DETERMINATION OF INSULIN RESISTANCE AND BETA CELL FUNCTION IN HEALTHY OBESE AND NON-OBESE INDIVIDUALS

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ABSTRACT

Background: Insulin resistance is the basic metabolic disorder associated with obesity. Beta cell function is closely related with insulin resistance. Little is known about insulin resistance and beta cell function in healthy obese and non-obese local population.

Objective: To determine insulin resistance and beta cell function in healthy obese and nonobese individuals of the local population.

Study Design: Case control study

Place andDuration of Study: AFIP Rawalpindi in collaboration with Department of Medicine Military Hospital (MH) Rawalpindi, from Aug 2008 to Mar 2009.

Methods: Eighty obese (n=40) and non-obese (n=40) subjects were selected by non-probability convenience sampling. Plasma insulin, glucose, and serum total cholesterol were estimated in fasting state. Insulin resistance was calculated by HOMA-IR and beta cell function by HOMA-β equation.

Results: Significant differences were observed between obese and non-obese individuals regarding insulin resistance, beta cell function, and BMI and serum total cholesterol. Mean insulin resistance in obese group was found to be 11.1 ± 5.1(range 7.0-16.2) and in non-obese group it was 0.9± 0.4 (range 0.5-1.3). This difference was highly significant (p=0.001). There was a highly significant difference between the two groups in term of beta cell function with mean rank 60.1 for obese group and 20.9 non obese groups (Asym sig. 2 tailed 0.000). Also the correlation (r = 0.064) between insulin resistance and beta cell function in obese group is highly significant (p = 0.000). Mean serum leptin levels were lower (6.3 ng/ml) in non-obese, and high (57.2 ng/ml) in the obese group.

Conclusions: Insulin resistance is found higher in obese individuals. Beta cell function is significantly different between obese and non obese groups.

Keywords: Beta cell function,BMI,Insulin resistance, Non-Obese, Obese.

INTRODUCTION

At the moment we are faced with the pandemics of Type 2 Diabetes mellitus (T2DM) and cardio vascular diseases (CVD)[1]. Sedentary lifestyle along with modern fast foods, have resulted in a global epidemic of diabetes mellitus[2]. It is predicted that it will rise from the current estimate of 190 million to 439 million in 2030. There will be a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries[2]. There has been a dramatic increase in the prevalence of diabetes in people of South Asian origin, which is observed throughout the world[3]. People of Indian, Sri Lankan, Pakistani and Bangladeshi origin carry a high risk of diabetes and cardiovascular disease[4]. To prevent the development of diabetes, individuals must be identified at an early stage of risk and managed with preventive measures such as lifestyle advice and pharmacological therapy. A key indicator of risk is insulin resistance (IR) that is the basic metabolic disorder associated with obesity. Evidence has been accumulating that insulin sensitivity and β-cell function are inextricably linked and should be measured simultaneously

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because their interplay is fundamental to glucose tolerance[5]. In the presence of advancing insulin resistance and inadequate beta-cell secretion, intra-abdominal fat accumulates, further aggravating insulin resistance[6]. Eventually the beta cell is overwhelmed and impaired glucose tolerance develops[6]. Leptin is an adipocyte derived hormone. It has an important role in weight regulation[7]. Leptin levels correlate with insulin levels; both are high in insulin resistance. Little is known about state of insulin resistance and beta cell function in healthy obese and nonobese in the local population. This study was designed to determine the insulin resistance and beta cell function in healthy obese and non-obese individuals included in the study.

METHODS

This case control study was conducted in AFIP Rawalpindi, from Aug 2008 to Mar 2009. A total of 80 obese and non-obese subjects were selected by non-probability convenience sampling. They were divided into 2 groups on the basis of BMI:

Obese: 27.5-40 kg/m^2, Non-obese:18.5-23.0 kg/m^2

These BMI values were used under the guidelines for Asian populations issued in the year 2000 by the International Association for the study of obesity and the International Obesity Task Force of World Health Organization, Western Pacific Region, Australia[8]. Only healthy obese individuals (not suffering from T2DM or hypertension/CAD) were included in this study, while overweight subjects (BMI 23.1-27.4 kg/m^2) were excluded.

After an overnight fast, blood samples were obtained in the morning between 0800–0900 hours. The plasma for glucose and insulin, serum for total cholesterol and leptin were separated 20 minutes after collection by centrifugation at a speed of 2000-3000 G for 10 minutes. Fasting plasma glucose, 1 hour; insulin within less than 30 minutes and serum total cholesterol concentrations were measured on the same day.

