

## Original Research Article

# Correlation between atherogenic factors in complicated and uncomplicated type 2 diabetes mellitus

Rajdeepak V. S.<sup>1\*</sup>, Rekha G.<sup>1</sup>, Jayashree S. C.<sup>2</sup>

<sup>1</sup>Department of General Medicine, Sapthagiri Institute of Medical Sciences, Bengaluru, Karnataka, India

<sup>2</sup>Department of Radiodiagnosis, Apollo Hospital, Bengaluru, Karnataka, India

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### \*Correspondence:

Dr. Rajdeepak V. S.,

E-mail: [rajdeepak.vs@gmail.com](mailto:rajdeepak.vs@gmail.com)

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## ABSTRACT

**Background:** Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. The factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization and increased glucose production. The vascular complications of DM are subdivided into microvascular (retinopathy, neuropathy, nephropathy) and macrovascular complications (coronary artery disease, peripheral vascular disease, cerebrovascular disease). There is an observed disparity between various vascular complications of diabetes and the atherogenic factors.

**Methods:** The patients with type 2 diabetes mellitus attending outpatient and inpatient departments in Dr. B. R. Ambedkar Medical College and hospital, from September 2014 to September 2016 were selected for this study. All patients were subjected to detailed history, physical examination and laboratory investigations with respect to complications of diabetes mellitus.

**Results:** In this study, 76% of the patients had poor glycemic control with elevated HbA1c >7%. 38% of patients had normal BMI. 36% of patients were overweight and 26% were obese. 62% of patients were either overweight or obese. Hypercholesterolemia was seen in 26% of patients with poor glycemic control. Hyperhomocysteinemia was present in 38% of patients with microvascular complications and 33% of patients with macrovascular complications.

**Conclusions:** Type 2 diabetes mellitus showed a strong correlation between glycemic status and incidence of diabetes complications. Hypercholesterolemia and hyperhomocysteinemia have added to the increased incidence of complications as additional factors in metabolic derangements as a consequence of poor glycemic control.

**Keywords:** Body mass index, Diabetes mellitus, Hypercholesterolemia, Microvascular complications, Serum homocysteine

## INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic

changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. With an increasing incidence worldwide, DM will be likely a leading cause of morbidity and mortality in the future.<sup>1</sup>

More than 10 million Americans carry the diagnosis of diabetes mellitus, and another 5 million are estimated to have undiagnosed diabetes.<sup>2</sup> Diabetes has emerged as the chronic non-communicable disease of concern in developing countries as well. With changing

environment, urbanization and altered lifestyles, diabetes is also increasingly identified as major cause of morbidity and mortality in India too, furthermore, Indians have high ethnic susceptibility for developing diabetes at a younger age group and develop vascular complications earliest and frequently during the natural progression of the disease.<sup>3</sup>

The alarming rise in non-communicable disease warrants an immediate attention of experts to develop better health care facilities. Also, it is essential not only to formulate effective treatment, but also to give importance on preventive aspects of diabetes and vascular morbidity in the Indian context at the primary and secondary levels.<sup>3</sup>

Major cause of morbidity and mortality among diabetic patients is cardiovascular involvement, commonly as coronary artery disease.<sup>3</sup> DM is known to be associated with premature and accelerated atherosclerosis. Patients with diabetes are at 2-4 times increased risk for coronary artery disease (CAD), stroke, and peripheral artery disease.<sup>4</sup> The Framingham study showed a twofold to threefold elevation in the risk of clinically evident atherosclerotic disease in patients with type 2 DM compared to those without diabetes.<sup>5</sup>

Lipoprotein metabolism disorder in type 2 DM is known as diabetic dyslipidemia. Establishing that strict glycemic control reduces the risk of macrovascular complications, has proven much more elusive, than the established beneficial effects of microvascular complications. Hence attention to other aspects of risk in the patient population assumes even greater importance, example control of dyslipidemia. Multiple studies in the general population now conclusively demonstrate that LDL cholesterol lowering is very effective in both primary and secondary CVD prevention.<sup>6</sup>

