100)*	*Control group (n = 50)*	*p-value*
Age (years)	53.7 ± 15.1	54.22 ± 11.64	NS
Blood sugar fasting (mg/dL)	245.60 ± 69.2	99.14 ± 12.58	0.000
S. homocysteine (µmol/L)	20.15 ± 7.13	10.19 ± 3.07	0.000
S. cholesterol (mg/dL)	172.50 ± 43.8	151.24 ± 28.23	0.000
S. triglycerides (mg/dL)	147.0 ± 68.6	115.32 ± 42.75	0.000
S. HDL-Chol (mg/dL)	42.0 ± 9.26	45.64 ± 6.93	NS
S. LDL-Chol (mg/dL)	101.0 ± 31.7	82.54 ± 21.70	0.000
S. VLDL-Chol (mg/dL)	29.39 ± 13.72	23.06 ± 8.55	0.000

NS: Nonsignificant



Graph 1: Comparison of homocysteine (µmol/L) between control and patient group

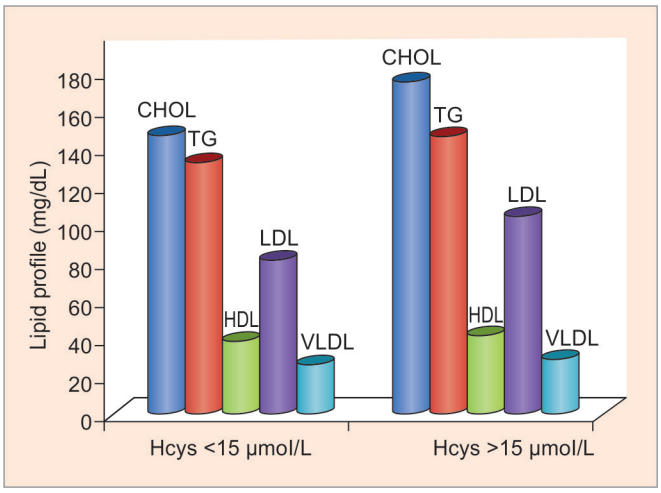


Graph 2: Comparison of S. lipid profile (mg/dL) between control and patient group

Table 2: Distribution of variables between normal and hyperhomocysteinemia subgroups

Variables	*S. homocysteine >15 µmol/L (n = 73)*	*S. homocysteine ≤15 µmol/L (n = 27)*	*p-value*
Blood sugar fasting (mg/dL)	245.9 ± 68.16	245.9 ± 73.10	NS
S. homocysteine (µmol/L)	23.0 ± 6.3	12.53 ± 1.12	0.000
S. cholesterol (mg/dL)	180.0 ± 43.9	151.26 ± 36.64	0.003
S. triglycerides (mg/dL)	151.0 ± 72.0	136.74 ± 58.47	NS
S. HDL-Chol (mg/dL)	42.58 ± 9.42	40.25 ± 8.77	NS
S. LDL-Chol (mg/dL)	107.6 ± 30.42	83.65 ± 28.91	0.000
S. VLDL-Chol (mg/dL)	30.14 ± 14.39	27.35 ± 11.69	NS

NS: Nonsignificant



Graph 3: Comparison of lipid profile (mg/dL) based on homocysteine group

Table 3: Distribution of S. homocysteine based on the HbA1c in type II diabetic patients

Variables	*HbA1c ≤ 8.0% (n = 22)*	*HbA1c > 8.0% (n = 37)*	*p-value*
S. homocysteine (µmol/L)	16.95 ± 6.05	21.24 ± 8.16	0.037

significant variation with higher mean values in the diabetic subjects.

Although a significant variation was not observed in case of HDL cholesterol, the level was slightly lower in type II diabetic patients.

