ORIGINAL ARTICLE

INSULIN RESISTANCE IN HUMAN SUBJECTS HAVING IMPAIRED GLUCOSE REGULATION

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ABSTRACT

Objective: To determine insulin resistance in human subjects having impaired glucose regulation (IGR) by Homeostasis Model Assessment for Insulin Resistance (HOMA-IR).

Design: Comparative cross-sectional study.

Duration of the Study: This study was carried out between September 2004 to September 2005, at the Department of Chemical Pathology and Clinical Endocrinology, Armed Forces Institute of Pathology (AFIP), Rawalpindi.

Patients and Methods: A total of 100 subjects with impaired glucose regulation were selected for evaluation of metabolic syndrome as per the criteria of National Cholesterol Education Program, Adult Treatment Panel III (NCEP, ATP III), along with 47 healthy age and gender-matched controls. Physical examination to determine blood pressure and waist circumference was carried out and so was sampling for plasma glucose, serum triglycerides, HDL-cholesterol and insulin. Insulin resistance was calculated by the HOMA-IR. Finally, subjects with and without metabolic syndrome were compared with controls (n=47), using one-way ANOVA for studying insulin resistance between groups, with Tukey's post-hoc comparison.

Results: The frequency of finding metabolic syndrome in cases of IGR remained 47%. The insulin resistance demonstrated stepwise worsening from control population (mean=1.54, 95 % CI: 1.77 - 2.37) to subjects suffering from only IGR (mean=2.07, 95 % CI: 1.77-2.37) to metabolic syndrome (mean= 2.67, 95 %, CI: 2.34 - 3.00) [$p < 0.001$].

Conclusion: Patients with impaired glucose regulation may have significant insulin resistance. It is, thus, recommended that a vigorous search be made to measure insulin resistance in all cases diagnosed to have impaired glucose regulation.

KEY WORDS: *Homeostasis Model Assessment for Insulin Resistance (HOMA-IR). Metabolic syndrome. Impaired glucose regulation (IGR). National Cholesterol Education Program Adult Treatment Panel III (NCEP, ATP III).*

INTRODUCTION

Individuals with diabetes mellitus and impaired glucose regulation have higher long-term morbidity in terms of its micro and macro vascular complications[1] This eventually leads to higher mortality and create undue economic burdens on health budget[2]. Moreover, it is also recognized that type 2 diabetes mellitus is linked with other disease processes like hypertension, obesity, and hyperlipidemia[3]. Raeven in 1998 named these abnormalities as "metabolic syndrome" and linked them with resistance to insulin action.[4] This association between various components of metabolic syndrome and resistance to insulin action has now been recognized through various consensus statements from organizations like World Health Organization (WHO), National Cholesterol Education Program, Adult Treatment Panel III (NCEP, ATP III), and European Group for study for Insulin Resistance (EGIR). [6-8] However, these definitions and position statements have been varying in terms of inclusion of various risk factors and possible requirements to establish insulin resistance for diagnosis.[7] The requirement for demonstrating underlying insulin resistance in these clinical subjects, found to have clustering of metabolic risk factors, is essential not only from epidemiological point of view, but also for the diagnostic work up.[9]

There are several markers for demonstration of insulin resistance. They range from technically difficult methods of insulin suppression test and hyperinsulinaemic euglycaemic clamp method to surrogates like Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), peak Oral Glucose Tolerance Test (OGTT) insulin levels and Frequently Sampled Intravenous Glucose Tolerance Test (FSIGTT).[10] The method of HOMA – IR has been used in different studies to establish relationship between the insulin resistance and metabolic syndrome.[11]

There are no previous studies that directly estimate the insulin resistance in local population with metabolic syndrome. A previous study from Lahore investigated the occurrence of metabolic syndrome in its diabetic population, but neither the recognized definitions of metabolic syndrome were used nor the insulin resistance was measured in its subject cases.[12] HOMA-IR is a very simple, reproducible and inexpensive method of demonstrating insulin resistance.[13, 14]

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The objective of this study was to use HOMA-IR to determine insulin resistance in subjects diagnosed as metabolic syndrome.