Recent clinical trials have demonstrated an unequivocal benefit of HMG-COA reductase inhibitor therapy. Having diabetes places the patient in same risk category as those with established atherosclerotic disease. The recent guidelines promulgated by American Diabetic Association recommend an aggressive approach to lipid lowering in the diabetic population.<sup>7</sup>

The prevalence of diabetes is increasing in young adults.<sup>8</sup> Longer exposure to hyperglycemia and other diabetes related abnormalities increase the likelihood that patients will develop chronic complications. Recognition and treatment of dyslipidemia, hyperhomocysteinemia at an early duration of diabetes, will reduce the incidence of vascular complications.

## METHODS

Patients with type 2 diabetes mellitus of age group 18 to 70 years attending outpatient and inpatient departments in Dr. B.R. Ambedkar Medical College and Hospital from

September 2014 to September 2016 were selected for this study after taking informed and written consent.

Patients with type 1 diabetes mellitus, hepatic, renal and thyroid disorders, pregnant and lactating women were excluded from the study.

All patients were subjected to detailed history regarding name, age, sex, occupation, general physical examination and systemic examination with special reference to neuropathy.

Following investigations were carried out to all the patients-FBS (fasting blood sugars), PPBS (post-prandial blood sugars), HbA1C (glycated hemoglobin), fasting lipid profile, serum homocysteine, serum creatinine, urine albumin and sugars, funduscopy, electrocardiograph and 2dimensional echocardiography.

### *Patients were diagnosed as diabetics if they meet the following criteria*

- Symptoms of diabetes plus random blood glucose concentration >200 mg/dl or
- Fasting plasma glucose >126 mg/dl or
- 2-hour plasma glucose >200 mg/dl during an oral glucose tolerance test.

All patients with an episode of ketoacidosis and requiring insulin for survival or patients who required insulin within first year of diagnosis for control of hyperglycemia were considered as type 1 diabetes mellitus and patients without an episode of ketoacidosis, controlled on oral hypoglycemic agents for more than a year after diagnosis were considered as type 2 diabetes mellitus.

The diagnostic criteria for dyslipidemia were taken as per NCEP, ATP III guidelines.<sup>9</sup>

Dyslipidemia is said to be present in the presence of any of the following:

- Total cholesterol  $\geq$ 200 mg/dl
- Triglycerides  $\geq$ 150 mg/dl
- HDL-C <40 mg/dl
- LDL-C  $\geq$ 130 mg/dl

Glycosylated Hb was estimated by an ion exchange resin method.

Total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C) were analysed by enzymatic method using Hitachi 902 analyzer.

Low density lipoprotein cholesterol (LDL-C) was calculated by Friedewald formula

i.e.  $LDL-C = TC - TG/5 - HDL$ .

**Measurement of total homocysteine (tHcy)**

Measurement of tHcy in serum was estimated by an enzyme conversion immunoassay (EIA). This assay is based on enzymatic conversion of tHcy (after reduction and release of endogenous homocysteine from proteins and/or disulfides) to S-adenosyl-L-homocysteine (SAH) by the action of SAH hydrolase, followed by quantification of SAH in a competitive immunoassay with the use of a monoclonal antibody against SAH.

**Diabetic retinopathy**

The ocular fundi examined by direct ophthalmoscopy, after mydriasis. Retinopathy when present classified as Non proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR was diagnosed when there is evidence of micro aneurysms, dot hemorrhages, exudates or cotton wool spots in the absence of any new vessels. PDR was diagnosed when any new vessels were present. NPDR and PDR were taken together as retinopathy for this study. Neuropathy was defined as failure to elicit knee and/or ankle reflexes after reinforcement with or without symptoms of neuropathy or gross sensory disturbance in both feet, in the absence of any other cause of neuropathy.

Nephropathy was considered when proteinuria was present.

