FREQUENCY OF METABOLIC SYNDROME IN TYPE 2 DIABETES AND ITS RELATIONSHIP WITH INSULIN RESISTANCE

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Background: The metabolic syndrome is a cluster of various cardiovascular disease risk factors: diabetes and pre-diabetes, abdominal obesity, hyperlipidaemia and high blood pressure. People with metabolic syndrome are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome. The objective of the study was to observe the frequency of metabolic syndrome (MetS) in patients with type 2 diabetes mellitus and study the relationship of insulin resistance with the metabolic syndrome and its different clinical parameters. **Methods:** The study was conducted at Combined Military Hospital, Malir, in about six months. Hundred and fifty-five patients with type 2 diabetes were included in the study, who were diagnosed after 25 years of age. All those suffering from any liver disease, non diabetic renal disease, thyroid hormonal disorder, advanced cardiac disease and cancers were excluded from the study. Insulin resistance was measured using homeostatic model assessment of insulin resistance (HOMA-IR) and International Diabetes Federation (IDF) criteria were used to diagnose metabolic syndrome. **Results**: Among 155 type 2 diabetic patients, 66.5% were having metabolic syndrome (MetS) according to IDF criteria. This frequency was significantly higher in women (84.7%) as compared to men (44.3%). Difference of means of HOMA-IR (Insulin resistance) in MetS present and MetS absent cases was statistically significant in men (p=0.02) but not in women (p=0.57), when compared through independent sample t-test. Insulin resistance (HOMA-IR) was not significantly correlated with waist circumference (r=0.24), BMI (r=0.16), triglycerides (r=0.22), HDL cholesterol (r=0.18) and HbA1c (r=0.35) but showed moderate correlation with fasting plasma glucose (r=0.44). Among 39 patients belonging to the 4th quartile of HOMA-IR, i.e., the most insulin resistant people, 79% patients had MetS according to IDF criteria, and 21% patients did not have MetS. **Conclusion:** It is concluded that the frequency of MetS is significantly high in patients with type 2 diabetes. Insulin resistance as measured through HOMA-IR does not show significant correlation with clinical parameters of MetS in type 2 diabetics.

Keywords: Metabolic syndrome, insulin resistance, HOMA-IR, IDF criteria

INTRODUCTION

The metabolic syndrome is a cluster of various cardiovascular disease risk factors: diabetes and pre-diabetes, abdominal obesity, hyperlipidaemia and high blood pressure. People with metabolic syndrome are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome.[1] In addition, people with metabolic syndrome have a fivefold greater risk of developing type 2 diabetes.[2]

Obesity, particularly abdominal obesity, is associated with resistance to the effects of insulin on peripheral glucose and fatty acid utilization, often leading to type 2 diabetes mellitus. Insulin resistance, the associated hyperinsulinemia and hyperglycaemia, and adipocyte cytokines (adipokines) may also lead to vascular endothelial dysfunction, an abnormal lipid profile, hypertension, and vascular inflammation, all of which promote the development of atherosclerotic cardiovascular disease (ASCVD).[3–5] A similar profile can be seen in individuals with abdominal obesity who do not have an excess of total body weight.[6]

The pathophysiological perspective of insulin resistance demonstrates how this single defect, leads to a variety of pathological changes, resulting in increased risk for a constellation of clinical conditions like type 2 diabetes, cardiovascular disease, essential hypertension, polycystic ovarian syndrome, non-alcoholic fatty liver disease, gallstone disease, cancer (i.e., breast cancer) and sleep apnoea.[7] The metabolic syndrome is the clinical epidemiological perspective which assembles a group of related metabolic risk factors and uses this grouping for the prediction of future cardiovascular events.

