Research Article

Plasma homocysteine level and carotid intima–media thickness in type 2 diabetic patients

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Abstract

Background: The morbidity of atherosclerosis in diabetic patients is two to three times higher than in the normal population. In recent years, plasma homocysteine (Hcy) levels, a sulfur containing non-protein amino acid in the metabolism of methionine, have been reported to be associated with vascular complications of diabetes.

Objective: The aim of this study was to evaluate the plasma total homocysteine (t Hcy) level and carotid intima–media thickness (CIMT) in normoalbuminuric and microalbuminuric type 2 diabetic patients.

Materials and Methods: Fifty type 2 diabetic patients with more than 5 year diabetic duration in the age group of 35–60 years were selected for this study. Twenty-five age-matched healthy individuals were selected as a control group. Plasma total homocysteine was assayed by ELISA and carotid intima–media thickness was assessed by B-mode ultrasonography.

Results: The plasma t Hcy level was significantly elevated in type 2 DM patients and there was also significant difference between microalbuminuric and normoalbuminuric type 2 DM patients. There was a significant positive correlation between t Hcy, CIMT, and HOMA-IR.

Conclusion: Significant elevation of homocysteine was observed in diabetic patients. Hence, assessment of plasma homocysteine level and CIMT could be useful to assess the atherosclerotic changes in T2 DM patients, and it could help in the prevention of cardiovascular complications.

KEY WORDS: total homocysteine (Hcy), carotid intima–media thickness (CIMT), insulin resistance (IR)

Introduction

Diabetes mellitus (DM) is an significant public health concern affecting life quality and individual's survival[1] and type 2 DM accounts for nearly 90% of all DM across the world.[2] It is characterized by a high incidence of vascular complications.[3] The main risk factors of vascular complications are poor glycemic control, insulin resistance (IR), and β-cell failure.[4,5]

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Homocysteine (Hcy) is the trans-methylation product of the essential sulfur containing amino acid methionine.[6,7] It is present in different forms. About 70–80% is protein-bound and the non-protein-bound Hcy is found as "mixed disulfide" (i.e., the dimer of Hcy and cysteine), homocysteine (the oxidized disulfide of Hcy), and reduced Hcy. Reduced Hcy forms only about 1% of the t Hcy content.[8] Hyperhomocysteinemia induces lipid peroxidation and endothelial cytotoxicity, increases platelet adhesiveness, enhances activation of the coagulation system, and stimulates vascular smooth muscle cell proliferation,[9] and is also associated with renal dysfunction.[10] Hoogeveen et al.[11] reported in Hoorn Study (a population-based survey of glucose tolerance and cardiovascular risk factors) that high levels of t Hcy was associated with microalbuminuria independent of other determinants. Lanfredini et al.[12] observed an elevated level of t Hcy in patients with type 2 diabetes and microalbuminuria. Acute and

prolonged exposure to Hcy had detrimental effects on glucose metabolism and insulin secretion.[13,14] IR plays an important role in the development of atherosclerotic disease via hyperglycemia, hypertension, and dyslipidemia.[15] High-plasma homocysteine levels have been shown to have positive correlation with cardiovascular risk.[16–18]

The measurement of the carotid intima–media thickness (CIMT) has been recognized as a powerful method for identifying subclinical atherosclerosis.[19,20] Thickening of the intima–media complex not only reflects local alterations but also corresponds to generalized atherosclerosis. CCA distensability diminishes with increasing severity of atherosclerosis.[21] The CIMT can be measured with a high degree of accuracy and reproducibility by B mode ultrasonography, which provides a reliable and valid estimate of the arterial wall thickness.[23] So the objective of this study was to evaluate plasma total homocysteine (t Hcy) level and its association with CIMT, a valid marker of generalized atherosclerosis in type 2 diabetic patients.

