



Original Research Article

Atherogenic Activity of Hypercholesterolemia and Hyperhomocysteinemia in Complicated Type 2 Diabetes Mellitus

Ramakrishna Chaturvedula¹, Venkateshwar Rao K², Dilip Rampure¹, Dharma Rao V¹, Vijay Bhaskar M³

¹Professor, Department of General Medicine, Mamata Medical College, Khammam, AP, India.

²Senior Resident, Department of General Medicine, Mamata Medical College, Khammam.

³Professor and Head, Department of Biochemistry, Mamata Medical College, Khammam.

Corresponding Author: Ramakrishna Chaturvedula

Received: 13/02/2014

Revised: 07/03/2014

Accepted: 11/03/2014

ABSTRACT

This study was carried out to analyze the atherogenic activity of hypercholesterolemia and homocysteinemia individually and collectively in complicated type 2 diabetes mellitus. 100 diabetic patients attending Mamata General Hospital, Khammam [AP] were included in this study and were divided into complicated and uncomplicated groups based on clinical features. All patients were subjected to BMI categorization, HbA1c level, Serum Creatinine levels, Urine for microalbumin, Serum Homocysteine level, Serum Cholesterol and clinical assessment for Retinopathy; Neuropathy along with cardiac evaluation was performed, with routine EKG. We found that hypercholesterolemia had higher rate of complications than hyperhomocysteinemia, but when both are elevated the combined effect revealed higher complications rates. This synergistic effect of cholesterol and homocysteine on atherogenesis and diabetic complication rate requires the need to lower homocysteine levels along with cholesterol reducing agents on a routine basis with VitB12 & folic acid supplementation.

Keywords: Atherogenesis, Hypercholesterolemia. Homocysteinemia, Type 2 diabetes mellitus

INTRODUCTION

Over the last years, there has been a great interest in homocysteine, primarily because of the realization that elevated levels of plasma homocysteine is an important risk factor for vascular occlusive diseases such as coronary artery disease. [1,2] Cerebral vascular accidents. [3] deep-vein thrombosis. [4] Homocysteine [Hcy] is a non-essential sulfur-containing amino acid whose metabolism stands at the intersection of two pathways: remethylation to methionine, which requires folate, vitamin B12 and vitamin B6; and transsulfuration to

cystathionine, which requires pyridoxal-5'-phosphate. [5] Genetically inherited defects of the enzymes involved in the remethylation or transsulfuration process of methionine or methylenetetrahydrofolate reductase thermolability are the most important determinants of marked Homocysteinemia. [6,7,8] Mild hyperhomocysteinemia seen in fasting conditions is due to mild impairment in the remethylation pathway due to nutrient deficiency as folate or vitamin B12 deficiencies. High levels of plasma homocysteine are toxic to the vascular endothelium via the formation of

free radicals. These free radicals cause direct injury to the endothelium by disrupting its integrity, exposing the underlying vascular matrix and smooth muscle, enhancing low density lipoprotein peroxidation and promoting a hypercoagulable state platelets activation and thrombus formation. [9,10]

The metabolic abnormality in type 2 DM, is accelerated atherogenesis which is responsible for all macro micro vascular complications. [11] Strong epidemiological evidence supports an association between glycaemia control and complications. UKPDS study. [12,13] indicated a linear relationship between CVD and HbA1C, while the slope of relationship between HbA1C and micro vascular complications is much steeper indicating that hyperglycaemia plays a greater role in both micro vascular and macro vascular complications. [14,15] Hypercholesterolemia nearly always accompanies the onset of diabetes and animal studies have indicated that glucose and lipids might act through synergistic mechanisms to accelerate atherosclerosis. ACCORD study and ADVANCE study have aggressively lowered glucose levels and inspire of strict glycaemia control found no beneficial effects. In contrast, lipid lowering in 2 DM showed more beneficial effects, suggesting that lipids play a more important role than glucose in 2DM. [15,16]