Because metabolic syndrome traits co-occur, patients identified with one or just a few traits are likely to have other traits as well as insulin resistance.[8] There are several definitions for the metabolic syndrome. The National Cholesterol Education Program (NCEP/ATP III) and International Diabetes Federation (IDF) definitions are the most widely used.[9,10] IDF criteria includes, increased waist circumference (ethnic specific values, e.g., Asian men ≥90 Cm and Asian women ≥80 Cm)

plus any two of, triglycerides >150 mg/dL (1.7 mmol/L) or treatment for elevated triglycerides, HDL cholesterol <40 mg/dL (1.03 mmol/l) in men or <50 mg/dL (1.29 mmol/l) in women, or treatment for low HDL, systolic blood pressure >130 mm Hg, diastolic blood pressure >85 mm Hg, or treatment for hypertension, fasting plasma glucose >100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes.[10]

It is now believed that metabolic syndrome is driving the twin global epidemics of type 2 diabetes and cardiovascular disease. South Asians have high prevalence of metabolic syndrome[11,12] and an unusually high tendency to develop type 2 diabetes mellitus and atherosclerotic cardiovascular disease (ASCVD).[13] In order to reduce the medical and economic burdens, it is imperative to identify patients of metabolic syndrome and treat them early with lifestyle modification and drugs, where needed.

In our diabetes clinic we collected data with an objective to see the frequency of metabolic syndrome (using IDF criteria) in our type 2 diabetic population and relationship of insulin resistance with the metabolic syndrome and its different clinical parameters. The aim was to assess the size of the diabetic population with clustering of cardiovascular risk factors in our population, so that the importance of lifestyle modification and treatment of insulin resistance could be effectively emphasised.

MATERIAL AND METHODS

It was a cross-sectional study, carried out at Diabetes Clinic, Combined Military Hospital, Malir, Karachi in patients of type 2 diabetes residing in and around Malir Cantt, Karachi. Out of about 200 type 2 diabetic patients, consecutively recruited at the diabetes clinic of Combined Military Hospital Malir Cantt, over a period of about six months from April 2007 to September 2007, 155 patients were included in the study, who met the following inclusion and exclusion criteria.

Patients of diabetes mellitus diagnosed after 25 years of age, who showed absence of ketosis at diagnosis or afterwards and absence of clinically evident autoimmune disease (like autoimmune thyroid disease, vitiligo etc.). These criteria were chosen to minimise the risk of including late onset type 1 diabetic patients. The patients who showed any evidence of non-diabetic renal disease or severe renal disease (serum creatinine >177 mmol/l [2.0 mg/dl]), severe heart failure (New York Heart Association class III or more), liver disease, cancer, autoimmune disease, thyroid hormonal disorder and any other condition that in our judgment could affect study participation or confound data interpretation, were excluded from

the study. Pregnant patients with diabetes were also excluded. Patients using drugs, which could alter insulin sensitivity such as hormone replacement therapy (HRT), steroids or anti-tuberculosis drugs except anti diabetic drugs, were also excluded from the study.

All patients were interviewed regarding duration of diabetes, presence of other co-morbid conditions, anti-diabetic and anti-hypertensive drug therapy. Duration of diabetes was calculated from the calendar year of data collection minus the calendar year of diabetes diagnosis.

All subjects enrolled in the study underwent detailed clinical examination, including measurements of height, weight, waist circumference, and blood pressure. Patients were considered hypertensive, if they were already on antihypertensive drugs or had a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥ 90mm Hg. Fasting venous blood was sampled from an antecubital vein from all patients for the measurement of plasma glucose, serum insulin, total cholesterol, HDL cholesterol, serum triglycerides, creatinine and HbA1c.

Glycosylated haemoglobin measurement was performed by the chromatographic assay with pre-weighted resins. Serum insulin analysis was performed using Immulite third generation kits of Diagnostic products corporation, 5210 Pacific Concourse Drive Los Angeles, on Immulite Hormone Analyser. Serum creatinine was performed using Linear Chemical kit based on original picrate reaction. Plasma glucose was performed on Microlab 200 Merck Marker semi-automated Chemical Analyser. Analysis of glucose by this method is based upon Trinder reaction in which glucose is oxidised to D-gluconate by glucose oxidase. Serum cholesterol, triglycerides and urine microalbumin were performed on Microlab 200 using Rondox commercial kits by standardised method.