Materials and Methods

Fifty type 2 diabetic patients of both sexes with more than 5 years duration aged between 35 and 60 years on oral hypoglycemic drugs, attending diabetic out-patient department of Rajah Muthiah Medical College and Hospital, Annamalai University, Annamalainagar, Tamil Nadu, India, were selected for the study. The diabetic patients were categorized into two groups according to urinary albumin-to-creatinine ratio (ACR): Group I 25 patients with normoalbuminuria (<30 mg/g creatinine) and Group II 25 patients with microalbuminuria (30–299 mg/g creatinine). Diabetic patients who were alcoholics, tobacco users, with hypertension, abnormal urinary sediment, urinary tract infection, history of other renal disease, active or chronic persistent infection or inflammatory disorders, neoplastic disorders, thyroid disorders, severe liver dysfunction, history of acute myocardial infarction, stroke, and occlusive peripheral vascular disease were excluded from the study. Twenty-five healthy age-matched subjects were selected as a control group. The informed consent was obtained from all the study subjects and the study was approved by the Institutional Human Ethics Committee (IHEC). Experiments were done in accordance with Helsinki declaration of 1975.

Biochemical Analysis

Fasting blood and urine samples were obtained from the subjects after enrollment. Blood samples were centrifuged at 2000´g for 10 min. Samples were analyzed for blood sugar, lipid profile, glycated hemoglobin (HbA1C), urinary albumin, and creatinine. Post-prandial venous plasma glucose (PPBS) estimation was also done. Plasma total homocysteine, insulin were assayed by ELISA.

Measurement of Carotid Intima–Media Thickness (CIMT)

The patient was examined in supine position with pillow kept between the shoulder blades to achieve extension of the neck, and neck exposure was enhanced by tilting and rotating the head away from the side being examined. Carotid arteries were imaged by using a high-resolution B-mode ultrasonography system having an electric linear transducer mid frequency of 7.5 MHz.[20]

Statistical analysis

Statistical analysis were carried out with SPSS 20.0. Values were expressed as mean ± standard deviation, p value < 0.05 was considered statistically significant. Normally distributed data were analyzed by using one-way ANOVA. The Pearson's correlation test was used for correlation analysis.

Results

The plasma t Hcy level was significantly elevated in type 2 DM patients and there was also significant difference between microalbuminuric and normoalbuminuric type 2 DM patients. There was a significant positive correlation between t Hcy, CIMT, and HOMA–IR [Tables 1–4].

Discussion

Diabetes is a major cause of both microvascular and macrovascular complications. Chronic exposure of elevated

Table 1: Baseline data of controls and type 2 diabetic patients

Parameters	Control (n = 25)	Group I Normoalbuminuric DM (n = 25)	Group II Microalbuminuric DM (n = 25)	p-value
Age	47.6 ± 4.3	48.3 ± 6.5	50.8 ± 5.5	0.118
Body mass index	25.4 ± 1.5	26.8 ± 3.7	25.8 ± 3.2	0.226
Waist/hip ratio	0.9 ± 0.04	0.92 ± 0.06	0.92 ± 0.04	0.439
DM duration (years)	—	8.2 ± 2.1	8.9 ± 2.8	0.298
Systolic BP (mm Hg)	114.1 ± 7.1	124.5 ± 16.2	127 ± 13.1	0.001
Diastolic (mm Hg)	73.8 ± 3.3	79.1 ± 7.9	78.7 ± 7.6	0.007

Data are expressed as mean ± SD; $p < 0.05$ was considered statistically significant.

