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Assessment of insulin sensitivity and resistance in non diabetic Punjabi population

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ABSTRACT

Introduction: The pathogenesis of type 2 diabetes mellitus has been closely associated with dysfunctions observed in Insulin formation and pancreatic β cell functioning. Hepatic glucose output and insulin secretion from fasting levels of glucose and insulin have been widely validated clinically and epidemiologically to form a mathematical tool for estimating insulin resistance and β cell function. The tool has been named as the homeostasis Model Assessment tool (HOMA) and QUICK I index. The present study was designed to evaluate various biochemical parameters in two insulin resistance groups established by cutoffs of HOMA index and QUICK I.

Materials and Methods: Total 5 00 non diabetic subjects attending the out-patient department of Sri Guru Ram Das Institute Of Medical Sciences and research Vallah, Sri Amritsar were included in the present study. After excluding 23 persons having HBA1C $>$ 7 % we were left with 477 subjects. They were analyzed for Fasting Blood Glucose, HBA1C, S. Insulin and Lipid Profile. HOMA-IR index and QUICK I index were calculated using formulas. On the basis of the cutoffs of the above indices, the non diabetic persons were divided into High and Low insulin resistance groups.

Results: Prevalence of insulin resistance in non diabetic general population was 41.5 % as estimated by cutoffs established by QUICK I index. It was much lower when HOMA IR index was used.

Conclusion: Quick I is the more sensitive index as compared to HOMA IR for the screening of Insulin resistance. Moreover, the amount of adipose tissue is the risk factor for Insulin resistance and not the sex.

1. Introduction

Insulin resistance and pre-diabetes precede Type 2 diabetes mellitus, although these often go undiagnosed. Insulin resistance is a syndrome resulting from diminished activity of the hormone, also being a subset of a large group called Metabolic syndrome. Maintaining a healthy body weight as per BMI guidelines and promoting physical activity can prevent its progression into Type 2 Diabetes Mellitus. This can only be achieved if Insulin resistance is diagnosed early.[1] Hyperinsulinemic euglycemic clamp (HEC) has been considered as the gold standard for diagnosing insulin sensitivity in patients. But, the amount of time and cost required for the test led to the identification and subsequent development of much simplified method for quantifying insulin sensitivity. During the last two decades the results obtained from fasting plasma glucose and insulin levels have been used for developing indices capable of calculating insulin sensitivity/resistance.[2,3] In addition, C-peptide has a prospect as possible diagnosing tool in HOMA modeling for both β-cell function and insulin resistance. This parameter is regularly used for analyzing the insulin secretion rather than insulin action. It is based on the concept that %S is determined by the action of insulin that directly controls the glucose metabolism in an individual. Therefore, the use of fasting insulin concentrations for the determination of %S is justified. The bias in determining β-cell function and insulin sensitivity is greatly reduced by the use of C-peptide and insulin.[4]

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Homeostasis model assessment was first developed in 1985 by Matthews et al. This method quantifies insulin resistance and β-cell functioning using the values of fasting plasma glucose and insulin or C-peptide. HOMA is a model of the relationship of glucose and insulin dynamics that predicts fasting steady-state glucose and insulin concentrations for a wide range of possible combinations of insulin resistance and β-cell function. The pancreatic β-cell response is responsible for determining the insulin levels. The glucose concentrations, on the other hand, are dependent on insulin-mediated glucose production by the liver. Therefore, defect in β-cell function will be reflected by gradual reduction in β-cell response to glucose-stimulated insulin secretion.[5,6] Similarly, insulin resistance can be correlated to reduced suppressive effect of insulin on glucose production by the liver. The HOMA model has been considered as a robust clinical and epidemiological tool for assessing insulin resistance. HOMA model was mainly designed as a structural model for measuring insulin sensitivity and for adjusting insulinogenic index appropriately. It is a sophisticated and complicated measure of insulin sensitivity.[7–9]

