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Research Article

A STUDY OF ASSOCIATION OF INSULIN RESISTANCE AND CARDIOMETABOLIC RISK FACTORS IN AN ADULT POPULATION WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT
Aim of the study was to study the association of insulin resistance using the HOMA IR (Homeostasis model assessment of Insulin Resistance) and cardio metabolic risk factors in adult subjects with type 2 diabetes mellitus. Settings and design was in this hospital based on cross sectional prospective study, a total of 313 adult subjects with type 2 diabetes mellitus were included after obtaining a valid informed written consent. Insulin resistance was estimated using the HOMA IR. Various variables such as body mass index(BMI), waist circumference, hip circumference, fasting blood glucose, fasting insulin levels, glycated hemoglobin (HbA1c), serum uric acid, total serum cholesterol, serum triglycerides, HDL-C, LDL-C and serum creatinine were estimated using standard methods. In this study we analyzed the association of insulin resistance with cardiometabolic risk factors as well as the variables mentioned above. Statistical analysis done using Pearson correlation coefficients to correlate HOMA-IR with selected cardiovascular disease risk factors. Correlation was considered significant at the 0.05 level (2-tailed). Unpaired ANOVA and Chi Square tests were the tests of significance for quantitative and qualitative data respectively. A strong positive correlation was noted between insulin resistance (HOMA IR score) and HbA1c (r= 0.338, p = 0.0001); and PPBG (r = 0.348, p = 0.0001). However no significant correlation was noted between HOMA IR score and other variables studied. Significant association was observed between HOMA IR score, HbA1c and BMI (p value of 0.024** and 0.000** respectively). ANOVA test proved that there was a statistically significant difference with waist circumference, HbA1c, PPBG, triglycerides and VLDL. Insulin resistance is positively associated with selected cardio metabolic risk factors such as diabetes mellitus and body mass index. The study emphasizes the need of an integrated approach based on lifestyle modification for prevention of various cardiovascular events arising as a result of insulin resistance.

Keywords: *Insulin Resistance, Cardio-Metabolic Risk Factors, Diabetes Mellitus, Adult Population, HOMA-IR*

INTRODUCTION
Insulin resistance (IR) is a pathological situation characterized by a lack of physiological response of peripheral tissues to insulin action, leading to the metabolic and hemodynamic disturbances known as the metabolic syndrome (Hanefeld, 1997). Many longitudinal studies in adults have demonstrated that insulin resistance is a risk factor of the development of type 2 diabetes (Bunt *et al.*, 2007; Lillioia *et al.*, 1993). The interest for IR and metabolic syndrome lies in their high prevalence in the population and the associated high death rate, fundamentally through coronary heart disease, even in non-diabetic subjects (Isomaa *et al., 2001;* Ford *et al.*, 2002). The gold standard test for diagnosing insulin resistance has been euglycemic-hyperinsulinemic glucose clamp (DeFronzo *et al.*, 1979). Because of its invasiveness, complexity and expense, the euglycemic glucose clamp method is of limited use for clinical screening exams and population-based epidemiological studies. The homeostasis model assessment of insulin resistance (HOMA-IR) was developed in response to the need for a simpler and more practical

measurement of insulin resistance. In this study, we studied the relationship of insulin resistance as estimated by HOMA-IR with cardio metabolic risk factors and various variables such as body mass index; waist circumference; hip circumference; fasting blood glucose; fasting insulin levels; glycated hemoglobin (HbA1c); serum uric acid; total serum cholesterol; serum triglycerides; HDL-C; LDL-C; and serum creatinine.

MATERIALS AND METHODS

This hospital based cross-sectional study was conducted in 313 adult subjects with type 2 diabetes mellitus who visited the outpatient department of Medicine, R L Jallappa Hospital, Tamaka, Kolar. Ethical clearance was obtained from the Institutional ethical committee and a valid informed written consent was obtained from all the subjects recruited for the study. The diagnosis of type 2 diabetes mellitus was based on previous history of diabetes mellitus or on World Health Organization criteria (Kahn *et al.,* 1993). All diabetic subjects aged above 20 years; those not on treatment with insulin and insulin sensitizers such as biguanides and pioglitazones were included in the study. Diabetic subjects with evidence of preexisting coronary artery disease, heart failure, ischemic stroke, hypothyroidism, liver failure, subjects on statin therapy were excluded from the study. A preformed questionnaire was used to obtain the clinical history. Blood samples were collected after 8 to 12 hours overnight fast and the samples were processed either immediately or during the first week after conservation at -20°C. Plasma glucose levels were measured by the glucose oxidase method, HbA1c by high- pressure liquid chromatography and plasma insulin levels by immunoradiometric assay. Serum creatinine, serum total cholesterol, triglyceride and HDL and VLDL cholesterol were measured by enzymatic methods adapted to an auto analyzer. The insulin resistance was determined by using the following formula: HOMA IR = Fasting glucose level (mg/dl) x Fasting insulin level (mU/ml) / 405.