Insulin resistance was determined using homeostatic model assessment of insulin resistance (HOMA-IR).[14] HOMA-IR index was calculated as fasting serum insulin (mU/ml) x fasting plasma glucose (mmol/l)/22.5.[14] For diagnosis of metabolic syndrome, IDF criteria was used, employing ethnic specific values of waist circumference for south Asian men ≥90 cm and women ≥80 cm.[10,15]

For statistical analysis of the results, statistical package SPSS version 10 was used. Data is presented in Mean±SD and frequency (percentage in respective sex). Ninety-five percent confidence interval for means of all clinical parameters has also been calculated. Statistical significance of difference of means was calculated through

independent sample *t*-test. Chi square test was used where two categorical variables were compared. Metabolic syndrome and hypertension have been dealt as dichotomous categorical variables, on account of their presence or absence in the studied population. The correlations were seen by applying Pearson's correlation coefficient. Statistical significance was assessed by using *p*<0.05.

RESULTS

On the basis of IDF criteria, 103 patients out of 155 (66.5%) fulfilled the criteria for metabolic syndrome (MetS) and 52 (33.5%) were not having MetS. Out of 85 women, 72 (84.7%) were positive and 13 (15.3%) were negative, 31 men out of 70 (44.3%) were positive and 39 (55.7%) were negative for MetS (*p*=-0.001). All the studied clinical parameters have been compared in two groups, i.e., type 2 diabetics having and not having metabolic syndrome, in both men and women (Table-1, 2).

In both men and women, difference in waist circumference, body mass index, and presence of hypertension, serum triglycerides and HDL cholesterol was highly significant, when compared in patients with and without metabolic syndrome. However all of these variables are included in the IDF criteria of MetS, except body mass index. Serum total cholesterol, insulin level and HOMA-IR values had a statistically significant difference in men, with and without MetS but not in women. Although mean serum insulin levels and mean HOMA-IR values were greater in women with MetS as compared to those without MetS, but difference in two groups was not as significant as in men.

Many variables are components of metabolic syndrome. HOMA-IR was not significantly correlated with waist circumference (r=0.24), BMI (r=0.16), triglycerides (r=0.22), HDL cholesterol (r=-0.18) and HbA1c (r=0.35) but showed correlation with FPG (r=0.44, p=0.0001). When this correlation was calculated in men and women separately in the studied sample, HOMA-IR did not show significant correlation with clinical parameters of metabolic syndrome.

When the patients with and without MetS were divided into four groups according to quartiles of HOMA-IR, 30.1% patients with MetS as compared to 15.4% patients without MetS belonged to 4th quartile of HOMA-IR, i.e., the most insulin resistant population (Figure-1). In simpler words, out of 39 patients belonging to the 4th quartile of HOMA-IR, i.e., the most insulin resistant people, 31 (79%) had MetS according to IDF criteria, and 8 (21%) patients did not have MetS. Seventy fifth (75th) percentile value of HOMA-IR was 4.17.

The relationship of insulin resistance (HOMA-IR) with the clinical parameters of metabolic syndrome was also studied by dividing the sample into two groups, on the basis of using or not using metformin. Eighty six patients were using metformin, there mean HOMA-IR was 3.30±2.58 and 69 patients were not using metformin, and had a mean HOMA-IR of 3.55±2.78. Both of these groups did not show any significant correlation with clinical parameters of metabolic syndrome. There were only 6 patients who were using thiazolidinediones, so the effect on the relationship of metabolic syndrome and insulin resistance was not significant.

Table-1: Comparison of Clinical Parameters in Men, with and without Metabolic Syndrome