Homocysteine is well established independent risk factor for development of Macrovascular diseased including CAD. [16,17] Patients with homocysteinemia display early onset of atherosclerosis and manifest arterial and venous thrombosis. The mechanism is believed to be due to formation of oxidation products such as homocysteine disulphide and homocysteine thiolactone in addition to homocysteine. Homocysteine levels in diabetes have been reported as low or elevated compared to control non diabetic groups. Homocysteine levels are elevated in 2DM and Metabolic

syndrome exhibiting Insulin resistance. Homocysteine levels are known to be influenced by Insulin concentration, insulin therapy, drugs like metformin and glitazones. The well defined atherogenic factor has been implicated in many studies and has reported a high correlation between elevated levels of homocysteine and microvascular complications' Correlation between Nephropathy and Neuropathy was strong while Retinopathy did not correlate well homocysteinemia. [18-20]

The individual atherogenic effects of cholesterol and homocysteine are well documented in 2 DM, the combined effect of these on the atherogenic complications in 2 DM are not clear. The contribution of elevated levels of homocysteine on the pre existing hypercholesteremic on the atherogenic complications needs better understanding. Elevated homocysteine levels, whether due to nutrient deficiencies or defective genes, can easily be normalized in virtually all cases, simply and inexpensively, using a combination of nutritional supplements. The most effective defense against homocysteine buildup is a combination of vitamins B-6, B-12 and folic acid, which convert homocysteine into nontoxic substances. [19,20] The therapeutic implications of lowering homocysteine levels and possible decreasing diabetic complications need further studies. The aim of this study is to determine the effect of hypercholesterolemia and homocysteinemia on Type 2 diabetic complications and assess the contribution of hyperhomocysteinemia to the 2DM complications

MATERIAL AND METHODS

Inclusion criteria

All type 2 confirmed Diabetics attending Mamata Medical College and General Hospital during the period June 2012 to June 2013 between the ages 18 and 60 years were included. All patients were

divided into two groups. One group without any diabetic complications and the other with complications. The basis of the above division was based on clinical evidence of diabetic complications.

All patients were subjected to BMI categorization, HbA1c level, Serum Creatinine levels, Urine for microalbumin, Serum Homocysteine level, Serum Cholesterol and clinical assessment for Retinopathy; Neuropathy along with cardiac evaluation was performed, with routine EKG.

Exclusion criteria

All active & chronic infections. All malignant conditions & all patients with COPD, Tobacco addiction and chronic alcoholics

RESULTS

In this study consisting of 100 diabetic patients almost equal number of male and female patients are induced. The majority of patients were in the age group 41-60 years comprising almost 63% of total patients. None of the patients were below 30 years of age probably due to the fact that study was conducted in a tertiary centre were most of the patients had symptoms/ complications related to diabetes. 18% of patients were in the age group 30-40 yrs and 16% of patients were in the age group 61-70 yrs.

30% of patients of both sexes had normal BMI, while 22% of males were overweight as compared to females [11%] comprising 33% of total diabetics. Obesity was found more in females as compared to males and accounts for 34% of total diabetics. Thus, 67% of total patients were either overweight or obese. 93% of all diabetic patients included in the study showed poor diabetic control with elevated Hba1c >7%. Males [50%] showed worst control as compared to females [43%]. Good control was only in 7% of cases. Increased

BMI and poor Glycemic status is directly proportional to Serum Cholesterol & Homocysteine levels. 31% of the diabetics had complications [Both macrovascular & microvascular] while 69% were uncomplicated. Males and females showed almost equal complications rate. 79% of diabetic patients showed hypercholesterolemia with almost equal proportion in males and females. 74% with poor glycemic control had hypercholesterolemia while only 2% showed normal cholesterol with good glycemic control. Poor glycemic control is directly proportional to hypercholesterolemia. 46% of diabetic patients included in study had elevated homocysteine with almost equal distribution in equal sexes homocysteine was elevated in 18 % of complicated diabetes and 28% of uncomplicated diabetes while 41% of uncomplicated diabetes and 13% of complicated diabetes showed normal homocysteine levels. From the present study, out of the 31 complicated diabetic patients, 54.8 % had elevated cholesterol and homocysteine, whereas, 16.2 % had only elevated homocysteine. 54.8 % had elevation of both cholesterol and homocysteine, 29 % had cholesterol elevated with normal homocysteine. From the above data, the inference that may be drawn is that hypercholesterolemia along with hyperhomocysteinemia contributed to higher complication rates as compared to either one alone. However, this needs larger number of studies to evaluate the possible synergistic effect and comparison with other lipoprotein moieties need to be evaluated.

