Original Research Article

Cardiovascular Risk in Type 2 Diabetes Mellitus with Metabolic Syndrome: A Hospital Based Pilot Study

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ABSTRACT

Metabolic syndrome is a constellation of risk factors such as central obesity, increased blood pressure, impaired glucose tolerance, altered lipid profile mainly low High Density Lipoproteins (HDL) and high Triglycerides (TG) which predispose the individual to increased risk for development of cardiovascular disease. The pathogenesis is complex but interaction of obesity, sedentary lifestyle and dietary and genetic factors are known for their contribution.

Prevalence of metabolic syndrome is high among Asians including Indians, and is on the rise. Individuals with metabolic syndrome have a 30%-40% probability of developing diabetes and/or cardiovascular disease consisting of prothrombotic and proinflammatory atherogenic and vaso-occlusive disease and their complications, depending on the number of components present.

In this context the aim of this study was to assess the prevalence of metabolic syndrome as defined by NCEP ATP III guidelines with a modification to the value for body mass index (BMI) that is more applicable to the Asian Indian population, and to look for the differences between the various components constituting metabolic syndrome.

In this study, 40 diabetic patients with metabolic syndrome were compared with 40 age and sex matched diabetic controls without metabolic syndrome. On evaluating the lipid profile; serum total Cholesterol, Triglyceride and Low Density Lipoprotein levels were found to be higher in cases when compared to the controls which were statistically significant (p<0.0001). Serum High Density Lipoprotein in cases was lower when compared to the controls but statistically not significant.

In diabetic subjects with any of the components of the metabolic syndrome, should be investigated thoroughly for the presence of cardiovascular disease and all the associated conditions should be treated aggressively so that some of the profound and life threatening consequences of the disease may be prevented or alleviated.

Key Words: Metabolic Syndrome, Diabetes, Dyslipidemia, Obesity, Hypertension.

INTRODUCTION

Metabolic syndrome, a constellation of risk factors such as central obesity, increased blood pressure, impaired glucose tolerance, altered lipid profile mainly low High Density Lipoproteins (HDL) and high

Triglycerides (TG) are known to predispose an individual to increased risk for development of cardiovascular disease. [1,2]

The pathogenesis is complex but interaction of obesity, sedentary lifestyle; dietary, genetic and environmental factors are known to be responsible for the development of Metabolic Syndrome. [2,3] Prevalence of metabolic syndrome is high among Asians including Indians, and is rising particularly with typical urban sedentary life style. Many studies among various population groups in India have reported high prevalence of metabolic syndrome. [4,5] Metabolic syndrome is a complex web of metabolic factors that are associated with two fold risk of cardiovascular disease and fivefold risk of diabetes. The metabolic syndrome is a multiplex risk factor for atherosclerotic cardiovascular disease. It consists of hyperglycemia, dyslipidemia, elevation of blood pressure, pro-thrombotic and pro-inflammatory states predisposing to atherosclerosis and vascular diseases. Individuals with metabolic syndrome have a 30%-40% probability of developing diabetes and/or cardiovascular disease within 20 years, depending on the number of components present. [6]

Metabolic syndrome appears to promote the development of atherosclerotic cardiovascular disease. Elevation of apoB containing lipoproteins initiates atherogenesis and drive lesion development. Atherosclerotic plaque development is accelerated by low levels of HDL-C, by elevated glucose levels and by inflammatory cytokines. [7,8]

This hospital based pilot study was planned to assess the cardiovascular risk of the various components of metabolic syndrome as defined by NCEP ATP III guidelines with a modification to the value for body mass index (BMI) that is more applicable to the Asian Indian population.

MATERIALS AND METHODS

The present study was undertaken in the Department of Biochemistry, Veer Surendra Sai Institute of Medical Science and Research, Burla, Sambalpur, Odisha, on patients admitted in the Departments of Medicine and Cardiology between Sept 2012 and Dec 2014. The study was conducted on 40 subjects with diabetes having Metabolic Syndrome taking 40 diabetic patients without metabolic syndrome as control.

The cardiovascular risk factors considered for the study were Fasting Blood sugar, Blood Pressure, Body Mass Index and Lipid Profile.