Coronary artery disease was diagnosed if there were ECG changes suggestive of recent or past myocardial infarction or by previous hospital records.

Ankle brachial index (ABI) of <0.8 was considered as evidence of peripheral vascular disease (PVD). Cerebrovascular disease was diagnosed by imaging or evidence of any focal deficit.

**Statistical analysis**

The statistical analysis was performed by STATA 11.2 (College Station TX USA). Chi square test has been used to measure the association between the gender with glycemic status, age with gender distribution, glycemic with gender distribution, complications with gender, hyperglycaemic with hypercholesterolemia, complications with glycemic status, complications with homocysteine levels and gender with homocysteine levels, and these are expressed as frequency and percentage. Mann Whitney test were used to find the significance difference between the duration of diabetes with micro and macro vascular diabetes and its expressed as mean and standard deviation. p<0.05 considered as statistically significance.

**RESULTS**

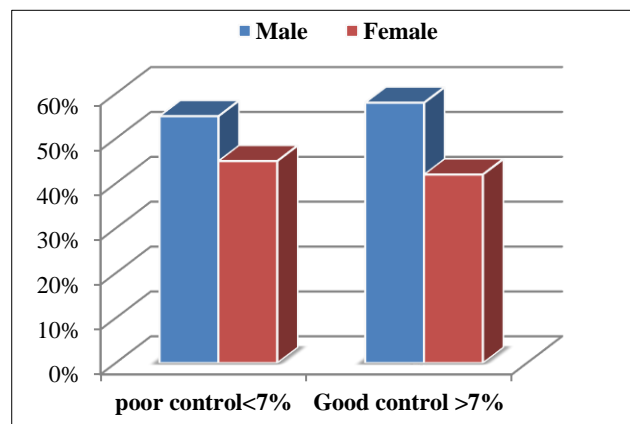
This study clinical data included 50 diabetic patients attending outpatient and inpatient departments of Dr. B.

R. Ambedkar Medical College from September 2014 to September 2016.

**Table 1: Age and gender distribution.**

	Male	Female	Total	p-value
31-40	3 (43%)	4 (57%)	7	0.647
41-50	8 (57%)	6 (43%)	14	
51-60	8 (50%)	8 (50%)	16	
>60	9 (69%)	4 (31%)	13	
Total	28	22	50	

In this study consisting of 50 diabetic patients, 28 (56%) patients were males and 22 (44%) patients were females. The majority of patients were in the age group 41-60 years comprising almost 60% 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 where most of the patients had symptoms or complications related to diabetes. 14% of patients were in the age group 31-40 years and 26% were in the age group above 61-70 years (Table 1).



**Figure 1: Glycemic status and gender distribution.**

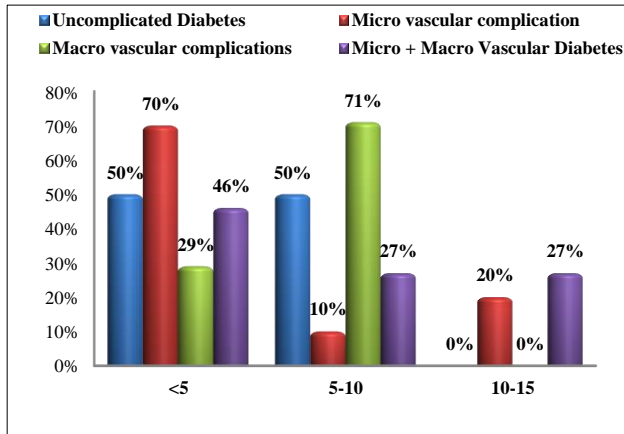
In this study, 38% had normal BMI, 36% were overweight and 26% were obese.

A total 76% of the patients in the study showed poor glycemic control with elevated HbA1C >7%. Males (55%) showed poor glycemic control as compared to females (45%). Good control was only in 24% of cases (Figure 1).