In this study consisting of 100 diabetic patients almost equal number of male and female patients are induced. The majority of patients were in the age group 41-60 years comprising almost 63% of total patients. None of the patients were below 30 years of age probably due to the fact that study was conducted in a tertiary centre

were most of the patients had symptoms/ complications related to diabetes . 18% of patients were in the age group 30-40 yrs and 16% of patients were in the age group 61-70 yrs.

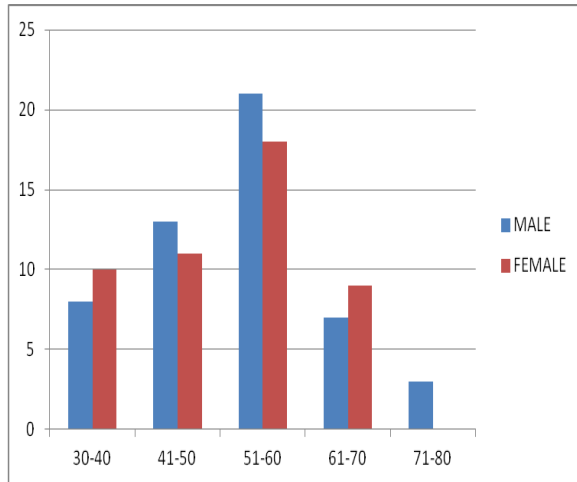


Figure 1: Age and Gender Distribution.

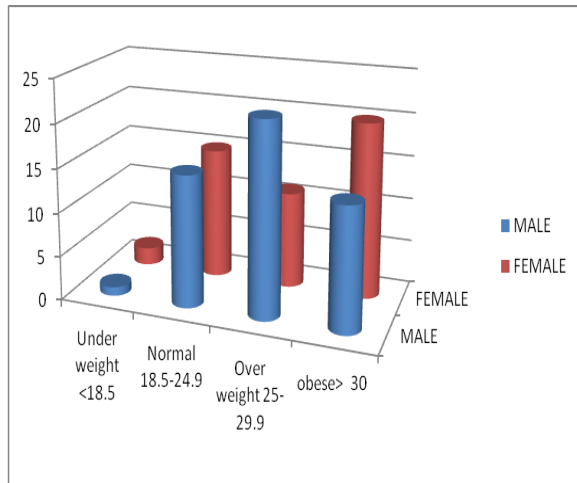


Figure 2: DISTRIBUTION BASED ON BMI.

30% of patients of both sexes had normal BMI, while 22% of males were overweight as compared to females [11%] comprising 33% of total diabetics. Obesity was found more in females as compared to males and accounts for 34% of total diabetics. Thus, 67% of total patients were either overweight or obese. 93% of all diabetic patients included in the study showed poor diabetic control with elevated

Hb1c >7%. Males [50%] showed worst control as compared to females [43%]. Good control was only in 7% of cases.

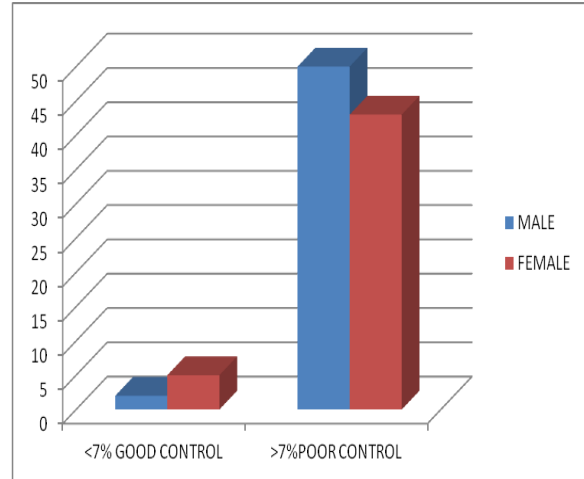


Figure 3: DISTRIBUTION BASED ON GLYCEMIC STATUS.