Clinical Parameters	Metabolic Syndrome Present (n=31)			Metabolic Syndrome Absent (n=39)			
		95% confidence interval for means			95% confidence interval for means		
	Mean±SD	Lower bound	Upper bound	Mean±SD	lower bound	Upper bound	*p*
Age (years)	59.1±9.2	55.8	62.6	51.9±11.3	48.1	55.4	0.006
Waist (cm)	102.4±9.2	98.9	105.8	87.2±6.5	85.1	89.3	0.001
Body Mass Index (BMI) (kg/m²)	29.0±3.5	27.8	30.3	23.7±2.9	22.7	24.6	0.001
Duration of diabetes (years)	7.2±5.9	4.9	9.3	5.7±5.8	3.8	7.6	0.30
Hypertension	22 (71%)			7 (18%)			0.001
Total Cholesterol (mmol/l)	4.6±0.5	4.5	4.8	4.4±0.3	4.2	4.5	0.03
Triglycerides (mmol/l)	1.8±0.3	1.7	1.9	1.7±0.3	1.6	1.8	0.02
HDL Cholesterol (mmol/l)	0.9±0.3	0.8	1.1	1.2±0.3	1.1	1.3	0.001
Creatinine (μmol/l)	82.5±19.0	75.5	89.4	78.6±12.3	73.3	83.8	0.35
HbA1c (%)	6.9±1.6	6.3	7.5	6.9±1.3	6.5	7.3	0.92
Fasting plasma glucose (mmol/l)	8.6±2.8	7.6	9.7	8.9±3.2	7.8	9.9	0.73
Insulin (μIU/ml)	10.3±8.8	7.1	13.6	6.5±3.0	5.5	7.4	0.01
HOMA-IR	4.0±3.4	2.8	5.2	2.6±1.7	2.0	3.1	0.02

Data is Mean±SD and frequency (percentage in respective sex) MS-metabolic syndrome

Table 2: Comparison of Clinical Parameters in Women, with and without Metabolic Syndrome

| Clinical Parameters	Metabolic Syndrome Present (n=72)			Metabolic Syndrome Absent (n=13)			p-value
	Mean±SD	95 % confidence interval for means		Mean±SD	95 % confidence interval for means		
		Lower Bound	Upper bound		Lower Bound	Upper bound	
Age (years)	53.0±10.2	50.6	55.4	50.1±11.8	43.2	57.3	0.36
Waist (cm)	97.3 ± 7.7	95.5	99.2	89.3±10.2	83.1	95.5	0.002
Body Mass Index (BMI) (kg/m^2)	29.7±4.0	28.8	30.7	25.7±4.1	23.3	28.2	0.001
Duration of diabetes (years)	6.0±5.0	4.8	7.2	5.7±4.6	2.9	8.5	0.84
Hypertension	46 (64%)	-	-	1 (8%)	-	-	0.001
Total Cholesterol (mmol/l)	4.4±0.6	4.2	4.5	4.2±0.6	3.9	4.6	0.41
Triglycerides (mmol/l)	1.8±0.3	1.7	1.9	1.4±0.4	1.2	1.6	0.001
HDL Cholesterol (mmol/l)	1.0±0.2	1.0	1.1	1.3±0.2	1.1	1.4	0.002
Creatinine (μmol/l)	76.9±13.5	73.7	80.1	78.7±12.3	71.3	86.1	0.64
HbA1c (%)	7.1±1.6	6.7	7.5	6.9±1.4	6.0	7.8	0.73
Fasting plasma glucose (mmol/l)	8.4±2.9	7.7	9.1	9.2±3.7	6.9	11.5	0.39
Insulin (μIU/ml)	9.7±6.0	8.3	11.1	7.4±3.2	5.4	9.4	0.18
HOMA-IR	3.6±2.7	2.9	4.2	3.1±2.1	1.8	4.4	0.57
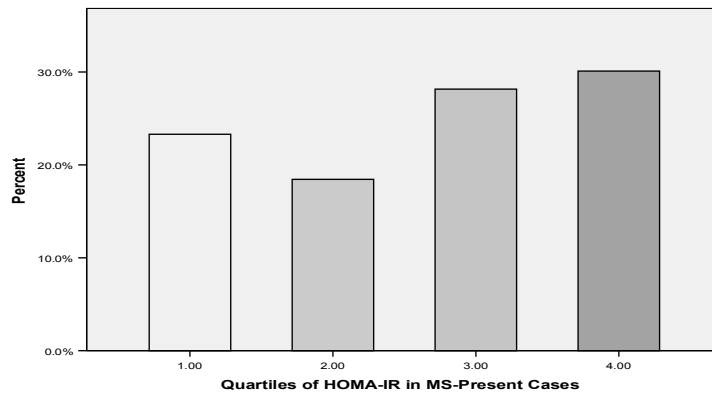
Figure-1: Distribution of MS (Metabolic Syndrome)-Present Cases in Type 2 Diabetes patients, grouped on the basis of quartiles of HOMA-IR