PATIENTS AND METHODS

This comparative cross-sectional analysis was carried out at the Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi, from April 2004 to September 2005. A total of 3664 cases were screened for presence of impaired glucose regulation by performing fasting plasma glucose. Four hundred and thirty-seven individuals demonstrated impaired fasting glucose and were requested to volunteer for further testing. Three hundred and thirty-seven subjects were excluded from further analysis on account of diagnosed diabetes, known pregnant status, hypertensives receiving treatment, and those who failed to demonstrate impaired glucose regulation on future analysis. After detailed explanation of the procedures, formal consent was taken. Forty-seven healthy age and gender-matched controls were also included in the study. These individuals were interviewed and examined to determine their blood pressure and waist circumference. Ten ml of blood was collected in medical fasting state for measurement of plasma glucose, serum triglycerides, HDL-cholesterol, and insulin. Plasma glucose was analyzed by method of GOD-PAP on Selectra –2 clinical chemistry analyzer, triglyceride by method of GPO-PAP on Saturno-300 clinical chemistry analyzer, HDL-cholesterol by indirect phosphotungstic acid method on Microlab–300 and insulin was analyzed by chemiluminescence's technique on Immulite–1000. These methodologies were as per NCEP specifications. Insulin resistance was calculated in all cases as per following formula of Matthews et al[15] :

$$\text{HOMA-IR} = \frac{\text{Plasma glucose (F) x Plasma insulin (F)}}{22.5.}$$

NCEP, ATP III defined criteria was employed to label subjects with metabolic syndrome.[15] The subjects were categorized into three groups as: Group 1 subjects with only impaired glucose regulation and no clinical metabolic syndrome; Group 2 – subjects diagnosed to have metabolic syndrome; and Group 3 – age and gender-matched controls.

Statistical package SPSS version 11 was used to analyze the data in terms of descriptive and inferential statistics. One-way ANOVA was used to demonstrate the statistical significance between the three groups, after satisfying the necessary requirements for using this statistical method. Laevene's statistics were used to confirm normality of data. Tukey's post-hoc comparison method was utilized to study the significance in between the groups once the ANOVA results showed significance (Table I). Regression analysis was used to study the effect of major confounders like age, education and urbanization status.

RESULTS

The frequency of occurrence of metabolic syndrome in the selected population of subjects with impaired glucose regulation remained 47% i.e., 47 out of 100 subjects. HOMA-IR, waist circumference, serum insulin and plasma glucose fasting showed statistically significant difference among groups. However, the post-hoc multiple comparisons by Tukey's method showed that the difference between the three groups was only significant for HOMA-IR. The homogeneity of variance was not satisfied in case of plasma glucose ($p = 0.005$) as this being the variable of choice selection. The effects of major confounders like age, sex, educational status and urbanization were also studied. Age was not found to be significant, while the results for urbanization and educational status was found to be significant ($p< 0.05$ and $p< 0.01$). Gender-based difference for insulin resistance was not significant between our sampled population, provided there was an overall higher occurrence of insulin resistance among males (Figure 1). Figure 2 depicts the comparison of insulin resistance between the three groups showing downhill course

Table I: Comparison of biochemical parameters between different groups (One-way ANOVA) .

Parameters	Groups	N	Mean	95% CI for Mean		(Significance)	Tukey's post-hoc
				Lower bound	Upper bound	One way ANOVA	comparison
Plasma glucose	1	47	6.766	6.49	7.03	*	*
Fasting	2	47	6.592	6.41	6.76		
(mmol/L)	3	47	4.710	4.51	4.90		
Serum HDL- C	1	47	1.102	1.03	1.16		
	2	47	1.138	1.07	1.20	NS	NS
	3	47	1.195	1.13	1.25		
Serum triglycerides	1	47	1.887	1.73	2.04		
(mmol/L)	2	47	1.746	1.58	1.90	NS	NS
	3	47	1.612	1.43	1.78		
Waist circumference (cm)	1	47	95.510	93.22	97.80	< 0.05	NS
	2	47	93.148	90.85	95.43		
	3	47	90.383	88.11	92.64		
Serum insulin in (mIU/L)	1	47	8.851	7.72	9.97	<0.05	NS
	2	47	7.175	6.12	8.22		
	3	47	7.127	6.09	8.16		
HOMA-IR	1	47	2.670	2.34	3.00		
	2	47	2.073	1.77	2.37	< 0.001	Gp-1 and Gp-2: < 0.05
	3	47	1.533	1.28	1.78		Gp-1 and Gp-3: < 0.001

* Plasma glucose was the selection variable.

