INSULIN RESISTANCE AND INSULIN SECRETION AT VARYING LEVELS OF GLUCOSE

Asif Ali, Waqar Azim*

Combined Military Hospital Rahim Yar Khan, *Army Medical College Rawalpindi

ABSTRACT

Objective: To compare the insulin resistance and insulin secretion among the subjects with impaired fasting glucose, normal glucose tolerance, impaired glucose tolerance (IGT), and type 2 diabetes mellitus by Homeostasis model assessment (HOMA)

Study Design: Comparative cross-sectional study

Place and Duration of Study: This study carried out from January 2006 to October 2006, at the department of pathology PNS Shifa Karachi.

Material and Methods: One hundred individuals (male 69 and female 31) were subjected to oral glucose tolerance test (OGTT). These individuals were classified into four groups, based on the results of 75-g OGTT. 1) Normal glucose tolerance (NGT). 2) Impaired fasting glucose (IFG). 3) Impaired glucose tolerance (IGT). 4) Diabetes mellitus (DM). We used the HOMA for the calculation of insulin resistance (IR) and insulin secretion (HOMA-βcell).

Results: The mean HOMA-IR was highest in IFG and DM. No significant difference in HOMA-IR was noted between IFG vs. IGT and DM (4.18±2.32, $p > 0.05$). The IGT group had significantly low HOMA-IR as compared to DM. IGT subjects had significantly high mean HOMA-β cell function (171.1 ± 117 $p<0.003$) from DM group. NGT group subjects had no significant difference in HOMA-β cell function as compared to IFG and IGT (145.58±130.0, $p > 0.05$). IFG group subjects had no significant difference in HOMA-β cell function as compared to IGT and DM (119.8±53.9 $p>0.05$).

Conclusion: The insulin resistance and insulin secretion are different at the different levels of glucose tolerance. IFG group has high insulin resistance and low insulin secretion, which is comparable to DM, while IGT group has low insulin resistance and high insulin secretion as compared to DM.

Keywords: HOMA-IR, HOMA-β cell function, oral glucose tolerance test, diabetes mellitus.

INTRODUCTION

The insulin resistance (IR) has been recognized since the 1930s. However, it was the development of sensitive assays for insulin and quantitative methods for estimating insulin action that made it possible to define the scope of the problem and its clinical implications[1]. Most individuals appear to develop IR when environmental factors interact with specific genetic predispositions that confer susceptibility[2]. The key environmental factors responsible for the development of IR are abnormalities of nutritional intake[3], leading to fetal malnutrition and/or adult obesity and decreased physical activity. The genetic factors have yet to be clarified. Changing lifestyles throughout the world have resulted in as much as 16 to 25 percent of some adult populations having IR, and an associated cluster of metabolic and cardiovascular risk factor abnormalities that have been termed "the metabolic syndrome"[4]. Type-2 diabetes is characterized by both decreased insulin secretion and insulin sensitivity, but the degree of contribution of these two factors in the etiology varies[5]. Impaired Glucose Tolerance (IGT), as defined by World Health Organization[6] (WHO) and American Diabetic Association (ADA)[7], is an established risk category for diabetes. Further more IGT is associated with an increase in cardiovascular-related mortality and all cause mortality. Impaired fasting glucose (IFG) is also a risk category for diabetes[8,9]. Insulin resistance and insulin secretion concur towards diabetes and glucose intolerance, but it is unclear that which defects arises first and which relates to either IFG or IGT, which reflect different alterations in glucose homeostasis[10]. Where as some reports show that subjects with IFG have hyperinsulinemia and/or worsening of insulin

Correspondence: Maj Asif Ali, Pathologist, Combined Military Hospital Rahim Yar Khan