**Table 2: Complications and gender distribution.**

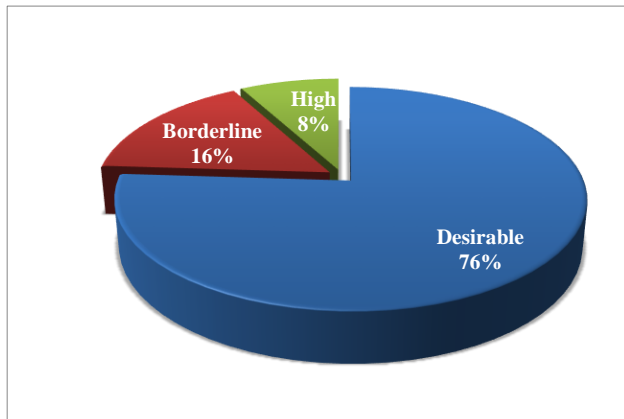
	Male	Female	Total	p-value
<b>Microvascular complications</b>				
Yes	13 (62%)	8 (38%)	21	0.474
No	15 (52%)	14 (48%)	29	
<b>Macrovascular complications</b>				
Yes	11 (61%)	7 (39%)	18	0.585
No	17 (53%)	15 (47%)	32	

A total 42% of the total patients showed microvascular complications and 36% of patients had macrovascular complications (Table 2).



**Figure 2: Complications in relation to duration of diabetes.**

In diabetic patients with <5 years duration, 50% had no complications, 70% had microvascular complications, 29% had macrovascular complications and 46% had both micro and macrovascular complications. In patients with 5 to 10 years duration, 50% had no complications, 10% had microvascular complications, 71% had macrovascular complications and 27% had both micro and macrovascular complications. In patients with 10 to 15 years duration, 20% had microvascular complications, 71% had macrovascular complications and 27% had both micro and macrovascular complications (Figure 2).



**Figure 3: Prevalence of hypercholesterolemia.**

**Table 3: Hypercholesterolemia and glycemic status.**

	Glycemic status		
	Poor control	Good control	Total
Desirable	28 (74%)	10 (83%)	38
Borderline high	6 (16%)	2 (17%)	8
High	4 (11%)	0	4
Total	38	12	50

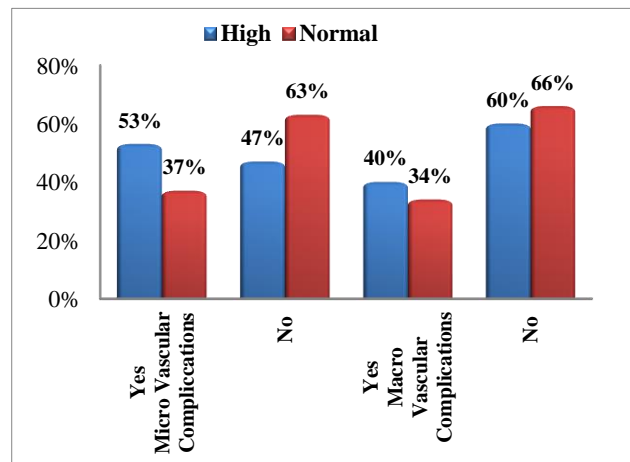
A total 24% of total patients showed hypercholesterolemia of which 16% of patients had borderline high and 8% had high cholesterol levels. (Figure 3).

Among 38 patients with poor glycemic control, 10 (26.31%) patients had hypercholesterolemia and among 12 patients with good glycemic control, 2 (16.66%) patients had hypercholesterolemia. Poor glycemic control is directly proportional to hypercholesterolemia (Table 3).

**Table 4: Complications in relation to glycemic status.**

Glycemic status	Poor control	Good control	Total	p-value
<b>Microvascular complications</b>				
Yes	19 (50%)	2 (17%)	21	0.041
No	19 (50%)	10 (83%)	29	
<b>Macrovascular complications</b>				
Yes	12 (32%)	6 (50%)	18	0.246
No	26 (68%)	6 (50%)	32	

A total 50% of patients with microvascular complications had poor glycemic control and 32% of patients with macrovascular complications had poor glycemic control (Table 4).