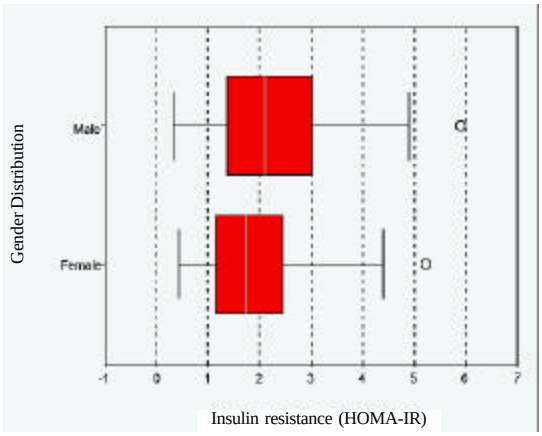

Figure 1: Gender difference for insulin resistance. (NS).

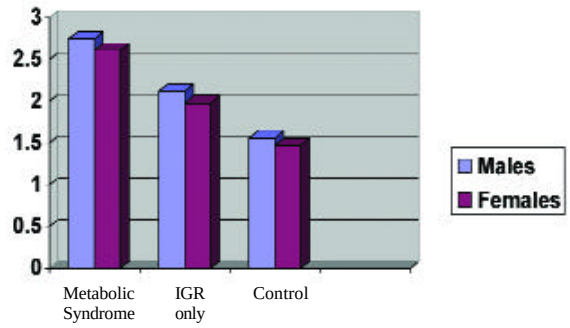

Figure 2: Comparison of insulin resistance (HOMA-IR) in different groups

of insulin resistance from metabolic syndrome to control population. Insulin resistance also increases with clustering of different components included in the definition of metabolic syndrome even without the presence of metabolic syndrome ($p < 0.001$) as shown in Figure 3.

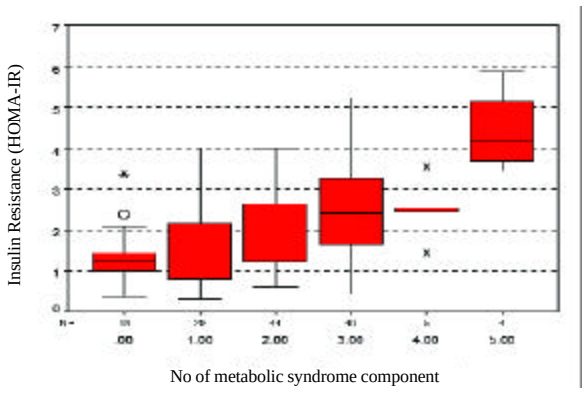

Figure 3: Linear regression analysis showing relationship between metabolic clustering of risk factors and insulin resistance ($p < 0.001$)

Discussion

This is a pioneer local study for directly demonstration of the connection between various components of metabolic syndrome and insulin resistance. Results from this study indicate that insulin resistance increases in a stepwise pattern from control population to impaired glucose regulation to subjects diagnosed to have metabolic syndrome. This finding may be an indication of the role of insulin resistance as the common ladder in the pathophysiological course in atherosclerosis.[9] Moreover, once the frequency of components of metabolic syndrome increases in a particular subject, the insulin resistance also increases. This highlights that each component, included in the diagnostic criteria for metabolic syndrome, has got a role to play in the overall mechanism of development of insulin resistance. This finding is in concordance with the published work of Isomaa et al. and Hanley et al.[16, 17]

The difference for insulin resistance between male and female subjects in this study remained insignificant; however, males showed an overall higher insulin resistance than their female counterparts. There are several contrasting studies round the globe, which have measured insulin resistance in the two genders. Some studies like Falker et al. have demonstrated higher insulin resistance in females as compared to males.[18] While other studies have similar conclusions in terms of gender differences.[19,20] The finding of lower insulin resistance among female subjects could be due to the reproductive life related hormonal changes, which have already been shown to be protective against various atherosclerotic events. However, a separate study must be planned to address this controversy with a larger sample size covering all age groups.

