Risk of Insulin Resistance in Normal Glucose Tolerant Subjects

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Abstract

Introduction : Metabolic syndrome (MS), with its huge baggage of complications, is emerging as a major threat to lead a healthy life, worldwide. Sedentary habits, urbanization, life style modifications, stress and anxiety contribute to its increasing incidence, not to mention diabetes and hypertension. Routine screening for diabetes fails to detect early MS. **Materials and methods:** 55 normal glucose tolerant (NGT) subjects, both males & females were selected for the study. Based on modified National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III criteria (Waist circumference-WC 80 cm FM, 90 cm M), they were grouped into - with and without metabolic syndrome (MS). Fasting blood glucose, total cholesterol, triglycerides, insulin levels and high density lipoprotein were estimated. Insulin resistance (IR) was calculated by HOMAIR formula. **Results :** TGL and insulin levels were elevated and HDL levels were decreased in MS group compared to those without MS & this was statistically significant. Among the 55 NGT subjects, 30 people had MS. The prevalence of MS was 43% and the prevalence of IR among NGT was 31%. **Conclusion:** Metabolic syndrome & IR occur in subjects with normal glucose tolerance also. Hence, screening of vulnerable people for MS should be done to detect potential diabetes mellitus (DM) & coronary artery disease (CAD) in early stages.

Keywords: Insulin resistance, Metabolic Syndrome, Diabetes mellitus

Introduction

In 1988 Reaven identified a syndrome X which composed of hyperglycaemia, insulin resistance, hypertension, raised VLDL-triglycerides with low HDL-cholesterol. Obesity was omitted, which was later found to be the most important component. Subsequently, numerous names were proposed and Metabolic Syndrome was finalized. For more than 80 years, the correlation of these risk factors is known.

In recent years, obesity prevalence has been increasing alarmingly and is linked with hypertension, type 2 DM and CAD.^[1,2] MS is the term used for the coexistence of these three diseases.^[3,4] Insulin resistance, an important feature of this disease, has been defined as a condition which requires more insulin than normal to attain its physiological effects. It can be due to insulin signaling cascade defects. Signaling network composed of numerous molecules is stimulated by insulin, which

initiates the activation of tyrosine kinase insulin receptor and insulin receptor substrate (IRS) proteins' phosphorylation.^[5] Serine/threonine kinases are activated by IRS proteins and PI3K signaling axis which in turn regulates the physiological effects of insulin, this pathway is impaired through protein level alterations and signaling molecules activities, transcription factors and enzymes in insulin resistance due to obesity.^[6]

A major public-health challenge worldwide is metabolic syndrome. It is a cluster of metabolic disorders: dyslipidaemia, hyperglycaemia, visceral obesity and hypertension. It is a deadly quartet which promotes

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atherosclerosis and increases the risk of CAD events. The heart of MS may be IR. There has been increasing focus on this group of related risk factors. The syndrome was first defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III report in 2001.^[7]

Long before the deterioration of glucose tolerance occurs, insulin resistance can be determined. It is influenced by obesity, even in the absence of diabetes. The presence of MS predicts CAD risk in nondiabetics and type 2 DM as well.^[8-10] Hence this study was undertaken. In our study we used HOMA IR to assess insulin resistance. β cell function and insulin resistance are assessed by HOMA using fasting blood glucose & insulin concentration.

Materials And Methods

This study was conducted from February 2018 to July 2018 over a period of 6 months. Ethical clearance was taken from the institute. Subjects referred for oral glucose tolerance test to the central biochemistry lab were screened and among them 55 normal glucose tolerant subjects were taken for the study. Subjects were in the age group of 25 – 60 years and both the sexes were included in the study. The data on family history of DM, smoking habits, alcohol consumption, hypertension & treatment history were gathered through a standard questionnaire. Informed written consent was taken from the subjects.

Using modified NCEP ATP III diagnostic Criteria , metabolic syndrome group included subjects having ≥ 3 parameters, which include fasting glucose > 100 mg/dl , TGL > 150 mg/dl, HDL < 40 mg/dl (Male) or < 50 mg/dl(Female), hypertension $\geq 130/85$ mm Hg/ on medication , waist circumference > 90 cm & > 80 cm in males and females respectively. Anthropometric measures like height (cm), Waist circumference (cm) were measured by using the standard methods.^[11]

Sample Collection and Analysis:

Blood samples collected after 12 hours of fasting in evacuated tubes for estimation of fasting blood glucose , lipid profile (TC, TGL, HDL) & Insulin. Samples were centrifuged. Plasma and serum were stored at -20°C until analysis and they were analysed as a batch. Glucose and lipid profile were analysed in Transasia – Erba EM200 automated systems using commercial kits. Serum Insulin was estimated in automated

chemiluminescence system using commercial kits by Bayer diagnostics (USA). For adequate quality control normal and abnormal reference controls & calibrators were run before analyzing each batch.