Table 1: COMPLICATIONS AND GENDER DISTRIBUTION.

	Uncomplicated Diabetes [%]	Complicated Diabetes [%]
Male	36	16
Female	33	15
Total	69	31

69% of diabetics patients included in the study showed no complications while 31% were found to have either microvascular or macrovascular complications.

Table 2: ELEVATED CHOLESTEROL & HOMOCYSTEINE BASED ON BMI

BMI	ELEVATED CHOLESTEROL	ELEVATED HOMOCYSTEINE
UNDERWEIGHT	2	1
NORMAL	24	14
OVERWEIGHT	27	15
OBESE	8	16
TOTAL	79	46

79% of diabetic patients included in this study showed hypercholesterolemia, 46% of diabetic patients had elevated homocysteine with almost overweight and obese patients accounted for 35% with hypercholesterolemia while 31% showed homocysteinemia.

Table 3: ELEVATED CHOLESTEROL & HOMOCYSTEINE LEVELS BASED ON GLYCEMIC STATUS

	Normal HbA1C	Poor control	Total
Elevated cholesterol	9	74	93
Elevated homocysteine	3	43	46

Poor glycaemic status was associated with higher levels of both cholesterol and homocysteine

Table 4: RELATIONSHIP BETWEEN CHOLESTEROL AND HOMOCYSTEINE LEVELS

No. of complicated DM	Elevated Cholesterol & Hcy [%]	Elevated Cholesterol Normal Hcy	Elevated Homocysteine Normal Cholesterol
31	17 [54.8]	09 [29 %]	05 [16.2]

Out of 31% complicated patients 54.8% showed hypercholesterolemia and homocysteinemia while 29% showed only hypercholesterolemia and 5% had only hyperhomocysteinemia.

DISCUSSION

Elevated plasma levels of homocysteine are accused for increasing the risk for atherosclerosis, stroke, peripheral neuropathy, cognitive impairment in elderly, possibly Alzheimer's disease. [21,22,23]

Distal polyneuropathy is a major complication of diabetes mellitus, and may lead to lower limb amputations. Both metabolic and vascular abnormalities may contribute to the development of impaired nerve function in diabetic patients. [20] Since, Hyperhomocysteinemia and type 2 diabetes mellitus [NIDDM] are both associated with premature vascular disease, we tried to investigate the association between homocysteine and the presence of neuropathy in type 2 diabetic patients.

In our study, plasma homocysteine level was found to be significantly higher in diabetic patients with atherogenic complications Our findings agreed with Ambrosch and colleagues [21] who estimated homocysteine level in 65 patients with type

2 diabetes; 43 of them had diabetic neuropathy, they found that the frequency of hyperhomocysteinemia was significantly increased in neuropathic patients rather than patients without neuropathy which concluded that homocysteine is independently associated with the prevalence of diabetic neuropathy in a collective of Type 2 diabetic patients.

On the contrary, a recent study [24] on 155 diabetics with type 2 diabetes mellitus concluded that homocysteinemia is probably not related to the prevalence of peripheral neuropathy in diabetics. This study divided the patients into two groups [Group I: tHcy \geq 15 micromol/l and Group II: tHcy <15 micromol/l] and found that the prevalence of peripheral neuropathy was similar in both groups. A similar conclusion was also reported by Hoogeveen and colleagues [25] found that hyperhomocysteinemia is not related to risk of distal somatic polyneuropathy in NIDDM.

Plasma folate and vitamin B12 influence homocysteine metabolism as co-substrate and cofactor, respectively. Homocysteine level is inversely related to plasma levels of these substances. Inadequate levels of these vitamins have important health consequences which could be independent of their role in homocysteine metabolism. [26,27]

In the Homocysteine Lowering Trialists' Collaboration, meta-analysis of 12 clinical trials [24,25] it was shown that folic acid by mouth [0.5–5 mg daily] resulted in a reduction of Hcy by 25%, the addition of 0.5 mg vitamin B₁₂ by mouth daily reduced the Hcy levels by another 3% to 10% over the reduction with folic acid alone.