Quantitative insulin sensitivity check index (QUICKI) is an empirically-derived mathematical equation of fasting blood glucose and plasma insulin concentrations. This mathematical model can provide accurate and reproducible results with better positive predictive power. This equation is an analogue of HOMA index and it modifies the data by calculating the logarithm and the reciprocal of the glucose-insulin product. This variation helps in skewing the distribution of fasting insulin values. QUICKI provides significant linear correlation between glucose clamp determinations of insulin sensitivity in contrast to the minimal-model estimates. This method is much useful for obese and diabetic individuals.[10,11]

The study aims at estimating and comparing insulin Resistance using QUICK I with the results obtained from HOMA-IR model. The study subjects would be classified into non-diabetic population high-insulin resistant (HIR) and low-in sulin-resistant (LIR) subgroups. Pre-defined cut-off points would be used for the purpose of classification. It would highlight whether there is difference in the results between the well established anthropometric and biochemical characteristics between LIR and HIR subgroups.

2. Materials and Methods

The present comparative study was conducted in the Department of Biochemistry, Sri Guru Ram Das Institute Of Medical Sciences And Research, Vallah, Amritsar after taking the permission from the Institutional Ethical committee. Total 5 00 non diabetic normotensive subjects, after obtaining informed consent were included in the study.

2.1. Exclusion criteria

Patients with the following history would be excluded from the study:

1. Type-1 or type 2 Diabetes Mellitus
2. Complications of DM
3. History of acute infections
4. Gross congestive heart failure
5. Tuberculosis
6. Gout
7. Rheumatoid arthritis
8. Skeletal muscle injury
9. Serum creatinine $>$ 1.5mg/dl
10. Renal failure
11. Individuals taking hypoglycemic drugs
12. Individuals on insulin therapy

2.2. Sampling

A detailed history and thorough clinical examination was carried out on each patient. Fasting blood samples after an overnight fast of 10-12 hours was drawn and samples were immediately processed and analyzed for serum Fasting blood Glucose, serum Insulin and HbA1C. Fasting blood sugar was estimated by GOD-POD Method (Trinder 1969) 12 and HbA1C by Biorad D10.[12] Serum insulin was estimated by Immunometric method on Vitros 5600 Integrated system which involves simultaneous reaction with biotynlated anti-insulin antibodies.[13]

23 persons having HBA1C $>$ 7 % were excluded from the study and we were thus left with only 477 non diabetic general population.

The pulsatile nature of insulin requires the use of the mean of three samples obtained within 5-min intervals was for computing HOMA index. The samples were handled carefully for preventing hemolysis, as it is associated with the degradation of insulin. Freezing the obtained samples has been associated with the degradation of C-peptide.

The insulin resistance among patients was identified indirectly using the below mentioned mathematical tool:

2.2.1. HOMA-IR: Homeostasis model assessment-insulin resistance[14]

The equation proposed by Matthews et al.:

$IR_{HOMA} = (I_0 \times G_0)/ 22.5$(mathematically: $e^{-Inx} = 1 / x$)

This tool has been used in large epidemiological studies using the fasting insulin and glucose values of the patients. The cut off values used in diagnosing HIR and LIR were 3.8.

2.2.2. Quick I Index : Quantitative insulin sensitivity check index[15]

The equation for this purpose is:

$QUICKI = 1/(\log I_0 + \log G_0)$

The cut off values of High Insulin Resistance Groups (HIR) was : 0.382 ± 0.007 for non-obese, 0.331 ± 0.010 for obese and 0.304 ± 0.007 for diabetic individuals.

The study population was further divided into High Insulin resistant (HIR) Groups and Low Insulin resistance (LIR) groups using the above cut-offs.

2.3. Statistical analysis

The comparison was done by students 't' test on the number of variables for each parameter. Logistic regression analysis was also done on the variables of each parameter.