An individual was considered as subject if he/she fulfills any three of the following criteria:

- Fasting Plasma Glucose more than 110 mg/dl
- Blood Pressure systolic greater than 130 and, or, diastolic greater than 90 mm of Hg
- Waist Circumference greater than 40 inch (men), and greater than 35 inch (women)
- Serum Triglycerides exceeding 150 mg/dl
- Serum HDL less than 40 mg/dl

Measurement of Blood Pressure:
Blood pressure was measured by standardized technique, using a Mercury sphygmomanometer in right arm, in comfortable sitting position.

Measurement of Body Mass Index:
BMI was calculated by dividing the body weight in kilogram by the square of height in meter.

Routine biochemical investigations were carried out in both the study groups by

standardized protocols using Cobas Integra 400, fully automated high throughput Chemistry analyzer, at the Department of Biochemistry, VIMSAR, Burla, Sambalpur, Odisha.

RESULTS

In the present study 40 cases with ages between 25-65 years (Mean $\pm$ SD 45.9$\pm$9.3) and 40 age and sex matched controls with ages between 28-65 years (Mean$\pm$ SD 45.5$\pm$10.1) have been studied.

Table 1: Shows age and sex distribution of the case and control subjects

Age Groups	Controls (n=40)			Case (n=40)		
	Male	Female	% of Total	Male	Female	% of Total
25-45	14	6	50	18	4	55
46-65	13	7	50	11	7	45
TOTAL	27	13	100	29	11	100

Table 2: Shows family history of diabetes among Case and Control groups.

Family History of Diabetes Mellitus	CONTROLS (n=40)	CASES (n=40)	TOTAL	'p' VALUE
POSITIVE	15 (38%)	27(67%)	42	<0.05
NEGATIVE	25(62%)	13 (33%)	38	

Out of 40 cases, 27 (67%) and out of 40 controls 15 subjects (38%) had positive family history of diabetes.

Table 3: Summarizes the Biophysical parameters of cases and Control subjects studied in both the groups

PARAMETERS	CONTROLS (n=40)		CASES (n=40)		't' VALUE	'p' VALUE
	MEAN$\pm$SD	RANGE	MEAN$\pm$SD	RANGE		
AGE(years)	45.5$\pm$10.1	28-65	45.9$\pm$9.3	25-65	-	-
AC(inch)	34.1$\pm$1.3	32-36	36.2$\pm$2.4	32-44	4.71	<0.0001
BMI(Kg/m^2)	26.4$\pm$2.5	23.3-32.2.	25.7$\pm$3.2	18.5-33.8	-1.11	>0.27
SBP(mmHg)	118.0$\pm$11.0	136-90	140.0$\pm$13.1	162-110	8.27	<0.0001
DBP(mmHg)	81.0$\pm$4.7	70-88	91.9$\pm$8.5	80-110	7.03	<0.0001

Table 4: Compares the fasting blood sugar level among case and control group.

PARAMETER	CONTROLS (n=40)		CASES (n=40)		t value	p value
	MEAN$\pm$SD	RANGE	MEAN$\pm$SD	RANGE		
FBS(mg/dl)	197$\pm$29.9	134-287	209$\pm$33.8	145-296	1.60	>0.11

Fasting blood sugar in cases 209$\pm$33.8 mg/dl with a range of 145-296 mg/dl was higher as compared to the controls 197$\pm$29.9 mg/dl with range of 134-287 mg/dl which was statistically not significant (p>0.11).

DISCUSSION

The current work was undertaken as a pilot study to evaluate the cardiovascular risk of metabolic syndrome in diabetic population. The South East Asian population is genetically predisposed to diabetes and cardiovascular diseases, and their numbers are consistently on the rise.

The prevalence of metabolic syndrome in Asian Indians varies according to the region, the extent of urbanization, lifestyle patterns, and socioeconomic /cultural factors. Recent data show that about one third of the urban populations in India's major cities have Metabolic Syndrome. So this study may help in the detection of cardiovascular risk factors and appropriate medical intervention in the early phase of disease.