**Figure 4: Homocysteine levels in relation to complications.**

Of total 21 patients with microvascular complications, 8 (38.09%) patients had hyperhomocysteinemia and in 18 patients with macrovascular complications, 6 (33.33%) patients had hyperhomocysteinemia (Figure 4).

**DISCUSSION**

A total of 50 type 2 diabetic patients were included in the study and the following categorization into complicated and uncomplicated subsets were correlated with duration of diabetes, body mass index, glycemic status as assessed

by HbA1C levels, serum cholesterol levels and serum homocysteine levels.

There is a correlation between complications and duration of diabetes mellitus, body mass index, glycemic status and elevated cholesterol levels as reported in many studies.

In this study, 62% of patients had a body mass index of  $\geq 25 \text{ kg/m}^2$  with a mean of  $26.84 \pm 4.31$  is supported with Bays HE et al with a mean of  $27.9 \pm 2.9$  and Gabriela Vazquez et al study with a mean of  $25.8 \pm 4.3$ .<sup>10,11</sup>

In diabetic patients with  $< 5$  years duration, 50% had no complications, 70% had microvascular complications, 29% had macrovascular complications and 46% had both micro and macrovascular complications. In patients with 5 to 10 years duration, 50% had no complications, 10% had microvascular complications, 71% had macrovascular complications and 27% had both micro and macrovascular complications. In patients with 10 to 15 years duration, 20% had microvascular complications, 71% had macrovascular complications and 27% had both micro and macrovascular complications.

The present study shows that obese patients had significantly elevated total cholesterol, triglycerides, and LDL-cholesterol and reduced HDL-cholesterol than non-obese. In a study by Gupta S et al, higher body mass index was associated with increased Total cholesterol, triglycerides, LDL-cholesterol.<sup>12</sup> These studies also suggest that Increased body mass index was associated with increasing hypercholesterolemia.

The present study suggests that hypercholesterolemia was more prevalent in diabetics and was associated with poor glycemic status. According to Al-Adsani A et al, total cholesterol, triglycerides, LDL-cholesterol levels were strongly associated with glycemic control.<sup>13</sup> In Ismail et al study, glycemic status was an important determinant of Total cholesterol, triglycerides, and LDL-cholesterol.<sup>14</sup>

This study also correlated well in support of other studies and established the fact of importance of euglycemic status with lifestyle modifications and appropriate anti-diabetic therapy and lipid lowering medication.

In this particular study, the role of serum homocysteine was additionally estimated to assess either singly or both together as additional factors affecting the diabetes complication.

A significant number of patients showed elevated homocysteine levels might have contributed to increased type 2 diabetes complications. This study was supported by Martin Buysschaert, Anne-Sophie Dramais: hyperhomocysteinemia in type 2 diabetes, relationship to microangiopathy, nephropathy and insulin resistance. They found that 31% of the cohort (Group 1) had raised total homocysteine (mean  $\pm 1$  SD) values, whereas Group

2 had normal values. The prevalence of microangiopathy was higher in Group 1 than in Group 2 subjects.<sup>15</sup>

In patients with increased cholesterol levels but normal homocysteine levels, showed lesser number of complications suggesting that homocysteine is probably an important contributor to the complications of diabetes.

There is a strong case for addition of vitamin B6, B12, folate along with lipid lowering medication which is cost effective and contributes to the low incidence of diabetes complications rate.

## CONCLUSION

Type 2 diabetes mellitus showed a significant correlation between glycemic status and incidence of diabetes complications. Hypercholesterolemia and homocysteine have added to the increased incidence of complications as additional factors in metabolic derangements as a consequence of poor glycemic control.

There is a strong case for routine addition of vitamin B6, B12, folate in addition to lipid lowering drugs on a routine basis.

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