3. Results

Among 500 subjects screened, 23 had overt diabetes and were advised for further investigations. Among these 477 subjects, 226 were Males and rest Females. (Table 1) The statistical analysis showed no difference between the sexes with regards to their mean age. As per the demographic strata, 29.6% males and 24.8% Females were obese.(Table 2)

As per the cut off of Quick I index, 41.5% subjects i.e 198 persons, were stratified in High Insulin resistance group. The mean insulin and Serum Triglycerides showed highly significant difference in two groups ($p<0.001$). (Table 3)

As per HOMA IR cut off, only 16.3% (78) individuals were diagnosed as insulin resistant.

4. Discussion

Diabetes Mellitus is a metabolic abnormality having serious acute and chronic complications. The rising number of cases has made it an epidemic for the world population. The type 2 diabetes mellitus prevalence among old individuals has been projected to increase to 135 million in 2025. This metabolic syndrome has been characterized by the presence of insulin resistance or impaired insulin secretion. This situation arises mainly due to reduced sensitivity of cells to the effects of insulin. Screening of insulin resistance from the very beginning may prevent its progression to overt diabetes and thus preventing many complications. Many authors have debated the high levels of insulin resistance preceding Diabetes which goes undetected and the debate is still prevailing.

In our study, we found significantly increased levels of serum Insulin in HIR group as compared to LIR group ($p<0.01$). The reason for this finding could be insulin resistance. This leads to more insulin production due to continuous hyperglycemia, in order to keep blood glucose levels from spiraling out of control. If hyperinsulinemia is not corrected, the pancreas eventually become exhausted resulting in diabetes. Similar findings were observed by G Srinivasa et al.[16]

Our findings of the factors such as percentages for overweight and obese individuals in both sexes were similar to as reported earlier by Bahirji et al[1] in comparison to that estimated by Alsiaf et al[17] who reported lower results. These conflicting results arise either due to the defined exclusion criteria or due to demographical variations among the two studies. In spite of this lower percentage, the fact that more than half of the Punjabi population is overweight or obese is alarming. Obesity has been considered as a global healthcare burden and concern due to several premature morbidities and a high mortality rate irrespective of the age groups considered.[17]

Almost 5 % of the randomly screened population had blood glucose values $\geq$ 7 mmol /L and had to be excluded according to our criteria. This highlights the occurrence of lower number of diabetic individuals in the study area. The use of the mathematical tools for analyzing insulin resistance is considered easy tool that may even prevent diagnostic delay.[1]

QUICKI requires a single fasting blood sample for calculating results in comparison to multiple and frequent pricks and lengthy tenure necessary for both the glucose clamp and the minimal model approach es for estimating insulin resistance. Still more to add on, the calculation benefits, QUICKI does not depend on a robust insulin secretory capacity, and can also be used to estimate insulin sensitivity in all diabetic individuals.(as opposed to the minimal model approach). In diabetics its necessary to withdraw medicines before estimating sensitivity levels in overt diabetics who have very high sugar values and practically cant be weaned off medications. Inherent limitations to QUICKI include difficulty in calculating sensitivity of insulin hormone in with type 1 diabetes due to the lack endogenous insulin secretion.[18]

Our study underestimated prevalence of insulin sensitivity in general population when calculated by HOMA index as compared to QUICK I index is used. The most crucial reason for underestimation by HOMA could be due to the fact that this method reflects only hepatic IR, while ignoring the other causes.[19] Our studied population included subjects that could be pre-diabetic with an FPG concentration between 100 and 125 mg/dL (5.6-6.9 mmol/L) and referred to as having IFG, as well as subjects that could have abnormal postprandial glucose excretion but normal FPG concentration and referred to as having impaired glucose tolerance (IGT).[20] Subjects with IFG have hepatic IR and thus can be detected by HOMA-IR. However, those subjects with IGT have peripheral IR and hence will be missed.[20]