Table 2: Biochemical data and CIMT of control and type 2 diabetic patients

Parameters	Control (*n* = 25)	Group I Normoalbuminuric DM (*n* = 25)	Group II Microalbuminuric DM (*n* = 25)	Group I vs. Group II *p*-value
Urine albumin-to-creatinine ratio (mg/gm of creatinine)	18.3 ± 2.6	23.4 ± 3.5*	161.8 ± 70.7	0.001
FBS (mg/dl)	81.9 ± 5.9	128.3 ± 40.1*	145.9 ± 53.6	0.19
PPBS (mg/dl)	108.1 ± 9.8	191.7 ± 56*	221 ± 82.1	0.13
HbA1C	5.4 ± 0.4	7.2 ± 0.8*	8.0 ± 1.1	0.007
Serum cholesterol (mg/dl)	168.8 ± 9.0	186.8 ± 20.4*	193.8 ± 21.8	0.24
Serum triglycerides (mg/dl)	95.5 ± 7.4	130.5 ± 39.3*	141.8 ± 38.1	0.30
HDL cholesterol (mg/dl)	43.7 ± 2.4	39.4 ± 3.0*	38.3 ± 2.3	0.18
LDL cholesterol (mg/dl)	105.9 ± 9.1	121.3 ± 16.5*	127.1 ± 20.8	0.28
Serum urea (mg/dl)	24.3 ± 4.6	28.1 ± 5.4*	33.4 ± 12.2	0.05
Serum creatinine (mg/dl)	0.6 ± 0.1	0.7 ± 0.2	0.9 ± 0.3	0.08
Insulin (μIU/ml)	6.5 ± 0.7	10.9 ± 4.1*	13.2 ± 5.0	0.08
HOMA-IR	1.3 ± 0.17	3.4 ± 1.6*	4.6 ± 2.2	0.03
Plasma Homocysteine (μmol/l)	5.4 ± 0.84	8.9 ± 1.7*	11.2 ± 2.1	0.001
Right CIMT (mm)	0.57 ± 0.02	0.73 ± 0.1*	0.85 ± 0.08	0.001
Left CIMT (mm)	0.61 ± 0.05	0.75 ± 0.06*	0.86 ± 0.05	0.001

*p-value < 0.05 vs. control.

Data are expressed as mean ± SD; $p < 0.05$ was considered statistically significant.

Table 3: Correlation between homocysteine and measured parameters

Parameters	Correlation coefficient (*r*)
ACR	0.709**
FBS	0.482**
PPBS	0.508**
Hb A1C	0.692**
Cholesterol	0.500**
Triglycerides	0.523**
HDL	–0.505**
LDL	0.448**
HOMA-IR	0.490**
Right CIMT	0.691**
Left CIMT	0.721**

**Correlation is significant at the 0.01 level (two-tailed).

Table4: Correlation between HOMA-IR and measured parameters

Parameters	Correlation coefficient (*r*)
ACR	0.314**
FBS	0.705**
PPBS	0.710**
HbA1C	0.649**
Cholesterol	0.181
Triglycerides	0.221
HDL	-0.379**
LDL	0.186
Right CIMT	0.589**
Left CIMT	0.587**

**Correlation is significant at the 0.01 level (two-tailed).

blood glucose and fatty acid concentrations can cause damage in different types of cells by a variety of mechanisms called glucolipotoxicity.[24,25] In Type 2 DM, the influence of disease duration seems to play a less important role because actual time of onset of disease remains unknown in a majority of patients.[26] So diagnosis of different clinical tests might be useful to prevent complications.

In this study, we observed that plasma t Hcy level was significantly increased in both normoalbuminuric and microalbuminuric type 2 diabetic patients, and it also had significant positive correlation with HbA1C and HOMA-IR. Several studies reported that elevated levels of homocysteine have been observed in a variety of patients with type 2 DM, metabolic syndrome, and obesity.[27–31] The in vitro studies have explained that homocysteine thiolactone inhibits insulin receptor tyrosine kinase activity leading to inhibition of phosphorylation of phosphatidylinositol 3-kinase (PI3K) and inhibition of glycogen synthesis.[32,33]

We have observed a strong positive correlation between t Hcy and CIMT. Several risk factors for increased CIMT in diabetic patients have been reported, but a recent study showed that duration of diabetes, waist-hip ratio, HbA1C, and hypertension had a significant positive association with CIMT.[34] High-homocysteine concentrations may exert an atherothrombotic effect through increasing oxidative stress.[35–37] It affects the properties of the extracellular matrix and increases smooth muscle cell proliferation, which might lead to endothelial dysfunction in diabetes.[38] Endothelial dysfunction is the common shared pathway for vascular pathology[39,40] and occurs early in the development of atherosclerosis, even before the formation of plaque, making it the core process in