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resistance, those with IGT have defective secretion in response to glucose loading[11]. Insulin resistance is also associated with other clinical conditions, which include Polycystic Cystic Ovarian Syndrome (PCOS), Non-Alcoholic Steato-Hepatitis (NASH), metabolic syndrome, and the much rare condition of lipodystrophy. Differences in insulin resistance and secretion may be of importance for planning an intervention program with the out come of STOP-NIDDM study using acarbose[12], and Diabetes Prevention Program using metformin[13], a differential preventive strategy may be considered for subtypes of preclinical abnormalities in glucose homeostasis. The oral glucose tolerance test (OGTT) is widely used procedure that was originally developed to classify carbohydrate tolerance[14]. The ability to dispose of carbohydrate depends on the insulin sensitivity and pancreatic Beta (β)-cell function. To estimate these two factors simultaneously is important in the pathogenesis of type 2 diabetes, because the estimate of β-cell function is influenced by the degree of IR[15]. Homeostatic Model Assessment (HOMA) of β-cell function and IR were first described in 1985. The technique is a method for assessing β-cell function and IR from basal glucose and insulin or C-peptide concentrations[16]. There is good correlation between estimates of IR derived from HOMA and from the euglycemic clamp between HOMA and the minimal model. Estimates of β-cell function using HOMA have been shown to correlate well with estimates using continuous infusion glucose model assessment (CIGMA) (another paradigm model), hyperglycemic clamps, and the acute insulin response from the intravenous glucose tolerance test (IVGTT) [15].

The objective of this study was to compare the insulin sensitivity and insulin secretion among the subjects with normal glucose tolerance, impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes mellitus by HOMA-IR and HOMA-β cell function.

MATERIALS AND METHODS

One hundred (male 69 and female 31) healthy nondiabetic subjects of above 40 years of age were selected by non probability convenient sampling. Subjects suffering form any chronic or acute disease, hospitalized or pregnant ladies and taking medicines like glucocorticoids, thiazides, β-adrenergic, dilantin, pentamidine drugs, were excluded form study. An OGTT was performed after 9-12 hour fasting. These subjects were classified into four groups, based on the results of 75-g OGTT. 1) Normal glucose tolerance (NGT) defined as fasting plasma glucose (FPG) levels <5.6 mmol/L and 2-hour plasma glucose (2-h PG) level <7.8 mmol/L (n=47). 2) Impaired fasting glucose (IFG) defined as FPG between 5.6-6.9 mmol/L and 2-h PG <7.8 mmol/L (n=6). 3) Impaired glucose tolerance (IGT) defined as FPG <5.6 mmol/L and 2-h PG between 7.8-11mmol/L (n=17). 4) Diabetes mellitus (DM) defined as FPG >7.0 mmol/L or 2-h PG >11.1 mmol/L. The BMI was calculated as body weight / height2 and expressed in kg/m2. The waist circumference was measured at the smallest circumference between the rib cage and the iliac crest, with the subject standing upright. Plasma Glucose was analyzed by glucose oxidase colorimetric enzymatic method using "Merck Markers" reagent kit. The specimens were analyzed on a random access chemistry analyzer (Selectra-2). Insulin estimation was carried out using the technique of chemiluminescence on immulite 1000 immunoassay analyzer.

The indices of insulin resistance (HOMA-IR and HOMA-β cell) were calculated from fasting plasma glucose and insulin concentrations as follows: HOMA-IR = (FPG mmol/L X INS μU/mL)/22.5, HOMA- β cell = 20 X INS μU/mL / (FPG mmol/L -3.5).

All data collected for different demographic and biochemical parameters of subjects with normal glucose tolerance, impaired fasting glucose, impaired glucose tolerance and diabetes mellitus were added to SPSS version 11.0. Descriptive statistics were calculated in terms of means and standard deviation 95% confidence intervals. Analysis of variance (ANOVA) was applied as statistical test to compare these variables among NGT, IFG, IGT, and DM groups. Probability value at $p<0.05$ was selected as level of significance.

RESULTS

The OGTT was performed in 100 patients, 47% were diagnosed as having normal glucose tolerance, 6% subjects were diagnosed as IFG, 17% were diagnosed as IGT and 30% were diagnosed as a case of DM as per classification of WHO and ADA. Descriptive statistics of clinical and biochemical parameters are shown in table-1. Except age, the BMI, waist circumference, fasting insulin, HOMA - IR and HOMA - β cell function were statistically different among groups, one way ANOVA, LSD post-hoc multiple comparison was used to know the significance between different groups (Table-2).

DM vs. NGT: The NGT group had significantly low BMI, waist circumference, fasting insulin levels, HOMA IR ($p<0.000$) and significantly high HOMA β cell function ($p<0.004$) as compared to DM (Table –1, 2).