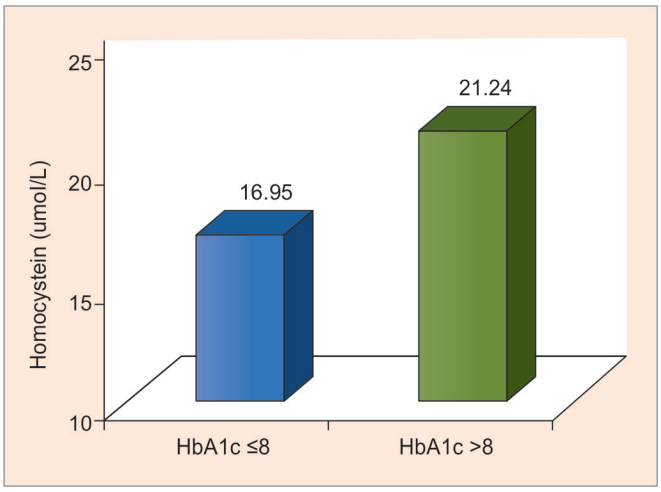
Further, the diabetic subjects (n = 100) were subgrouped based on the serum homocysteine levels. A serum homocysteine level of >15.0 µmol/L is termed as hyperhomocysteinemia; 27 patients of type II DM had homocysteine level <15.0 µmol/L and 73 had homocysteine level >15.0 µmol/L. The mean blood glucose in the two subgroups was almost same with no significant variation (Table 2).

On comparing serum lipid profile among the two subgroups, it was observed that there was a significant increase in the levels of serum cholesterol and LDL-cholesterol in the subgroup with hyperhomocysteinemia (Table 2 and Graph 3). Serum homocysteine levels were also compared in the diabetic subjects in relation to the glycemic control.

Of the total 100 diabetic patients enrolled in the study, 59 were evaluated for HbA1c, which is a reliable marker of glycemic control. Patients with a poor glycemic control (HbA1c > 8.0%) were found to have significantly higher serum homocysteine levels (Table 3 and Graph 4).

DISCUSSION

Diabetes mellitus is one of the leading causes of morbidity and mortality across the world and hence, is a global health



Graph 4: Comparison of S. homocysteine (µmol/L) based on HbA1c group

problem. Moreover, the complications associated with this disease have an adverse effect on the quality of life.[14] Homocysteine is a sulfur containing nonessential amino acid formed by demethylation of methionine as an intermediate during its conversion to cysteine. It has gained recognition as an important risk factor for arteriosclerosis.

Hyperhomocysteinemia refers to elevated homocysteine in plasma, generally >15.0 µmol/L and is a major contributing factor for atherosclerotic disease, both in diabetic and nondiabetic subjects. Hyperhomocysteinemia in diabetic subjects may lead to the development of chronic vascular complications.

Despite many research works conducted to study significance of homocysteine in diabetic patients, the association between hyperhomocysteinemia and cardiovascular risk remains unclear. Condition of DM influences several lipid metabolism mechanisms. The increased prevalence of coronary heart disease (CHD) among diabetics may be attributed to diabetes-induced dyslipidemia, particularly increase in the LDL component.

The present study was planned to evaluate the association of homocysteine and components of lipid profile in diabetic patients. 73% of the diabetic subjects had serum homocysteine >15 µmol/L. Wide range of health disorders, such as CVD, stroke, etc. have been associated with elevated homocysteine levels.

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. In a similar study by Sniderman et al,[15] hypertriglyceridemia along with increased numbers of small dense LDL particles and low levels of HDL cholesterol were reported.

Several studies have demonstrated a positive correlation between glucose intolerance and CVD with obesity, dyslipidemia, hypertension, polycystic ovaries, smoking, sedentary lifestyle, certain ethnic groups, poorly regulated diabetes, and hyperinsulinemia due to any reason or risk factors. However, not all of these factors are able to explain the strong association of diabetes with premature atherosclerosis.

Recently, it has been suggested that homocysteinemia can be an independent predictor of risk associated with DM, especially atherothrombotic events. Elevated plasma homocysteine concentration is considered as an independent risk factor for atherosclerosis in subjects with normal glucose tolerance. Although type-II diabetes is associated with premature atherosclerosis, very few studies have explored the association among hyperhomocysteinemia and micro/macroangiopathy complications with contradictory results.