40 diabetic patients with metabolic syndrome and 40 age and sex matched controls that were diabetic, without metabolic syndromes have been studied. Among the case group 45% were female and 55% were male. Our study groups were divided in two age groups: 25-45 years and 46-65 years. (Table II)

Statistics in India is almost equivalent to the world population regarding the prevalence of metabolic syndrome and surprisingly the prevalence in India is more

in women than in men, both in rural as in urban population.

Family history of diabetes was present in 67% of cases but only in 38% of control group. Family history of diabetes was found to significantly correlate with the subsequent development of diabetes in these subjects, as found by some workers [9] (p<0.001). (Table III)

Mean blood pressure for controls and hypertensive subjects were 118/81 mm Hg and 140/92 mm Hg respectively The rise in systolic and diastolic blood pressure in cases as compared to control group was statistically significant (p<0.0001) (Table IV).The present study was supported by a similar study by Chuang et al [10] who observed prevalence of high blood pressure among patients with metabolic syndrome.

The body mass index (BMI) found in cases was 25.7±3.2 Kg/m^2 and control was 25.4±2.5 Kg/m^2 which was statistically not significant (p>0.27). (Table VI). We observed that abdominal obesity (as measured by abdominal circumference) was more in cases (36.2±2.4 inch) than in controls (34.1±1.3 inch), and was a potent risk factor for genesis of cardiovascular disease.

In a study to compare variations in BMI with the effect of cumulative features of metabolic syndrome on the risk of ischemic heart disease, St. Pierre et al. (2005) followed a group of 1824 non-diabetic men for a period of 13 years. During this 13-year period, 284 first ischemic heart disease events were recorded. Although men with a BMI >/= 30 were most likely to accumulate features of the insulin resistance syndrome, the risk of ischemic heart disease was not significantly higher in this group compared with the normal BMI group. [11]

However, obese men that accumulated more than four features of the insulin resistance syndrome were at increased risk of ischemic heart disease. The researchers concluded that BMI alone poorly reflects the risk of ischemic heart disease associated with the features of insulin resistance syndrome.

However obesity (BMI>30 Kg/m2) is an independent cardiovascular risk factor for adverse prognosis in diabetes. A Vask et al studied the association of BMI with diabetes. They found significantly more diabetic than control persons with BMI above 25 Kg/m2 (p<0.0001). [12] Tuomo Rankinen et al on their study showed that excess body weight is associated with an increase risk of developing diabetes where as weight loss has been shown to lower incidence of diabetes. [13]

In our study on evaluating the lipid profile; serum total cholesterol, triglyceride, low density lipoprotein levels were higher in cases when compared to the controls which were statistically significant (p<0.0001). Serum HDL-C in cases was lower when compared to the controls found to be statistically not significant (p>0.05). (Table VII)

Cadwell et al conducted study of lipid profile and blood glucose in metabolic syndrome patients. They found that the mean cholesterol in hypertensive patients as compared to the healthy controls which was statistically significant (p<0.0001). The increase in mean HDL in control group as compared to hypertensive patients was not statistically significant (p>0.05). The mean LDL of cases was higher than the control which was statistically significant (p<0.0001). [14]

Hypertension and dyslipidemia are well-established and partially overlapping risk factors for cardiovascular disease. Moreover, hypertension and dyslipidemia are manifestations of the metabolic syndrome, which is also a consequence of the interaction of genes and the environment. The pathogenesis of

hypertension and the metabolic syndrome is only partly understood, but endothelial dysfunction likely plays a role in both.

Dekker, et al. (2005) using data from The Hoorn Study compared the 10 year risk of fatal and non-fatal cardiovascular disease with different definitions of Metabolic Syndrome, i.e., ATP III, WHO, EGIR, and American College of Endocrinology. The ATP III definition was associated with a two-fold increase in age-adjusted risk of fatal cardiovascular disease in men and nonfatal cardiovascular disease in women. [15] In our study we have applied the criteria formulated by NCEP ATP III, and we found the potential risk factors of cardiovascular diseases like high blood pressure and dyslipidemia was more in cases than in controls which is in agreement with the findings of the above study.

Elevated triglyceride level and low HDL-C level are relevant in subjects with metabolic syndrome. In our study we got elevated level of triglyceride in cases with mean of 208.0±47.0 mg/dl than in controls with mean of 136.0±24.0 mg/dl which was statistically significant.