The results from this study can be of valuable usage, especially for the local population. The mean HOMA-IR among groups varied from 1.54 in control population to 2.07 in cases with IGR and 2.67 in subjects with metabolic syndrome. Different studies have found similar pattern of insulin resistance among healthy population to subjects with insulin resistance syndrome. Meigs et al. have reported a mean value of 2.70 for subjects with metabolic syndrome versus 1. 3 for healthy individuals.[21] Similarly, Ascaso et al have reported values of 2.60 for metabolic syndrome.[22]

The overall significance remains in the fact that insulin resistance has been identified as the common player in the process of atherosclerosis leading to long-term sequelae in the shape of cardiovascular complications and stroke.[23] Moreover, the subjects, who only demonstrate impaired glucose regulation, and not diabetes mellitus, have been linked to increased development of various cardiovascular related problems.[24]

The present-day wait-and-see policy in terms of monitoring their plasma glucose profiles, has not resulted in any reduction of mortality and morbidity of complications related to diabetes mellitus.[25] Identifying IGR subjects with clustering of other metabolic or clinical risk factors may become a concept of primary prevention in future. In this connection, measures of insulin resistance can become the most predictable biochemical method to stratify subjects with metabolic risk factors i.e., metabolic syndrome from the ones with only IGR. Here, insulin resistance as measured by method of HOMA-IR, may help in clinical scenarios on account of its simplicity and cost-effectiveness. Moreover, HOMA-IR incorporates two

components; one is the plasma glucose and other is the serum insulin, so any inherent variability because of so many patient related variables can be reduced.[26, 27] Thus keeping in view the inter-individual variations, the ease of identifying one singular target for intervention and the statistical significance of the findings, it seems appropriate to consider insulin resistance as a method to identify subjects with metabolic syndrome.

Before discussing the clinical implications, one important observation may be the fact that cardiovascular related mortality in our setup may not be related to the obesity defined cut-offs as defined by western studies.[28] Only 7 of the total 100 subjects with impaired glucose regulation crossed the NCEP defined cut-offs for obesity. Now, this observation highlights the fact that obesity must be defined in a different way in our population. This seems more acceptable as our part of population has small body frames and heights in comparison to their western counterparts. Some of the Chinese studies have reported waist circumference of as low as 90 cm for males, and 80 cm for females.[29] This study was focused to address this aspect, but separate epidemiological studies must be directed to this finding as simply defining appropriate cut-offs for our population may identify more individuals with a greater risk for metabolic syndrome.

Different studies have identified various confounders in the development and progression of metabolic syndrome. The important ones include age, gender, educational status, urbanization and socioeconomic status.[30] This study has only identified educational status and urbanization as the major confounders. Perhaps the wisdom acquired by having more education by staying closer to centers of excellence (cities) had to be paid in terms of higher insulin resistance. However, age was not found to be significant factor in this study. This finding contrasts to some of the previously published works.[30, 31] The probable reasons to this dichotomy could be the life style and dietary modifications, which are being adopted differently by different set of socioeconomic classes. The other reason could be the economic factors which are more determined by urbanization in this part of the world and which brings with it the curse of sedentary life styles and cholesterol rich diet intake.[32]

There were few limitations of this study. Firstly, the effects of socioeconomic factors have not been excluded. Secondly, the review of literature suggests that psychological stress-related events may play a role in the development of various clinical and biochemical risk factors. Thus, psychological stress may confound the results. Lastly, the sample size mainly constituted an urbanized population so a real contrast between urban and rural community cannot be made. But as already highlighted that insulin resistance may be the final outcome of a number of processes, all eventually leading to accelerated atherosclerosis.

This study has several important clinical implications. Firstly, a common approach towards managing subjects with metabolic abnormalities grouped under the heading of metabolic syndrome will save time and cost and improve clinical outfit of management. Secondly, the clinical interest may shift in future from identifying various metabolic and clinical atherosclerotic and inflammatory risk factors separately to only demonstrating insulin resistance in the diagnosis and monitoring of metabolic diseases. Thirdly, this study addresses the scenario of metabolic syndrome in our local population, which has a major trend of urbanization. The defined cut-offs by the western studies in the opinion of the authors may not perfectly suit our setup. This aspect is especially important in consideration of obesity definition.

CONCLUSION

Metabolic syndrome is a common occurrence in our population of impaired glucose regulation. Moreover, the insulin resistance, as determined by method of HOMA-IR, showed stepwise worsening from control population to subjects with only impaired glucose regulation to NCEP defined metabolic syndrome patients.

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