Measure of IR by HOMA

The HOMA IR to measure IR, is calculated by measuring fasting glucose and fasting insulin levels {product of insulin (mu/L) & glucose concentration (mg/dl) } which is divided by a constant 405.^[12] The cut off value used was 3.00 which is 75th percentile of our study population .

Results:

The results were shown as mean. p value was used to compare the groups , p value < 0.05 was significant . SPSS software was used for data analysis. Table 1 shows that there is a significant statistical difference between subjects with & without MS with reference to WC (p 0.001), SBP (p0.001), TGL (0.002), HDL (0.001), insulin (0.018) and HOMA (0.009). Table: 2 Represents the prevalence of Insulin resistance in total NGT subjects, in subjects with MS & without MS.

Table 1: Mean(SD) of the biochemical and biological parameters between subjects with MS & without MS

Sub group	With MS n=30	Without MS n=25	P value
FG (mg/dl)	94.8	90.2	0.54
Insulin (mu/L)	14.6	9.7	0.018
HOMA	3.3	2.1	0.009
Waist (cm)	98.2	82.3	0.001
SBP (mmHg)	140.2	130.4	0.001
DBP (mmHg)	88.2	80.4	0.002
TC (mg/dl)	224.7	185.6	0.001
TGL (mg/dl)	140.2	109.1	0.002
HDL (mg/dl)	36.4	46.2	0.001

n = no of subjects, p < 0.05 significant.

Table 2: Insulin resistance in NGT subjects with MS and without MS

NGT subjects	With IR n (%)	Without IR n (%)	Total n (%)
With MS	13 (43%)	22 (57%)	35(100%)
Without MS	4(16%)	21 (84%)	25(100%)
Total	17 (31%)	38 (69%)	55(100%)

Discussion

Due to clustering of metabolic and atherosclerotic risk factors, MS is a strong determinant of type 2 DM and CAD.^[13] Apparently, a substantial number of healthy individuals suffer from this so called metabolic syndrome. Obesity and IR are being considered central to its pathophysiology

In consistent with this, the prevalence of MS in NGT subjects, in our study, shows about 54% (out of 55 NGT subjects 30 subjects were having MS). Out of 55 NGT, 17 were having insulin resistance, as assessed by HOMA, which means a prevalence of 31%. The occurrence of IR in subjects with MS was 43%, which is quite alarming, and the prevalence of IR in subjects without MS was 16%. Hence our study indicates that more than a quarter of people with normal glucose tolerance suffer from insulin resistance & will be prone for CAD & DM in future.

In our study we observed that subjects with elevated levels of HOMA IR, insulin and waist circumference had MS than those without MS. Waist circumference shows a higher statistical significance. This implies that the major risk factor for MS is obesity. So simply by measuring the waist circumference in every day clinical practice, precautions can be taken to keep MS and thus DM, CAD etc, at bay.

As mentioned earlier, even in the absence of diabetes, insulin resistance can be determined long before the deterioration of glucose tolerance occurs. It is highly influenced by obesity. There is inadequate esterification of free fatty acids (FFA) in the adipocytes due to insulin resistance. Hence, FFA enter the circulation and subsequently the liver leading to increased synthesis of TGL.^[14] CETP (Cholesterol Ester Transfer Protein) mediates the synthesis of TGL rich HDL, in the presence of raised TGL. This is more prone for catabolism by the kidney. An increase in fatty acid metabolites such as DAG (Di Acyl Glycerol), fatty acyl CoA occurs due to increasing delivery of FFA to muscle and decreased intracellular metabolism. Serine – Threonine kinase cascade is activated by these metabolites thus leading to phosphorylation of insulin receptor substrates IRS – 1 & IRS – 2. Ability of IRS to activate phosphatidylinositol (PI3) kinase decreases. Consequently, hyperglycemia occurs over a period of time due to diminishing of events downstream of insulin receptor signaling and glucose transport activity.^[15]

Thus the major beginning events leading to diabetes at a later age are insulin resistance and obesity. Abdominal obesity is a clinical marker for insulin resistance. Vulnerable people should be screened for MS & IR to detect DM at a predisease stage, so that onset of diabetes & its complications can be delayed by early interventions like life style modifications and pharmacological treatment.

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