On the other hand, supplements combining folic acid and vitamins B₆ and B₁₂ did not reduce the risk of major cardiovascular events in patients with coronary artery disease [CAD]. Nusier and El-Dawairi [26] also approved that

hyperhomocysteinemia is considered a risk for CAD development, however, vitamin B12 and folic acid supplements did not reduce the risk of myocardial infarction in such patients. [28]

In our patients, Homocysteine level was positively correlated to the duration of DM, Glycemic status and HbA1c, BMI, Hypercholesterolemia indicate proper control of diabetes may lower homocysteine level, and subsequently decrease risk of diabetic complications.

CONCLUSION

This study shows that in complicated 2DM, only elevated Cholesterol had a higher incidence of complications as compared to homocysteine when compared individually. Complications are significantly increased when both cholesterol and homocysteine are elevated suggesting that probably elevated cholesterol & homocysteine are synergistic in increased rate of complications through different mechanisms. The authors feel that a routine specific supplementation with B12 & Folic acid to all diabetics along with statins is indicated. More studies are required with larger numbers to validate the above viewpoint

REFERENCES

1. Wald NJ, Watt HC, Law MR, Weir DG, McPartlin J, Scott JM. Homocysteine and ischemic heart disease: results of a prospective study with implications regarding prevention. *Arch Intern Med.* 1998; 158: 862–7.
2. Nygard O, Nordrehaug JE, Refsum H, Ueland PM, Farstad M, Vollset SE. Plasma Homocysteine levels and mortality in patients with coronary artery disease. *N Engl J Med.* 1997; 337: 230–6.
3. Hankey GJ, Eikelbom JW. Homocysteine and stroke. *Curr Opin Neurol.* 2001; 14: 95–102.
4. Loralie J, Ray JG, Evrovski J, Yeo E, Cole DE. Hyperhomocysteinemia and the Increased Risk of Venous Thromboembolism. *Arch Int Med.* 2000;160:961-4,
5. Finkelstein JD. The metabolism of homocysteine: pathways and regulation. *Eur J Pediatr.* 1998; 157: 40–4.
6. Ogier de Baulny H, Gerard M, Saudubray JM, Zittoun J. Remethylation defects: guidelines for clinical diagnosis and treatment. *Eur J Pediatr.* 1998; 157[Suppl 2]: S77–S83.
7. Mudd SH, Skovby F, Levy HL, Pettigrew KD, Wilcken B, Pyeritz RE, et al. The natural history of homocysteinuria due to cystathionine beta-synthase deficiency. *Am J Hum Genet.* 1985; 37: 1–31.
8. Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. *Nat Genet.* 1995; 10: 111–3.
9. Van den Berg M, Boers GH, Franken DG, Blom HJ, Van Kamp GJ, Jakobs C, et al. Hyperhomocysteinemia and endothelial dysfunction in young patients with peripheral arterial occlusive disease. *Eur J Clin Invest.* 1995; 25: 176–81.
10. Upchurch GR Jr, Welch GN, Fabian AJ, Freedman JE, Johnson JL, Keaney JF Jr, et al. Homocysteine decreases bioavailable nitric oxide by a mechanism involving glutathione peroxidase. *J Biol Chem.* 1997; 272: 1712–1717.