Theoretically, the above could also be applied to QUICKI, and subjects with IGT are expected to be missed. However, compared to HOMA-IR, QUICKI is reported to have the advantage of being applicable to wider ranges of insulin sensitivity,[20] which might explain the much higher percentage labeled as HIR. But unlike what was noted when HOMA-IR was used, the HIR

Table 1: Demographic and anthropometric characteristics of the study group

Parameter	Males	Females
Age (years)	62.8	58.4
Weight (Kg)	72.4	67.3
Height (cm)	167.0	156.8
BMI (kg/m2)	26.5	27.7
Obese as per BMI (%)	29.6	24.8
Waist Hip Ratio	0.89	0.78
Family history of diabetes mellitus n (%)	51.3 %	52.6 %

Table 2: Comparison of mean serum biochemical parameters in males and females

Parameter	Male	Female
Number of subjects	226 (47.3 %)	251(52.7%)
Total Cholesterol (mg%)	189.2 + 14.2	210.6 + 25.4
Triglycerides (mg%)	162.5 + 22.0	140.4 + 25.5
LDL Cholesterol (mg%)	110.2 + 18.8	112.2 + 13.4
HDL (mg%)	48.23 + 11.23	45.23 + 12.16
Fasting Glucose (mg%)	106.4 + 20.50	98.90 + 21.62
HBA1C (%)	5.6 + 0.8 %	5.3 + 1.2 %
Insulin IU/L	8.23 + 2.8	7.9 + 4.7

Table 3: Comparison of Mean serum Biochemical parameters in HIR and LIR group as per QUICK I.

Parameter	HIR (n=198) 41.5%	LIR (n=279) 58.5%	P value
Total Cholesterol (mg%)	220.66 + 12.4	202.42 + 18.9	0.060
Triglycerides (mg%)	168.89 $\pm$ 43.1	124.22 $\pm$ 18.09	0.001
LDL Cholesterol (mg%)	149.52 $\pm$ 31.05	130.28 + 23.42	0.041
HDL (mg%)	41.28 + 8.2	46.4 + 5.8	0.090
Fasting Glucose (mg%)	118.2 + 12.2	102.4 + 13.2	0.025
HBA1C (%)	5.7 + 0.5 %	4.9 + 0.8 %	0.030
Insulin	12.8 + 3.2	7.2 + 2.8	0.001

subgroup identified by QUICKI did not have most of the well-recognized biochemical characteristics of insulin resistance, and the calculated means or medians of their measured parameters did not significantly differ from those of the LIR subgroup.[20,21] Therefore, QUICKI could be responsible for overestimation according to the defined cut-off values in Punjabi population.[22–26] QUICKI can identify HIR individuals much before the actual occurrence of biochemical abnormalities.[21]

Including FFA into the QUICKI formula could be useful in early detection, especially in view of the foll owing: (1) Elevated fasting FFA concentration correlates with insulin resistance much earlier than hyperglycemia, as lipolysis is more sensitive to insulin;[26] (2) even slight increase in levels of plasma FFA concentration in healthy individuals can induce insulin resistance, and (3) insulin resistance of lipolysis described upto 10% of the variation in insulin sensitivity (4) in normal subjects; (5) dysfunctional regulation of lipolysis was observed in patients with insulin resistance. Literature survey reveals that modified QUICKI is correlated with clamp measurement with much improved results than the original QUICKI or HOMA-IR.

5. Limitation of the study

Further estimation Free fatty acid concentration could have been done to estimate the prevalence of insulin sensitivity by Modified QUICK I formula which have already been regarded better in terms of predicting Insulin sensitivity because of incorporation of Free fatty acid concentrations.

6. Conclusion

QUICKI is a new and improved replacement for HOMA-IR. The results of QUCIKI correlate with those obtained from HOMA. The limitations of QUICKI are similar to those of HOMA index. However, QUICKI has been observed to have higher sensitivity for detection of insulin in mildly resistant individuals or lean individuals having β-cell dysfunction in comparison to HOMA-IR.

7. Source of funding

None.

8. Conflict of interest

None.

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