Hyperhomocysteinemia has been demonstrated in type-II DM in previous studies,[16,17] and may be a contributory factor in the development of vascular complications.[18] According to Wijekoon et al,[19] 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. Elevated levels of serum homocysteine have been associated with state of CHD.

Several epidemiological studies have shown a relationship between serum homocysteine level and CHD.[20-22] In previous studies on diabetic patients, the association between increased plasma homocysteine levels and occurrence of CHD has been strong in case–control as well as cross-sectional studies.[23-25]

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[25-29] may be complicated. Puri et al[30] have reported that the mean level of homocysteine in diabetic patients was almost twice that in the controls. While 72.55% patients had homocysteine levels >18 µmol/L, only 26.67% controls had increased levels.

These findings are similar to the observations of present study in which 73% of the patients in diabetic group had homocysteine levels >15.0 µmol/L (Table 3). In the above-mentioned study, in the hyper lipid subgroup, homocysteine was 28.86 ± 13.02 µmol/L, while in the normolipid subgroup it was 26.46 ± 13.44 µmol/L. Thus no significant difference was exhibited in the homocysteine levels, in relation to the lipid profile.

According to Abraham et al,[31] 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 by-product, 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 molecules may contribute to oxidation of LDL, and hence, endothelial dysfunction further promotes proliferation of the smooth muscles of blood vessels. In the present study, higher serum cholesterol and LDL levels were reported in the diabetic subgroup with hyperhomocysteinemia.

Type-II DM patients suffer a greater risk of developing vascular disease due to deranged lipid profile; HDL cholesterol concentration is abnormally low in type II diabetic patients, which is unrelated to control of diabetes.[32] Lipid abnormalities in type II diabetic patients are described as increased serum TGs, VLDL, LDL, and low level of HDL.

According to Krauss,[33] each of these dyslipidemic features is associated with an increased risk of CVD. Increased secretion of TGs rich in VLDL from liver and its impaired clearance may be the probable pathophysiology of this dyslipidemia. Small, dense LDL particles are produced as a result of intravascular processing of specific large VLDL precursors. Ronald et al[34] demonstrated that lipid abnormalities are due to resistance to insulin and hyperglycemia. Similarly, Tushuizen et al[35] discussed that high postprandial blood sugars and high lipid levels are risk factors for vascular diseases. In another study by Shera et al,[36] it was proposed that uncontrolled diabetes may lead to higher macro as well as microvascular complications and is further related to longer duration of disease, poor glycemic control, increased body weight, and hypertension. The vascular complications were ischemic heart disease, myocardial infarction, and cerebrovascular accident.

The overall findings of the present study, thus, confirm that homocysteine levels are significantly higher in the type II diabetic patients and may contribute to the development of endothelial dysfunction and related complications. Hyperhomocysteinemia further leads to dyslipidemia and vice-versa. Glycemic control also seems to affect the homocysteine levels in such patients.

The study, therefore, recommends research on larger patient groups to assess the association of glycemic control with hyperhomocysteinemia. The study suggests that proper counseling and maintenance of a healthy lifestyle so as to ensure good glycemic control and healthy lipid profile can be helpful in avoiding hyperhomocysteinemia and its related complications.

CONCLUSION

The present study suggests that type II diabetic patients are at a risk of developing hyperhomocysteinemia as well as dyslipidemia. 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.

Long-standing diabetes can lead to severe complications, but adopting a healthy lifestyle, especially maintaining a good glycemic control can be very helpful in proper patient management and in averting the occurrence of such complications. Estimation of serum homocysteine and serum lipid profile is therefore, recommended as part of the screening and follow-up of type II diabetic patients.

Serum homocysteine levels can be minimized by supplementation of folic acid and vitamin B12. Proper counseling of the patient especially for adopting a healthy lifestyle, including balanced diet and routine workout, can play a significant role in controlling dyslipidemia.