IFG vs. NGT: The IFG group subjects had significantly high BMI, waist circumference, fasting insulin levels and HOMA IR ($p<0.003$) as compared to NGT, while no significant difference noted in HOMA β Cell function ($p>0.05$) noted between IFG and NGT (Table –1, 2).

IFG vs. DM: No any significant difference was noted in BMI, waist circumference, fasting insulin levels, HOMA IR ($p>0.05$) and HOMA β-cell function ($p>0.05$) between IFG and DM (Table –1, 2).

IGT vs. NGT: the IGT group subjects had significantly high BMI, waist circumference, fasting insulin levels and HOMA IR ($p<0.04$) as compared to NGT, while no significant difference noted in HOMA β Cell function ($p>0.05$) between IGT and NGT (Table –1, 2).

IGT vs. DM: The IGT group subjects had no significant difference in BMI, fasting insulin levels, while there was a singnificantly low HOMA IR ($p<0.016$) and significantly high HOMA β cell function ($p<0.003$) noted in IGT as compared to DM (Table –1, 2).

IFG vs IGT: No significant difference in BMI, waist circumference, fasting insulin levels, HOMA IR, HOMA β Cell function ($p>0.05$) was noted between IFG and IGT (Table –1, 2).

DISCUSSION

The results of this study indicate that IFG and IGT are two different states of glucose metabolism, they are comparable to each other but when they are compared to DM, the IGT group proved to be less insulin resistant and have more insulin secretion, while IFG subjects has comparable insulin resistance and insulin secretion to DM.

In this study, we calculated indices of insulin resistance/sensitivity (HOMA–IR) and

Table-1: Clinical and Laboratory Characteristics of Subjects with Varying Degree of Glucose Tolerance.

	NGT, n=47	IFG, n=6	IGT, N=17	DM, N=30
Age (Yr)	48.0 ± 8.6	56.8 ± 15.3	49.05 ± 7.46	48.60 ± 7.97
BMI (KG/M²)	25.15 ± 3.70	27.58 ± 2.48	30.44 ± 6.08	29.28 ± 5.09
Waist Circumference (CM)	91.80 ±10.17	96.91 ± 8.68	105.7 ± 11.25	98.92 ± 11.46
Fasting Insulin (µU/ML)	7.73 ± 3.74	14.33 ± 9.53	12.20 ± 6.31	12.07 ± 9.21
HOMA-IR	1.64 ± 0.81	4.18 ± 2.3	2.76 ± 1.39	4.18 ± 2.99
HOMA B Cell	145.5 ±130.0	119.8 ± 53.94	171.1 ± 117.0	74.45±13.59

Table-2: Comparison of Clinical and Laboratory Characteristics of Subjects with Varying Degree of Glucose Tolerance

	DM vs. NGT	IFG vs. NGT	IFG vs. DM	IGT vs. NGT	IGT vs. DM	IFG vs. IGT
BMI (kg/m²)	p<0.000	p>0.05	p>0.05	P<0.000	p>0.05	p>0.05
Waist Circumference (cm)	p<0.005	p>0.05	p>0.05	P<0.000	p<0.039	p>0.05
Fasting Insulin (µU/mL)	p< 0.005	p<0.007	p>0.05	P<0.017	p>0.05	p>0.05
HOMA-IR	p<0.000	p<0.003	p>0.05	P<0.041	p<0.016	p>0.05
HOMA β Cell	p<0.004	p>0.05	p>0.05	p>0.05	p<0.003	p>0.05

insulin secretion (HOMA - β cell) from fasting plasma glucose and fasting insulin by HOMA[16]. The 100 subjects under went OGTT and they were classified into four groups of NGT, IFG, IGT and DM according to classification of WHO and ADA. After the ADA diagnostic criteria of 2003[7], impaired glucose homeostasis can be defined not only by 2-h PG of 7.8–11.1 mmol/L but also by FPG of 5.6–6.9 mmol/L. Impaired glucose homeostasis can be divided into subgroups, implying a close linkage between the WHO category of IGT and the new category of IFG, considered intermediate steps between normal and diabetic glucose homeostasis[6].

Our results, consistent with recent reports in different ethnic groups[17,18], clearly demonstrate that IFG and IGT subjects belong to different populations with altered glucose metabolism. The diversity between IFG and IGT groups involves both insulin secretion and resistance. There is considerable controversy regarding the relative contributions of insulin resistance and abnormal insulin secretion in the pathogenesis of IGT[19] and this is now accounted for by the new category of IFG.