Fasting plasma glucose level was measured on Selectra-2 (automated chemistry analyzer by Merck), using a GOD-PAP method. Plasma insulin was analyzed, on an automated hormone analyzer Access 2 Beckman Coulter, using Chemiluminescence method. Serum total cholesterol levels were measured on Selectra-2 by CHOD-PAP method. Serum leptin samples were aliquoted, frozen at -20°C, for analysis later on. The quantitative determination of serum leptin was conducted by Enzyme-Linked Immunosorbent assay (ELISA) technique, using commercially available reagent kit, DRG® Leptin (Sandwich) ELISA (EIA-2395) by RUO, Germany.

Insulin resistance was calculated by Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) equation. This mathematical model is a commonly used method to assess insulin resistance and ß-cell function and requires only fasting glucose and insulin levels. Mathews *et al* described the original HOMA model in 1985 with a formula for approximate estimation[9]:

HOMA-IR = [Plasma glucose fasting (mmol/L) x Plasma insulin fasting (m IU/L)] / 22.5

There is no agreed upon cutoff value for insulin resistance. A value > 2.5 was considered as evidence of insulin resistance. Homeostasis Model Assessment of beta cell function (HOMA-β) was also calculated by following formula:

HOMA-β = 20 x fasting insulin / fasting glucose - 3.5 = %

All statistical analysis was performed using the statistical package for the social sciences (SPSS, Version15). For each variable, mean, standard deviation, and ranges were calculated. *p* values for comparison of serum leptin level and BMI; similarly insulin resistance and BMI were determined in healthy obese and non-obese subjects.

RESULTS

Comparison of baseline characteristics i.e. age, height, weight, BMI, fasting plasma glucose,

fasting plasma insulin, insulin resistance and serum leptin levels of obese and nonobese groups, is given in the Table-1.

There were 33 (66%) females in obese group and 32 (64%) females in non-obese group (p=0.834, Fig-1). BMI had a strong relation to insulin resistance (r=0. 37, p value =0. 001) in the leptin levels were lower (6.3 ng/ml) in non-obese, and high (57.2 ng/ml) in the obese group.

DISCUSSION

The South Asians are at a greater risk of developing T2DM and CVD even at lower BMI[3]. The number of T2DM and CVD cases are on an

Table-1: Baseline characteristics of obese and non-obese subjects.

Parameters	Obese (n=40) Mean (SD)	Non obese/controls (n=50) Mean (SD)	p-values
Age (years)	38.8 (8.2)	33.5(7.7)	0.001
Height (cms)	163(6.8)	167(7.0)	0.004
Weight (kg)	83.3(7.4)	59.6(7.0)	0.001
BMI (kg/m2)	31.7(3.0)	21.2 (1.5)	0.001
FP Glucose (mmol/l)	6.2(1.3)	5.0(0.5)	0.001
FP Insulin(IU/ml)	40.1(14.7)	3.4(1.8)	0.001
Insulin resistance (HOMA-IR)	11.2(5.1)	0.8(0.5)	0.001
S leptin (ng/ml)	57.2(24.6)	6.3(3.1)	0.001
T. Cholesterol (mg/dl)	239(16.0)	145(27.0)	0.001
Beta cell function (HOMA-β = %)	Median= 301.4	Median=41.6	Mann-Whitney Asym. (2tailed) 0.000

obese group. Mean insulin resistance in obese group was found to be 11.1 ± 5.1(range 7.0-16.2) and in non-obese group was 0.9 ± 0.4 (range 0.5-1.3). This difference was highly significant (p=0.001). Mean insulin resistance in obese group was 9.6 in males and 12.6 in females; Beta cell function was determined by HOMA-β. Median of Beta cell function in obese group was found to be 301.4% and in the non - obese group it was 41.6%. There was a highly significant difference between the two groups in term of beta cell function with mean rank 60.1 for obese group and 20.9 for non-obese group (Asym. sig. 2 tailed 0.000). Also the correlation (r = 0.064) between insulin resistance and beta cell function in obese group is highly significant (p = 0.000). In a non - obese group, mean serum total cholesterol was found lower 145 mg/dl (range 44-199 mg/dl) while in obese group it was higher 239 mg/dl (range 207-271 mg/dl). We also measured serum leptin levels which are indicative of adiposity. Mean serum increase in our setup. The clustering of central obesity, dyslipidaemia, hypertension, and hyperglycemia known as metabolic syndrome or insulin resistance syndrome has been associated with a 2-3 fold increase in T2DM and CVD[8]. It is recognized that the features of the insulin resistance syndrome can be present 10 years preceding T2DM and CVD[1]. In a study in a normal urban population of Karachi, insulin resistance defined by 75th percentile of HOMA-IR was 1.94[11]. In our study mean insulin resistance in non-obese (normal population; BMI 23-25 kg/m2) group was 0.9± 0.4 and in obese group (BMI > 27.5 kg/m^2) was found to be 11.1 ± 5.1, revealing a highly significant (p=0.001) difference.