the development of atherosclerosis.[41] Selhub et al.[42] reported that a cross-sectional study of elderly subjects from the Framingham Heart Study showed that high-plasma t Hcy concentrations and low concentrations of folate and vitamin B6, through their role in Hcy metabolism, are associated with an increased risk of carotid-artery stenosis in the elderly. In addition, IR may also play an important role in the development of atherosclerotic disease as it may be an expression of diffuse arterial endothelial dysfunction contributing to atherosclerosis, leading directly to arterial damage through toxic effects of hyperinsulinemia.[43] There is also a possible link between plasma insulin level and the activity of key enzymes involved in homocysteine metabolism, including 5, 10-methylene tetrahydrofolate reductase (MTHFR), cystathionine β-synthase (CBS). The enzyme methylene tetrahydrofolate reductase is responsible for the reduction of 5, 10-methylene-THF to 5-methyl-THF, the required substrate in the re-methylation process where B12 acts as a cofactor.[44,45] Durga et al.[46] reported that erythrocyte folate status, rather than serum and plasma folate, was inversely associated with CIMT, and concluded that low-folate concentrations, independent of hyperhomocysteinemia may promote atherogenesis.[46]

Conclusion

In conclusion, homocysteine could be considered as an independent risk factor involved in vascular dysfunction in type 2 DM patients. Hence, assessment of plasma homocysteine level and CIMT could be useful to assess the atherosclerotic changes in T2 DM patients, and it could help in the prevention of cardiovascular complications.