Marroquin et al. (2004) found in his study that the mortality associated with metabolic syndrome cases is due to cardiovascular diseases which is aggravated by atherogenic dyslipidemia such as elevated triglyceride and low HDL-C. High density lipoprotein is involved in reverse cholesterol transport is protective for cardiovascular diseases. Thus low levels of HDL-C in cases of metabolic syndrome are a risk factor for CVD. [16]

The role of isolated Hypertriglyceridemia as a cardio vascular risk factor is still controversial. However a recent study by Rajmohan et al on diabetic individuals surviving a myocardial infarction showed no evidence of an association of isolated hypertriglyceridemia with coronary artery disease.

In our study, cases had markedly low values of HDL-C with (34.7±8.61 mg/dl) compared to control (45.0±7.19 mg/dl). Increased prevalence of low HDL-C has been reported earlier by Enas et al [17] who found that only 4% of Asian Indian men and 5% Asian Indian women had optimal HDL-C levels.

Low HDL-C levels are a strong predictor of occurrence and reoccurrence of Myocardial infract (MI) and stroke and are associated with premature and severe CAD. Obesity reduces HDL-C levels, and obese patients with MS and atherogenic dyslipidemia almost always have low HDL-C levels. Our study shows that around 35% of subjects having low HDL-C were either overweight or obese.

Saley, et al. (2005) conducted a study to determine to what extent dyslipidemia contributed to increase the risk of cardiovascular events associated with Metabolic Syndrome. [18] The study showed strong association of dyslipidemia with incidence of CVD, which is in corroboration with our study.

With respect to cardiovascular disease morbidity and mortality and Metabolic Syndrome, it is not surprising that several studies have indicated an increase in cardiovascular mortality and morbidity in those with Metabolic Syndrome. [18-21]

In our study the incidence of metabolic syndrome in diabetics is associated with cardiovascular risk factors like hypertension and dyslipidemia, but in control group diabetics without metabolic syndrome are at lower risk of developing cardiovascular diseases.

A study that yielded similar results, Malik, et al. (2004) compared the incidence of coronary heart disease in diabetics with metabolic syndrome was much higher than in diabetics without metabolic syndrome. [19]

The importance of high serum cholesterol, especially a high level of low-

density lipoprotein (LDL) cholesterol, as a risk factor for coronary artery disease is well established. Likewise, efficacy for decreasing risk for coronary artery disease by LDL-lowering therapy has been documented through clinical trials.

However, many high-risk patients manifest elevated serum triglyceride levels, and the role of hypertriglyceridemia in causation of coronary artery disease remains to be elucidated. Nonetheless, there is growing evidence that hypertriglyceridemia and low HDL-C is a marker for increased risk for coronary artery disease.

Finally, in a study that used only the WHO definition of Metabolic Syndrome, Isomaa, et al. (2001) estimated the prevalence and cardiovascular risk associated with the Metabolic Syndrome using 4483 subjects, 35 to 70 years old from the Botnia Study. He found that the risk for coronary heart disease and stroke was increased three-fold in subjects with the syndrome and cardiovascular mortality was markedly increased (12.0% vs. 2.2%) in subjects with the Metabolic Syndrome. [21]

CONCLUSION

The Metabolic Syndrome, a highly prevalent entity is a clustering of risk factors of metabolic origin that are accompanied by increased risks of cardiovascular disease. These risk factors are dyslipidemia, elevated blood pressure, raised plasma glucose and an atherogenic pro-thrombotic and pro-inflammatory state. Our study showed that diabetic patients with metabolic syndrome are more vulnerable for development of cardiovascular disease than diabetics without metabolic syndrome.

Two major underlying risk factors for the metabolic syndrome are obesity and Insulin resistance; exacerbated by physical inactivity, advancing age, endocrinal and genetic factors. The condition is progressive which further enhances the risk of cardiovascular disease.

In diabetic subjects with any of the components of the metabolic syndrome, should be investigated thoroughly for the presence of cardiovascular disease and all the associated conditions should be treated aggressively so that some of the profound and life threatening consequences of the disease may be prevented or alleviated.

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