DISCUSSION

In this cross-sectional study of 155 type 2 diabetic patients, we have found the prevalence of MetS (according to IDF Criteria) to be 66.5%. This prevalence was significantly higher in women (84.7%) as compared to men (44.3%). The main reason seems to be a very high rate of obesity in females, average waist circumference being 97.36 Cm and BMI 29.79 Kg/min^2 in women having metabolic syndrome. Moreover, 55.3% of the women were hypertensive as compared to 41.4% of the men.

Abdominal obesity is common in south Asians and evident in non obese people. They have high percentage of body fat, thick subcutaneous adipose tissue, low muscle mass, insulin resistance and hyperinsulinaemia. This body composition is conducive to the development of metabolic syndrome.[16] According to a recent study on South Indians, the prevalence of the metabolic syndrome was estimated to be 25.8%, in the general population, according to the IDF definition.[12] A very recent study has reported the prevalence of metabolic syndrome in Pakistan according to different definitions, from 18% to 46%, comparable to the data from other South Asian countries.[17] In a study at Shanghai, in 1008 patients with type 2 diabetes over 30 years of age, prevalence of MetS according to IDF criteria was 50%.[18] In 2007, The Diabetes in Germany (DIG) study investigated the prevalence of MetS in more than four thousand type 2 diabetics between 35–80 years of age.[19] The prevalence of MetS according to IDF criteria was 82.6% and females were significantly more affected than males. Very high prevalence of MetS in this German population is due to the fact that 92% of patients had central obesity according to IDF criteria. Therefore high prevalence of MetS in type 2 diabetics seems to be a universal phenomenon.

We have not found a significant correlation between insulin resistance and clinical parameters of metabolic syndrome like waist circumference, BMI, hypertension, serum triglycerides and HDL cholesterol. Another regional study earlier, also suggested that correlation between insulin resistance and clinical parameters of metabolic syndrome is lost when patients develop diabetes.[20] When this correlation was studied in men and women separately in the studied sample, the pattern of association remained same in men, but in women waist circumference, BMI and metabolic syndrome did not have statistically significant association, whereas triglycerides, FPG, and HbA1c showed a positive association. Patients, who were not using metformin, had higher mean insulin resistance and HOMA-IR as compared to those who were using metformin. None of the two groups showed any significant correlation with clinical parameters of metabolic syndrome when compared separately.

We have also noticed that type 2 diabetic patients who had very high insulin resistance, i.e., HOMA-IR value in the fourth quartile were more likely to have MetS. Out of 39 patients belonging to the 4th quartile of HOMA-IR, i.e., the most insulin resistant people, 79% patients had MetS according to IDF criteria, and 21% patients did not have MetS.

In individuals with diabetes, the coexistence of other metabolic syndrome factors denotes a higher risk for future development of atherosclerotic cardiovascular disease.[21] The predominant underlying risk factors for the syndrome seem to be abdominal obesity[22] and insulin resistance[23,24], supported by our study as well. Other associated conditions can be physical inactivity, aging, hormonal imbalance, and an atherogenic diet (e.g., diet rich in saturated fat and cholesterol).

The aim of clinical management in individuals with the MetS is to reduce risk for clinical atherosclerotic cardiovascular disease (ASCVD). Even in people with the metabolic syndrome, first-line therapy is directed toward the major risk factors: LDL-Cholesterol above goal, hypertension, and diabetes. Prevention of type 2 diabetes mellitus is another goal when it is not present in a person with the metabolic syndrome. For individuals with established diabetes, risk factor management must be intensified to diminish their higher risk for ASCVD. The prime emphasis in the management of the metabolic syndrome is to modify underlying risk factors (obesity, physical inactivity, and atherogenic diet) through lifestyle changes. If absolute risk is high enough, consideration can be given to incorporating drug therapy to the regimen. The priority of drug therapy is elevations of LDL-C, hypertension and hyperglycaemia.

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