11. Genest J Jr, Audelin MC, Lonn E. Homocysteine: To screen and treat or wait and see? *Can Med Assoc J.* 2000; 163:37-8
12. UK Prospective Diabetes Study [UKPDS] Group. 1998. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes [UKPDS 33]. *Lancet.* 352: 837–853.
13. Quinlivan EP, McPartlin J, McNulty H, Ward M, Strain JJ, Weir DG, et al. Importance of both folic acid and vitamin B12 in reduction of risk of vascular disease. *Lancet* 2002; 359:227-228,
14. Turner, R. C., H. Millns, H. A. Neil, I. M. Stratton, S. E. Manley, D. R. Matthews, and R. R. Holman. 1998. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study [UKPDS: 23]. *BMJ.* 316: 823–828.
15. Renard, C. B., F. Kramer, F. Johansson, N. Lamharzi, L. R. Tannock, M. G. von Herrath, A. Chait, and K. E. Bornfeldt. 2004. Diabetes and diabetes-associated lipid abnormalities have distinct effects on initiation and progression of atherosclerotic lesions. *J. Clin. Invest.* 114: 659–668.
16. Elias AN, Eng S. Homocysteine concentrations in patients with diabetes mellitus--relationship to microvascular and macrovascular disease. *Diabetes Obes Metab.* 2005 Mar;7[2]:117-21
17. Drzewoski J, Czupryniak L, Chwatko G, Bald E. Hyperhomocysteinemia in poorly controlled type 2 diabetes patients. *Diabetes Nutr Metab* 2000;13:319–324.
18. Duis DA, Fernandez N, Arranz ML, Aller R, Izaola O, Romero E. Total homocysteine levels relation with chronic complications of diabetes, body composition, and other cardiovascular risk factors in a population of patients with diabetes mellitus type 2. *J Diabetes Complications.* 2005; 19[1]:42-619.
19. Hoogeveen EK, Kostense PJ, Valk GD, Bertelsmann FW, Jakobs C, DekkerJM, et al. Hyperhomocysteinemia is not related to risk of distal somatic polyneuropathy. *J Intern Med.* 1999; 246: 561–6.
20. Lim HS, Heo YR: Plasma total homocysteine, folate, and vitamin B12 status in Korean adults. *J Nutr Sci Vitminol.* 2002; 48: 290-7.
21. Ambrosch, A, Dierkes, J, Lobmann, R, Kuhne, W, Konig, W, Luley, C, et al. Relation between homocysteinemia and diabetic neuropathy in patients with Type 2 diabetes mellitus. *Diabet Med.* 2001; 18[3]: 185-92
22. Diaz-Arrastia R. Homocysteine and Neurologic Disease. *Arch Neurol.* 2000; 57:1422-7.
23. Faraci FM. Hyperhomocysteinemia: a million ways to lose control. *Atheroscler Thromb Vasc Biol.* 2003;23: 371-3.
24. Turner, R. C., H. Millns, H. A. Neil, I. M. Stratton, S. E. Manley, D. R. Matthews, and R. R. Holman. 1998. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study [UKPDS: 23]. *BMJ.* 316: 823–828.
25. Renard, C. B., F. Kramer, F. Johansson, N. Lamharzi, L. R.

- Tannock, M. G. von Herrath, A. Chait, and K. E. Bornfeldt. 2004. Diabetes and diabetes-associated lipid abnormalities have distinct effects on initiation and progression of atherosclerotic lesions. *J. Clin. Invest.* 114: 659–668.
26. Patel, A., S. MacMahon, J. Chalmers, B. Neal, L. Billot, M. Woodward, M. Marre, M. Cooper, P. Glasziou, D. Grobbee, et al. 2008. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N. Engl. J. Med.* 358: 2560–2572.
27. Holman, R. R., S. K. Paul, M. A. Bethel, D. R. Matthews, and H. A. Neil. 2008. 10-Year follow-up of intensive glucose control in type 2 diabetes. *N. Engl. J. Med.* 359: 1565–1576.
28. UK Prospective Diabetes Study [UKPDS] Group. 1998. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes [UKPDS 33]. *Lancet.* 352: 837–853.

How to cite this article: Chaturvedula R, Venkateshwar RK, Rampure D et. al. Atherogenic activity of hypercholesterolemia and hyperhomocysteinemia in complicated type 2 diabetes mellitus. *Int J Health Sci Res.* 2014;4(4):61-68.

International Journal of Health Sciences & Research (IJHSR)

Publish your work in this journal

The International Journal of Health Sciences & Research is a multidisciplinary indexed open access double-blind peer-reviewed international journal that publishes original research articles from all areas of health sciences and allied branches. This monthly journal is characterised by rapid publication of reviews, original research and case reports across all the fields of health sciences. The details of journal are available on its official website (www.ijhsr.org).

Submit your manuscript by email: editor.ijhsr@gmail.com OR editor.ijhsr@yahoo.com