Statistical analysis: Pearson correlation coefficients were used to correlate HOMA-IR with selected cardiovascular disease risk factors. Correlation was considered significant at the 0.05 level (2-tailed). Unpaired ANOVA and Chi Square tests were the tests of significance for quantitative and qualitative data respectively.

RESULTS AND DISCUSSION

Results: In this hospital based cross sectional study of 313 subjects with type 2 diabetes mellitus, 112 were females and 201 were males. The mean age of the subjects was 54.98 ± 11.69 (mean ± SD). The mean age at diagnosis of diabetes mellitus was 48.3 ± 11.6 years. Mean BMI, FBG, Fasting Insulin, HbA1c, HOMA IR score were 25.7 ± 11.3, 149.43 ± 73.78, 13.87 ± 10.68, 9.21 ± 2.62 and 5.21 ± 5.19 respectively. Differences in clinical parameters between male and female subjects are shown in Table 1.

Table 1: Profile of the study subjects

Parameters	Mean ± SD Male (n=201)	Female (n=112)
Age	56.19 ± 12.24	52.81 ± 10.34
Age at onset of Diabetes	49.24 ± 12.10	46.67 ± 10.50
BMI	24.58 ± 3.85	27.77 ± 18.12
Waist Circumference (WC)	94.85 ± 10.88	94.57 ± 9.14
FBG (Fasting Blood Glucose)	147.83 ± 74.58	152.30 ± 72.57
Fasting Insulin	13.85 ± 11.10	13.9 ± 9.94
HbA1c	9.29 ± 2.60	9.05 ± 2.67
Serum Creatinine	1.06 ± 0.82	0.86 ± 0.74
Serum Uric acid	4.65 ± 1.18	4.34 ± 1.11
Total Cholesterol (T Chol)	169.23 ± 37.99	185.54 ± 41.67
TGs (Triglycerides)	185.07 ± 91.99	197.36 ± 90.22
HDL (High density lipoprotein)	38.07 ± 6.21	38.00 ± 5.24

LDL (Low density lipoprotein)	92.97 ± 31.96	105.77 ± 37.12
VLDL (Very low density lipoprotein)	39.31 ± 21.01	41.16 ± 20.10
PPBG (Post prandial blood glucose)	250.49 ± 93.82	253.08 ± 94.61
HOMA IR	5.19 ± 5.42	5.25 ± 4.77

Among the clinical parameters studied, BMI and HbA1c were significantly associated with HOMA IR score i.e an increase in BMI and HbA1c is associated with an increase in HOMA IR score, as shown in Table 2.

Table 2: Association between HOMA IR and other parameters

Parameters	Values	HOMA IR Score				p value
		<1.80 (n = 66)	1.81 to 3.45 (n = 88)	3.46 to 6.06 (n = 78)	>6.07 (n = 81)	
BMI	<22.9	28	21	22	24	
	23 to 24.9	18	22	20	11	0.024**
	>25	20	45	36	46	
HbA1c	<6.5	23	17	5	7	
	>6.5	43	71	73	74	0.000**

p value significant at 0.05

Pearson correlation showed that there is significant positive correlation between HOMA IR and HbA1c (r = 0.338, p = 0.0001) i.e as the HbA1c increases there is also an increase in HOMA IR score significantly. Similarly there was significant positive correlation between HOMA IR and PPBG (r = 0.348, p = 0.0001). There was no significant correlation between HOMA IR and other parameters like BMI, serum creatinine, uric acid and lipid parameters as shown in Table 3.