The study recommends further research on the influence of HbA1c levels on other inflammatory markers and their association with homocysteine in type II diabetic patients.

REFERENCES

1. Baynest HW. Classification, pathophysiology, diagnosis and management of diabetes mellitus. J Diabetes Metabol 2015;6(5):1-9.
2. International Diabetes Federation (IDF). Country estimates table 2011. IDF Diabetes Atlas, 2012. p. 6.
3. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes—estimates for the year 2000 and projections for 2030. Diabetes Care 2004 May;27(3):1047-1053.
4. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2005 Jan;1(suppl 1):537-542.
5. Bhowmik B, Afsana F, Diep LM, Munir SB, Wright E, Mahmood S, Azad Khan AK, Hussain A. Increasing prevalence of type 2 diabetes in a rural Bangladeshi population: a population based study for 10 years. Diabetes Metab J 2013 Feb;37(1):46-53.
6. Lehto S, Ronnemaa T, Pyorala K, Laakso M. Cardiovascular risk factors clustering with endogenous hyperinsulinaemia predict death from coronary heart disease in patients with type II diabetes. Diabetologia 2000 Feb;43(2):148-155.
7. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998 Jul;339(4):229-234.
8. Cattaneo M. Hyperhomocysteinemia and thrombosis. Lipids 2001;36:13-26.