References

1. Soares AL, Fernandes AP, Cardoso JE, Sousa MO, Lasmar MC, Novelli BA, Lages GF, Dusse LM, Vieira LM, Lwaleed BA, Carvalho MG. Plasma total homocysteine levels and methylenetetrahydrofolate reductase gene polymorphism in patients with type 2 diabetes mellitus. Pathophysiol Haemost Thromb 2008;36(5):275–81.
2. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001;414:782–7.
3. King GL, Kunisaki M, Nishio Y, Inoguchi T, Shiba T, Xia P. Biochemical and molecular mechanisms in the development of diabetic vascular complications. Diabetes 1996;45:105–8.
4. Venkat NK, Gregg EW, Fagot-Campagna A, Engelgau MM, Vinicor F. Diabetes: a common, growing, serious, costly, and potentially preventable public health problem. Diabetes Res Clin Pract 2000;50:77–84.
5. Mtiraoui N, Ezzidi I, Chaieb M, Marmouche H, Aouni Z, Chaieb A, Mahjoub T, Vaxillaire M, Almawi WY. MTHFR C677T and A1298C gene polymorphisms and hyperhomocysteinemia as risk factors of diabetic nephropathy in type 2 diabetes patients. Diabetes Res Clin Pract 2007;75(1):99–106.
6. Medina MA, Amores-Sanchez MI. Homocysteine: an emergent cardiovascular risk factor? Eur J Clin Invest 2000;30:754–62.
7. Emoto M, Kanda H, Shoji T, Kawagishi T, Komatsu M, Mori K, Tahara H, Ishimura E, Inaba M, Okuno Y, Nishizawa Y. Impact of ınsulin resistance and nephropathy on homocysteine in type 2 diabetes. Diabetes Care 2001;24:533–8.
8. Mudd SH, Finkelstein JD, Refsum H, Ueland PM, Malinow MR, Lentz SR, Jacobsen DW, Brattström L, Wilcken B, Wilcken DE, Blom HJ, Stabler SP, Allen RH, Selhub J, Rosenberg IH. Homocysteine and its disulfide derivatives: a suggested consensus terminology. Arterioscler Thromb Vasc Biol 2000;20(7):1704–6.
9. Fonseca V, Guba SC, Fink LM. Hyperhomocysteinaemia and the endocrine system: implications for atherosclerosis and thrombosis. Endocr Rev 1999;20:738–59.
10. Bostom AG, Shemin D, Verhoef P, Nadeau MR, Jacques PF, Selhub J, Dworkin L, Rosenberg IH. Elevated fasting total plasma homocysteine levels and cardiovascular disease outcomes in maintenance dialysis patients: a prospective study. Arterioscler Thromb Vasc Biol 1997;17:2554–8.
11. Hoogeveen EK, Kostense PJ, Jager A, Heine RJ, Jakobs C, Bouter LM, Donker AJ, Stehouwer CD: Serum homocysteine level and protein intake are related to risk of microalbuminuria: the Hoorn Study. Kidney Int 1998;54:203–9.
12. Lanfredini M, Fiorina P, Peca MG, Veronelli A, Mello A, Astorri E, Dall'Aglio P, Craveri A: Fasting and post-methionine load homocyst(e)ine values are correlated with microalbuminuria and could contribute to worsening vascular damage in non-insulin-dependent diabetes mellitus patients. Metabolism 1998;47:915–21.
13. Patterson S, Flatt PR, Brennan L, Newsholme P, McClenaghan NH. Detrimental actions of metabolic syndrome risk factor, homocysteine, on pancreatic beta-cell glucose metabolism and insulin secretion. J Endocrinol 2006;189:301–10.
14. Patterson S, Flatt PR, McClenaghan NH. Homocysteine-induced impairment of insulin secretion from clonal pancreatic BRIN-BD11 beta-cells is not prevented by catalase. Pancreas 2007;34:144–51.
15. Reaven GM: Banting lecture 1988: role of insulin resistance in human disease. Diabetes 1988;37:1595–607.
16. Zou CG, Banerjee R. Homocysteine and redox signaling. Antioxid Redox Signal 2005;7:547–59.
17. Boushey BS, Beresford SA, Omen GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular diseases: probable benefits of increasing folic acid intakes. JAMA 1995;274:1049–57.
18. Verhoef P, Stampfer MJ, Buring JE, Gaziano JM, Allen RH, Stabler SP, Reynolds RD, Kok FJ, Hennekens CH, Willett WC. Homocysteine metabolism and risk of myocardial infarction: relation with vitamins B6, B12, and folate. Am J Epidemiol 1996;143:845–59.
19. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M: Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007;115(4):459–67.
20. Nomura K, Hamamoto Y, Takahara S, Kikuchi O, Honjo S, Ikeda H, Wada Y, Nabe K, Okumra R, Koshiyama H: Relationship between carotid intima media thickness and silent cerebral infarction in Japanese subjects with type 2 diabetes. Diabetes Care 2010;33(1):168–70.
21. Hirai T, Sasayama S, Kawasaki T, Yagi S. Stiffness of systemic arteries in patients with myocardial infarction: a non-invasive method to predict severity of coronary atherosclerosis. Circulation 1989;80:78–86.
22. McGarry PA, McMohan CA, Montenegro MR. General finding of the International Atherosclerosis Project. Lab Invest 1968;18:498–502.