Table 3: Correlation between HOMA IR score and cardio metabolic risk factors

	HbA1c	PPBG	Serum Creatinine	Serum Uric acid	Total cholestrol	TGs	HDL	LDL	VLDL
r value	0.338**	0.348**	-0.062	-0.080	0.035	0.083	-0.059	-0.016	0.052
p value	0.000	0.000	0.278	0.158	0.542	0.144	0.296	0.776	0.363

*** p value significant at 0.01*

HOMA IR score was categorized in to 4 grades and analysis of variance (ANOVA) test proved that there was statistically significant difference with waist circumference, HbA1c, PPBG, triglycerides and VLDL between the groups and within the groups, as shown in Table 4.

Table 4: ANOVA test between HOMA IR and cardio metabolic risk factors

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
Waist Circumference	Between Groups	860.465	3	286.822	2.757	0.043**
	Within Groups	32144.595	309	104.028		
	Total	33005.061	312			
HbA1c	Between Groups	360.560	3	120.187	20.753	0.000**
	Within Groups	1789.503	309	5.791		
	Total	2150.063	312			
PPBG	Between Groups	521167.523	3	173722.508	24.051	0.000**
	Within Groups	2224748.782	308	7223.210		
	Total	2745916.304	311			
T. CHOL	Between Groups	6948.423	3	2316.141	1.450	0.228

	Within Groups	493702.887	309	1597.744		
	Total	500651.310	312			
TGS	Between Groups	108790.124	3	36263.375	4.485	0.004**
	Within Groups	2498455.895	309	8085.618		
	Total	2607246.019	312			
HDL-C	Between Groups	124.242	3	41.414	1.202	0.309
	Within Groups	10646.940	309	34.456		
	Total	10771.182	312			
LDL-C	Between Groups	5226.230	3	1742.077	1.479	0.220
	Within Groups	363951.041	309	1177.835		
	Total	369177.272	312			
VLDL	Between Groups	4886.361	3	1628.787	3.915	0.009**
	Within Groups	128545.850	309	416.006		
	Total	133432.211	312			

Discussion

Insulin resistance is highly prevalent not only in the diabetic population but also in the general population of non-diabetics. Insulin resistance is an important mechanism for the development and progression of diabetes mellitus and atherosclerotic disease, a common cause of mortality in diabetic patients (Reaven, 1998; DeFronzo, 1992). The main clinical interest for the study of insulin resistance lies in its fundamental role in the development of type 2 diabetes mellitus, hypertension and coronary events. In the present study we analyzed the association of insulin resistance with various variables considered as cardio metabolic risk factors. The insulin resistance was estimated using the HOMA IR model.

In the present study there was strong positive correlation between insulin resistance (HOMA IR Score) and diabetes mellitus (in the form of HbA1c and PPBG), whereas there was no significant correlation between HOMA IR and other parameters such as lipid profile; body mass index, waist circumference, serum creatinine, serum uric acid. Significant association was observed between HOMA IR score, HbA1c and BMI. ANOVA test proved that there was statistically significant difference with waist circumference, HbA1c, PPBG, triglycerides and VLDL.

Insulin resistance is related to several cardiovascular risk factors, including hyperglycemia, dyslipidemia, hypertension, thrombophilia, and cigarette smoking. Insulin resistance and hyperinsulinemia may be causally related to type 2 diabetes mellitus, hypertension and cardiovascular disease (Li *et al.*, 2003; Sowers and Frohlich, 2004). A study of Japanese adults reported that post-glucose tolerance insulin concentrations were correlated with hypertriglyceridemia, low HDL-Cholesterol concentration, and hypertension (Yamada et al., 1994). Another study reported that body mass index and waist circumference were positively correlated with HOMA-IR values (Chailurkit et al., 2007). Similarly there is evidence that calorie restriction, weight loss, and physical exercise improve insulin sensitivity (Franssila-Kallunki *et al.*, 1992; Goodpaster *et al.*, 2003). There are also studies which report a positive correlation between insulin resistance and parameters such as hypertension, low HDL-Cholesterol concentration and serum uric acid levels (Yamada et al., 1994; Short *et al.*, 2003; Cai *et al.*, 2009; Jaipakdee *et al.*, 2013; Cohen *et al.*, 2012). However in our study, no significant correlation of these parameters with insulin resistance was noted.

In conclusion, in our study there was strong correlation noted between insulin resistance (as determined by HOMA-IR score) and HbA1c and PPBG. HbA1c and BMI were significantly associated with the HOMA IR Score. The study emphasizes the need of an integrated approach based on lifestyle modification for prevention of various cardiovascular events arising as a result of insulin resistance.

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