In present study, insulin resistance was calculated using HOMA-IR equation developed by Mathews et al[8]. HOMA-IR is commonly used for population based studies because of its easy manageability. This model of estimation by

Mathews et. al, has been found to correlate well with the insulin secretion and insulin sensitivity indices of clamp studies[4]. There are variations in the cutoff values of HOMA for insulin resistance due to the lack of established standards for population based studies as well as variability of insulin assay procedures[12,13]. We used a cut off value for insulin resistance index as > 2.5 in obese group using HOMA-IR, while in various other studies the range varies between 1.73-2.5[4,12,14]. The incidence of insulin resistance was significantly higher in the obese group than in the normal (non-obese) group as reported by Oneshi et al[15]. They found index of insulin resistance > 2.0 in the obese group having insulin resistance; while in present study, we found it to be >2.5 in the obese group. In another local study[13] carried out on obese subjects who also had type 2 diabetes, mean HOMA-IR was found to be 4.1.

Some studies have shown that obesity has a central role in the development of insulin resistance[16-18]. The present study showed that obesity (BMI) had a strong relation to insulin resistance (r=0. 37, *p*-value =0.001), which is in accordance with above mentioned studies. Other parameters related to obesity like serum leptin were elevated in the obese group (Table-2). Serum total cholesterol is an important parameter for assessing insulin resistance syndrome[19]. It was found at higher range in the obese group according to National Cholesterol Education Program Adult Treatment Panel-III for definition of insulin resistance defined criteria[18]. It is important to note that the selected subjects in the present study were healthy, not suffering from diabetes mellitus, cardiovascular disease, and depression but still had high insulin resistance, which appears to be related to obesity.

Wallace et alhas suggested that insulin sensitivity and β-cell function are inextricably linked[4]; they should be measured simultaneously because their interplay is fundamental to glucose tolerance. Our observation is also same. We found that the subjects in obese group had hyper-insulinemia (fasting plasma insulin-FPI 15.1 ± 7.1 mIU/ml), and a highly significant difference was observed between the two groups in term of beta cell function (Asym. sig. 2 tailed, 0.000). Also the

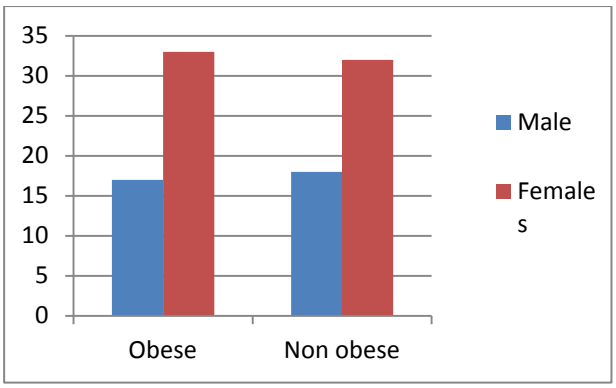

Figure-1: Male to female ratio in obese and non obese subjects.

correlation (r=0.064) between insulin resistance and beta cell function in obese group is highly significant (*p*=0.000). In this study, although fasting plasma glucose was within the normal range (5.8±1.1mmol/l), but it was significantly higher than the non-obese subjects (4.9 ± 0.9 mmol/l). Indeed, fasting hyper-insulinemia, known to reflect decreased insulin sensitivity, and decreased insulin secretion together constitute the strongest independent predictor of type 2 diabetes[20]. Other risk factors like hyper cholesterolemia and hyper leptinemia also accompanied hyper-insulinemia in obese group. Weight reduction is important in this regard. This may improve insulin resistance and beta cell function, and prevent development of type 2 diabetes.

CONCLUSION

Insulin resistance and beta cell function are significantly correlated in obese individuals. Insulin resistance is found higher in obese individuals. Beta cell function is significantly different between obese and non obese groups.

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