Considering the information yielded by the HOMA analysis, we can say that both insulin secretion and insulin resistance is defective in IFG than in IGT subjects when compared with DM. the data published form Botnia study is in agreement with our results that insulin resistance measured by HOMA was more increased in those in IFG than in those with IGT[10], and more severe defect in insulin secretion was also found in subject of IFG in Pima Indians[20]. Several studies on insulin secretion and resistance in IGT subjects attempted to determine which of these two defects predominates during the early stage of the disease and which constitutes the primary abnormality[20]. Although the results of most cross-sectional studies of IGT subjects indicate that insulin resistance represents a major feature (in contrast to over study), extended follow-up shows that reduced insulin secretion is strongly predictive of progression to overt diabetes[21]. Defects in insulin resistance or secretion have different effects on fasting and postprandial glucose metabolism. This has been demonstrated in studies conducted on identical twins of parents with type 2 diabetes[22], hemipancreatectomized normal subjects[23], and insulin resistant Asian subjects[24], data, which collectively show that the onset of fasting metabolic abnormalities occurs in response to an impairment of insulin secretion, whereas insulin resistance preferentially affects postprandial glucose metabolism. Fasting plasma glucose, which depends essentially on hepatic glucose production, is strongly influenced by the feedback between liver and β-cells. In our study, in fact, subjects with IFG had not significantly lower fasting insulin levels than IGT subjects. Moreover, they exhibited a lower HOMA β-cell, the insulin secretion index based on baseline findings. Therefore, they would need to secrete more insulin to control their fasting glycemia. Normal insulin action is important in clearing an oral glucose load[25]. In our study, subjects with IGT showed significantly higher HOMA β-cell (insulin secretion) than those with DM as compared to those with IFG. They also had significantly lower insulin resistance as compared to DM, but there was no significant difference in insulin resistance in between IFG and DM. In other words, the excessive insulin secretion of these patients is sufficient to control their 2-hour plasma glucose. This demonstrates the presence of marked insulin resistance in IFG group is comparable to DM but insulin resistance is not severe in IGT and there is increased insulin secretion in IGT group subjects as well, which prevent the blood glucose to enter in diabetic range. Consequently, our findings suggest that IFG and IGT subjects represent two distinct populations with altered glucose metabolism. IGT people have less insulin resistance and relatively high insulin secretion as compared to diabetes, while IFG subjects are comparable with the DM in terms of insulin resistance and insulin secretion. Hence, our study results show that IGT is the second stage after NGT and IFG is the final stage on road to DM. This supported our hypothesis that insulin resistance and insulin secretion is different at different levels of glucose during oral glucose tolerance test. Both fasting plasma glucose and 2-hour plasma

glucose are useful diagnostic tools along with measurement of insulin resistance and secretion for identification of subjects at risk of developing diabetes. Since their combined use allows the identification of subjects with IFG and IGT as suggested by festa and colleagues that subjects with increase insulin resistance are likely to benefit from early intervention for preventing CVD and type 2 DM[26]. This distinction may help clinicians in choosing strategies to prevent diabetes and it complications.

The present study may be clinically relevant; first because it confirm the identification of subgroups between the nondiabetic and diabetic individuals with their severity of problem, that may benefit from insulin sensitizing agents and life style modification, second because the same groups of individuals may be exposed to an increased cardiovascular risk and there fore be benefited from early CVD prevention.

This study reports data from cross-sectional analysis; therefore, no conclusions regarding cause-effect relationships can be made. In addition, this studies although report data of small number of patients particularly of the IFG group, even than the results were in agreement to some international studies. On the other hand, this study is pioneer study analyzing the insulin resistance and insulin secretion at different levels of glucose tolerance in the Pakistani subjects, resulting into generation of baseline data for the further studies to be done in this country.

In summary, this study reflects that subjects with IFG are more insulin resistant and have decreased insulin secretion, which is comparable with DM.

CONCLUSION

Since IFG subjects has comparable HOMA IR (insulin resistance) and HOMA β-cell function (insulin secretion) to DM, while IGT subjects are less insulin resistant and has high insulin secretion as compared to DM. Hence IFG may be taken as serious as DM, as compared to IGT.

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