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Original Article

Risk factors of diabetes in North Indians with metabolic syndrome

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ABSTRACT

Aim: Metabolic syndrome progresses to diabetes and determinants of this progression like hyperinsulinemia, hypertriglyceridemia and genetic factors have been speculative. The present study was aimed at quantifying the insulin resistance and influence of family history of diabetes in subjects with metabolic syndrome developing prediabetes and diabetes.

Methods: Consecutive subjects attending the endocrine clinic were evaluated for metabolic syndrome as per definition of International Diabetes Federation, 2005. The family history of diabetes in their first degree relatives was ascertained and Homeostasis model assessment of Insulin resistance (HOMA-IR), Homeostasis model assessment for beta cell function (HOMA-B) and Quantitative insulin sensitivity check index (QUICKI) were calculated in 163 subjects enrolled.

Results: HOMA-IR was higher ($p < 0.05$) but HOMA-B and QUICKI were lower ($p < 0.0001$) in subjects with metabolic syndrome + prediabetes or diabetes compared to metabolic syndrome with normal glucose tolerance. HOMA-B was lower and prevalence of prediabetes and diabetes was higher in metabolic syndrome subjects with family history of diabetes than in those without such family history ($p < 0.05$).

Conclusions: subjects with metabolic syndrome having prediabetes and diabetes had more severe insulin resistance than those with metabolic syndrome only. Beta cell dysfunction was remarkable and prevalence of prediabetes was high in metabolic syndrome subjects with family history of diabetes. Both the severity of the insulin resistance and family history of diabetes are therefore proposed to be determinants of diminished Beta cell function leading to diabetes in metabolic syndrome.

1. Introduction

Various studies have shown that insulin resistance (IR) and metabolic syndrome (MetS) exist in most of the patients with diabetes before its onset [1]. The prevalence of MetS was 26% in urban Indian population [2], 87% in the young Indian obese [3] and 77% in Indian immigrants [4]. It was reported as 86.6% after age adjusted in Southwest American Indians of all ages in USA with type 2 diabetes [5]. The Framingham heart study had shown that subjects with MetS had five times increased risk of new onset of diabetes both in men and women [6]. Predictors for conversion of MetS to diabetes have been speculative. Severity of insulin resistance (IR) or hyperinsulinemia, other parameters of MetS and the genetic defects have been proposed to be predictors [1]. The objective of our study was to quantify the IR in subjects with MetS who developed prediabetes, diabetes or had family history (FH) of diabetes.

2. Patients and methods

The study was approved by the institutional ethics committee. Subjects with age >20 years attending the endocrine out-patient clinic of the university hospital were consecutively enrolled and written consent was obtained. All the subjects were screened for MetS as per the criteria of International Diabetes Federation (IDF 2005) [1] for South Asian Indian ethnicity.

A detailed clinical data of the patients were noted on a preset proforma. Waist circumference (WC) was measured immediately above iliac crest in the standing position at the end of a gentle expiration. Mean of three readings for body mass index (BMI), WC

Abbreviations: IR, insulin resistance; MetS, metabolic syndrome; FH, family history; BCF, beta cell function; IS, insulin sensitivity; HOMA-IR, homeostasis model assessment for insulin resistance; HOMA-B, homeostasis model assessment for beta cell function; QUICKI (HOMA-S), qunatitative insulin sensitivity check index/ homeostasis model assessment for insulin sensitivity; BMI, body mass index; WC, waist circumference; OGTT, oral glucose tolerance test; IDF, International Diabetes Federation; NGT, normal glucose tolerant; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

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and two blood pressure readings taken 5 min apart in supine position was noted. Smoking, alcohol and tobacco consumption, exercise, hypothyroidism, liver and kidney dysfunction, insulin therapy, drugs other than oral hypoglycemic agents that alter insulin sensitivity (IS) and beta cell function (BCF) were kept in exclusion criteria. Glucose tolerance status was assessed as per the World Health Organization (WHO, 1999) criteria.

Patients attending endocrine unit for overweight, obesity, and type 2 diabetes were screened out for presence of metabolic syndrome. Of the 390 participants 164 did not fulfill the IDF MetS criteria. Sixty three male MetS participants had one of the exclusion criteria of the study. The remaining 163 subjects were grouped as (A) having FH and group (B) with no FH of diabetes in their first degree relative.

Blood samples were collected in fasting and 2 h after glucose challenge for estimation of glucose and lipids using respective kits (ERBA Diagnostics, Mannheim, Germany). Insulin was measured by sandwich ELISA method (DRG International Inc., USA) that has no cross reactivity with similar protein. Intra- and inter-assay coefficient of variance (C.V.) was 2.1–7.2% and 6.3–8.8% respectively.