23. Frouse Jr. An evaluation of methods for imaging and quantifying coronary and carotid lumen stenosis and atherosclerosis. Circulation 1993;87:1117–33.
24. Rampello L, Vecchio I, Battaglia G, Malaguarnera G, Rampello L. Diabetic neuropathy: elements of epidemiology and pathophysiology. Acta Medica Mediterranea 2012;3:219–26.
25. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC Jr, Sowers JR. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 1999;100:1134–46.
26. Ko SH, Park SA, Cho JH, Song KH, Yoon KH, Cha BY, Son HY, Yoo KD, Moon KW, Park YM, Ahn YB Progression of cardiovascular autonomic dysfunction in patients with type 2 diabetes-A 7-year follow-up study. Diabetes Care 2008;31:1832–40.
27. Emoto M, Kanda H, Shoji T, Kawagishi T, Komatsu M, Mori K, Tahara H, Ishimura E, Inaba M, Okuno Y, Nishizawa Y. Impact of insulin resistance and nephropathy on homocysteine in type 2 diabetes. Diabetes Care 2001;24:533–8.
28. Meigs JB, Jacques PF, Selhub J, Singer DE, Nathan DM, Rifai N and D'Agostino RB, Wilson PW. Fasting plasma homocysteine levels in the insulin resistance syndrome: the Framingham offspring study. Diabetes Care 2001;24:1403–10.
29. Sanchez-Margalet V, Valle M, Ruz FJ, Gascon F, Mateo J, Goberna R. Elevated plasma total homocysteine levels in hyperinsulinemic obese subjects. J Nutr Biochem 2002;13:75–9.
30. Fonseca VA, Fink LM, Kern PA. Insulin sensitivity and plasma homocysteine concentrations in non-diabetic obese and normal weight subjects. Atherosclerosis 2003;167:105–9.
31. Martos R, Valle M, Morales R, Canete R, Gavilan MI, Sanchez-Margalet V. Hyperhomocysteinemia correlates with insulin resistance and low-grade systemic inflammation in obese prepubertal children. Metabolism 2006;55:72–7.
32. Najib S, Sa´nchez-Margalet V. Homocysteine thiolactone inhibits insulin signaling: protective effect of glutathione. J Mol Endocrinol 2001;27:85–91.
33. Najib S, Sa´nchez-Margalet V. Homocysteine thiolactone inhibits insulin-stimulated DNA and protein synthesis: possible role of mitogen-ctivated protein kinase (MAPK), glycogen synthase kinase-3 (GSK-3) and p70 S6K phosphorylation. J Mol Endocrinol 2005;34:119–26.
34. Gayathri R, Chandni R, Udayabhaskaran V. Carotid artery intima media thickness in relation with atherosclerotic risk factors in patients with type 2 diabetes mellitus. J Assoc Physicians India 2012;60:20–4.
35. Hoogeveen EK, Kostense PJ, Jager A, Heine RJ, Jakobs C, Bouter LM, Donker AJM, Stehouwer CDA. Serum homocysteine level and protein intake are related to risk of microalbuminuria: the Hoorn Study. KidneyInt 1998;54:203–9.
36. Bellamy MF, McDowell IFW, Ramsey MW, Brownlee M, Bones C, Newcombe RG, Lewis MJ. Hyperhomocysteinemia after an oral methionine load acutely impairs endothelial function in healthy adults. Circulation 1998;98:1848–52.
37. Chambers JC, McGregor A, Jean-Marie J, Obeid OA, Kooner JS. Demonstration of rapid onset vascular endothelial dysfunction after hyperhomocysteinemia: an effect reversible with vitamin C therapy. Circulation 1999:99:1156–60.
38. Nourooz-Zadeh J, Tajaddini-Sarmadi J, McCarthy S, Betteridge DJ, Wolff SP. Elevated levels of authentic plasma hydroperoxides NIDDM. Diabetes 1995;44:1054–8.
39. Bellamy MF, McDowell IF. Putative mechanisms for vascular damage by homocysteine. J Inherit Metab Dis 1997;20:307–15.
40. Schalkwijk CG, Stehouwer CD. Vascular complications in diabetes mellitus: the role of endothelial dysfunction. Clin Sci (Lond) 2005;109:143–59.
41. Quyyumi AA. Endothelial function in health and disease: new insights into the genesis of cardiovascular disease. Am J Med 1998;105:32–9.
42. Selhub J, Jacques PF, Bostom AG, D'Agostino RB, Wilson PW, Belanger AJ, O'Leary DH, Wolf PA, Schaefer EJ, Rosenberg IH. Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis. N Engl J Med 1995;332:286–91.
43. Stout RW. Insulin and atheroma: a 20-yr perspective. Diabetes Care 1990;13:631–54.
44. Abbasi F, Facchini F, Humphreys MH, Reaven GM. Plasma homocysteine concentrations in healthy volunteers are not related to differences in insulin-mediated glucose disposal. Atherosclerosis 1999;146:175–8.
45. Gallistl S, Sudi K, Mangge H, Erwa W, Borkenstein M. Insulin is an independent correlate of plasma homocysteine levels in obese children and adolescents. Diabetes Care 2000;23:1348–52.
46. Durga J, Bots ML, Schouten EG, Kok FJ, Verhoef P. Low concentrations of folate, not hyperhomocysteinemia, are associated with carotid intima-media thickness. Atherosclerosis 2005;179:285–92.

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