9. Drzewoski J, Czupryniak L, Chwotko G, Bald F. Hyperhomocysteinemia in poorly controlled type 2 diabetes mellitus patients. Diab Nutr Metab 2000 Dec;13(6):319-324.
10. Gallistl S, Sudi K, Managge H. Insulin is an independent correlate of plasma homocysteine levels in obese children and adolescents. Diabetes Care 2000 Sep;23(9):1348-1352.
11. Sainani GS, Karatela RA. Plasma leptin in insulin-resistant and insulin-nonresistant coronary artery disease and its association with cardio-metabolic risk factors among Asian Indians. Metab Syndr Relat Disord 2009 Aug;7(4):335-340.
12. Chiang EP, Wang YC, Chen WW, Tang FY. Effects of insulin and glucose on cellular metabolic fluxes in homocysteine transsulfuration, remethylation, S-adenosylmethionine synthesis, and global deoxyribonucleic acid methylation. J Clin Endocrinol Metab 2009 Mar;94(3):1017-1025.
13. Li H, Lewis A, Brodsky S, Rieger R, Iden C, Goligorsky MS. Homocysteine induces 3-hydroxy-3-methylglutaryl coenzyme A reductase in vascular endothelial cells: a mechanism for development of atherosclerosis? Circulation 2002 Mar;105(9): 1037-1043.
14. Lorenzo G, Ragoobir Singh D, Errol Y, Morrison SA, Choo-Kang E, Donovan MG, Martorell E. Lipid profile of type 2 diabetic and hypertensive patients in the Jamaican population. J Lab Phys 2010 Jan;2(1):25-30.
15. Sniderman AD, Scantlebury TH, Cianflone K. Hypertriglyceridemic hyperapo B: the unappreciated atherogenic dyslipoproteinemia in type 2 diabetes mellitus. Ann Intern Med 2001 Sep;135(6):447-459.
16. El Oudi M, Aouni Z, Ouertani H, Mazigh C, Machghoul S. Effect of lipopenic and hypotensive treatment on homocysteine levels in type 2 diabetics. Vascular Health Risk Manag 2010 May;6:327-332.
17. Ebseunun MO, Obajobi EO. Elevated plasma homocysteine in type 2 diabetes mellitus: a risk factor for cardiovascular diseases. Pan Afr Med J 2012;12:48.
18. Kajbaf F, Ghaffari MA, Kajbaf MJ. Reduced serum homocysteine levels in diabetic patients. Iran J Pathol 2012;7(1):14-18.
19. Wijekoon EP, Brosnan ME, Brosnan JT. Homocysteine metabolism in diabetes. Biochem Soc Trans 2007 Nov;35(Pt 5): 1175-1179.
20. Verhoef P, Stampfer MJ. Prospective studies of homocysteine and cardiovascular disease. Nutr Rev 1995 Oct;53(10):283-288.
21. Brattstrom L. Vitamins as homocysteine lowering agents. J Nutr 1996 Apr;126(4 Suppl):1276-1280.
22. Den Heijer M, Koster T, Blom HJ, Bos GM, Briet E, Reitsma PH, Vandenbroucke JP, Rosendaal FR. Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. N Engl J Med 1996 Mar;334(12):759-762.
23. Hoogeveen EK, Kostense PJ, Beks PJ, Mackaay AJ, Jakobs C, Bouter LM, Heine RJ, Stehouwer CD. Hyperhomocysteinemia is associated with an increased risk of cardiovascular disease, especially in non-insulin-dependent diabetes mellitus: a population-based study. Arterioscler Thromb Vasc Biol 1998;18:133-138.
24. Okada E, Oida K, Tada H, Asazuma K, Eguchi K, Tohda G, Kosada S, Takahashi S, Miyamori I. Hyperhomocysteinemia is a risk factor for coronary arteriosclerosis in Japanese patients with type 2 diabetes. Diabetes Care 1999 May;22(3):484-490.
25. Smulders YM, Rakic M, Slaats EH, Treskes M, Sijbrands EJ, Odekerken DA, Stehouwer CD, Silberbusch J. Fasting and post-methionine homocysteine levels in NIDDM: determinants and correlations with retinopathy, albuminuria, and cardiovascular disease. Diabetes Care 1999 Jan;22(1): 125-132.
26. Agardh CD, Agardh E, Andersson A, Hultberg B. Lack of association between plasma homocysteine levels and microangiopathy in type 1 diabetes mellitus. Scand J Clin Lab Invest 1998 Dec;54(8):637-641.
27. Chico A, Perez A, Cordoba A, Arcelus R, Carreras G, de Leiva A, Gonzalez-Sastre F, Blanco-Vaca F. Plasma homocysteine is related to albumin excretion rate in patients with diabetes mellitus: a new link between diabetic nephropathy and cardiovascular disease? Diabetologia 1998 Jun;41(6):684-693.
28. Wollesen F, Brattstrom L, Refsum H, Ueland PM, Berglund L, Berne C. Plasma total homocysteine and cysteine in relation to glomerular filtration rate in diabetes mellitus. Kidney Int 1999 Mar;55(3):1028-1035.
29. Stabler S, Estacio R, Jeffers B, Cohen J, Allen R, Schrier R. Total homocysteine is associated with nephropathy in non-insulin-dependent diabetes mellitus. Metabolism 1999 Sep;48(9): 1096-1101.
30. Puri A, Gupta OK, Dwivedi RN, Bharadwaj RPS, Na-rain VS, Singh S. Homocysteine and lipid levels in young patients with coronary artery disease. J Assoc Phys India 2003 Jul;51:681-685.
31. Abraham JM, Cho L. The homocysteine hypothesis: still relevant to the prevention and treatment of cardiovascular disease? Cleve Clin J Med 2010 Dec;77(12):911-918.
32. Samia J, Asghar S, Fayaz. Relation of high density lipoprotein cholesterol concentration to type of diabetes and its control. Biomedica 2000;16:19-24.
33. Krauss RM. Lipids and lipoproteins in patients with type 2 diabetes. Diabetes Care 2004 Jun;27(6):1496-1504.
34. Ronald M. Lipid and lipoproteins in type 2 diabetes. Diabetes Care 2004 Jun;27(6):1496-1504.
35. Tushuizen M, Diamant M, Heine R. Postprandial dysmetabolism and cardiovascular disease in type 2 diabetes. Postgrad Med J 2005 Jan;81(951):1-6.
36. Shera A, Jawad F. Prevalence of chronic complications and associated factors in Type 2 Diabetes. J Pak Med Assoc 2004 Feb;54(2):54-59.