2.1. Homeostasis model assessment of insulin resistance (HOMA-IR)

We estimated insulin resistance (IR) using the HOMA of insulin resistance (HOMA-IR) index, which is defined as the product of fasting glucose (mmol/L) and fasting insulin (μU/mL) divided by 22.5. Low HOMA-IR values indicate high insulin sensitivity, whereas high HOMA-IR values indicate low insulin sensitivity (insulin resistance) [7–9]. Taking into account of MetS components in an adult Spanish population the threshold value of HOMA-IR dropped from 3.46 using 90th percentile criteria to 2.05. In non-diabetic women of the same study, a significant non-linear effect of age on the accuracy of HOMA-IR was detected. In non-diabetic men, the cut-off values were 1.85 [8].

$$\text{HOMA-IR} = \frac{\text{FPG (mmol/1)} \times \text{Fasting plasma insulin (FPI) (}\mu\text{U/ml)}}{22.5}$$

2.2. Homeostasis model assessment of Beta cell function (HOMA-B)

The HOMA of β-cell function (HOMA-B) index, computed as the product of 20 and fasting insulin (μU/mL) levels divided by the value of fasting glucose (mmol/L) concentrations minus 3.5, has been proposed to be a good measure of β-cell function [9,10].

$$\text{MOMA-B} = \frac{20 \times \text{FPI (}\mu\text{U/ml)}}{(\text{FPG (mmol/1)} - 3.5)}$$

2.3. The Quantitative Insulin Sensitivity Check Index (QUICKI)

QUICKI [11] also called as HOMA-Sensitivity (HOMA-S) is based on the logarithmic transformation of fasting glucose and fasting insulin. QUICKI and HOMA-S are highly correlated (R = 0.99) in a database of 204 young and elderly subjects [12].

$$\text{QUICKI} = \frac{1}{(\log \text{insulin in } \mu\text{U/ml} \; + \; \log \text{glycemia in mg/dl})}$$

Statistical analysis: HOMA-IR, HOMA-B and QUICKI (HOMA-S) were calculated [13]. Continuous variables were log transformed if they are not normally distributed. ANOVA or Mann–Whitney U test were used as appropriate to test difference between the variables. Spearmen correlation analysis was performed to test association of the variables with HOMA-B, HOMA-IR. Data was presented as mean (±S.E.) unless otherwise mentioned. $p < 0.05$ was considered to be significant.

3. Results

A total of 163 subjects (male/female N = 69/94) fulfilling IDF MetS criteria were selected following our study protocol. Age of the subjects ranged from 22 to 70 with a mean (±S.D.) of 41.7(±11.7) years. Newly detected type 2 diabetes was found in 6 (8.5%) individuals. Family history of diabetes was noticed in 20.8% (n = 5/16, 5/32), 50% (2/5, 5/9), 36.4% (0/4, 8/18), 50% (0/2, 4/6) and 36.6% (11/42, 15/29) of normal glucose tolerant (NGT), impaired glucose tolerant (IGT), impaired fasting glucose (IFG), IGT-IFG together and diabetes respectively.

Demographic and biochemical characteristics of study participants stratified on the basis of OGTT were also given in Table 1. The mean age of MetS + NGT status was similar to MetS + prediabetes but subjects in the former group were younger than MetS + diabetes group. BMI and WC was similar for all the groups while mean FPG and A1C ($p < 0.0001$), total cholesterol and HOMA-IR ($p < 0.05$) were significantly different among MetS with NGT and MetS with prediabetes. Mean values of SBP, DBP, total cholesterol and TGL

Table 1
Demographic and biochemical characteristics of subjects with MetS.

	Prediabetes[§]	p-value prediabetes vs NGT	NGT	p-value NGT vs diabetes	Diabetes[£]
	N (M/F) = 44 (11/33)		N (M/F) = 48 (16/32)		N (M/F) = 71 (42/29)
Age (years)	35.9(±1.7)[†]	NS	38(±1.8)	<0.0001	47.2(±1.1)[¶]
BMI (kg/m^2)	30.0(±1.0)[†]	NS	29.7(±0.7)	NS	28.6(±0.5)[†]
Systolic B.P. (mmHg)	136.7(±3.0) [†]	NS	130.4(±2.4)	NS	138.8(±2.1)
Diastolic B.P. (mmHg)	88(±1.3)	NS	86.5(±1.2)	NS	91.1(±1.3)
WC (cms)	93.5(±1.2)[†]	NS	94.9(±1.5)	NS	96.5(±1.1)[†]
HbA1c (%)	5.2(±0.1)[¶]	<0.0001	4.0(±0.2)	<0.0001	7.0(±0.3)[¶]
FPG (mmol/L)	5.6(±0.2)[¶]	<0.0001	4.4(±0.2)	<0.0001	8.7(±0.4)[¶]
CHOL (mmol/L)	4.6(±0.1)[¶]	<0.0001	4.0(±0.2)	<0.05	4.6(±0.15)[#]
TGL (mmol/L)	1.7(±0.08)[†]	NS	1.6(±0.1)	< 0.05	2.0(±0.1)[#]
HDL (mmol/L)	1.0(±0.04)[†]	NS	0.9(±0.06)	NS	0.9(±0.03)[†]
INSF (pmol/L)	92.7(±6.1)[†]	NS	88.1(±9.5)	<0.005	117.5(±5.1)[$]
HOMAIR	3.3(±0.2)	< 0.05	2.5(±0.3)	<0.0001	6.5(±0.4)[¶]
QUICKI	0.329(±0.005)[†]	NS	0.3(±0.007)	<0.0001	0.3(±0.002)[¶]
HOMA-B	133.6(±11.8)[†]	NS	172.2(±15.5)	< 0.0001	84.2(±5.7)[¶]

Data are presented as mean (±SE); [¶]$p < 0.0001$; [$]$p < 0.005$; [#]$p < 0.05$; [†]$p$ = Non-significant;
p-value comparisons were given for NGT vs Prediabetes[§], NGT vs diabetes[£];
NGT = normal glucose tolerance; MetS = metabolic syndrome; FH = family history; BMI = body mass index; WC = waist circumference; FPG = fasting plasma glucose; TGL = triglyceride; HDL = high density lipoprotein cholesterol; INSF = fasting insulin.