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Is body mass index related to insulin resistance in Asian population

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Abstract
Background: Insulin resistance is one among the major factors for the cause of type 2 diabetes or its antecedent impaired glucose tolerance. According to traditional thinking, the major cause of IR is increasing BMI, which ultimately leads to comorbidities like dyslipidemia, micro and macrovascular complications. Rising BMI or waist circumference are clearly linked to insulin resistance and risk for T2DM, a number of adipose derived factors have attracted interest with respect to determining insulin resistance.
Materials and methods: The study was both retrospective and prospective which was conducted at Believers church medical college hospital, Thiruvalla, Kerala, India. This study was approved by the Institutional Ethical Committee and patient consent was also taken. The study was conducted in 72 subjects for a duration of 2 years (July 2017 to October 2019).
Result: The study revealed the relation between the BMI and IR in ethnic population. The results obtained were contradictory to the traditional fact that an increase in BMI is related to the increase in IR. According to our results there is no relation between the BMI and IR (r=-0.025, p=0.833).
Conclusion: Hence concluded that BMI and IR are not correlated. The increase in the BMI is not the reason for the IR. The increase in the visceral fat may be the factor for IR. According to our study, we also conclude that insulin secretion and β cell mass (%) are correlated with IR. We could identify that insulin secretion is inverse correlated to the IR whereas a positive correlation between the β cell mass (%) and IR.

Keywords: β cell mass (%), body mass index, insulin, insulin resistance, normal weight obesity, type 2 diabetes mellitus

1. Introduction

Type 2 diabetes or its antecedent impaired glucose tolerance is one of a cluster of conditions which is thought to be caused by the resistance to insulin action. Patients with type 2 diabetes (T2DM) often have comorbidities like dyslipidaemia, non-alcoholic fatty liver and in women, polycystic ovarian syndrome and this cluster is often called the insulin resistant syndrome or metabolic syndrome. The primary cause of insulin resistance (IR) remains unclear. The major cause of insulin resistance is obesity. Intra-abdominal central adipose tissue is metabolically active and it releases large quantities of free fatty acids (FFAS) which may induce insulin resistance, because they compete with glucose as an energy supply for oxidation in peripheral tissue such as muscle.

The adipose tissue releases a number of hormones which act on specific receptors to influence insulin in other tissues. Because of the venous drainage of visceral adipose tissue into a portal vein, the central obesity may have a potent influence on insulin sensitivity in the liver and hence it adversely affects gluconeogenesis and hepatic lipid metabolism. Accumulation of fat in the liver is a common association with central obesity and IR.

Insulin imparts its effect not only on the skeletal muscle but also on many tissues including adipose, liver, endothelium and immune cells. Lipotropic individuals have an impaired ability to store subcutaneous fat and as a consequence they accumulate fat in visceral and ectopic tissues and so have marked IR [1].

Certain ethnic groups at heightened diabetic risk may have a tendency to store fat centrally sooner (i.e. lower body mass index (BMI in kg/m^2)) than European whites and consequently develop average BMI values and around a decade earlier [2].

Women with 50 to 60 kg/m^2 remain insulin sensitive and normo-lipemic. Imaging studies have shown these individuals to have low levels of visceral and ectopic fat and high subcutaneous fat content [3].

Table 1: Obesity classification according to WHO and Asia-Pacific guidelines

Class	WHO (BMI in kg/m^2)	Asia-Pacific (BMI in kg/m^2)
Underweight	<18.5	<18.5
Normal	18.5–24.9	18.5–22.9
Overweight	25.0–29.9	23.0–24.9
Obese	≥30.0	≥25.0

Location of fat storage (subcutaneous vs visceral /ectopic) appears as to the BMI and time that an individual develops metabolic complications linked to IR. Liver fat accumulation is closer to the time of development of diabetes whereas muscle IR is an earlier development. Vascular IR is contributed by perivascular fat and dysfunction via a process of adverse vasocrine signaling leading in turn to impaired nutrient blood

flow. Recent evidence indicates fat may accumulate in the pancreas to contribute to β cell dysfunction and thus development of diabetes. IR must be associated with raised triglycerides levels. Low HDL level is also a feature of IR. Higher apolipoproteins B levels and greater small dense LDL are linked with IR [4].

In most of the individuals muscle IR appears to be long standing and earlier abnormality [5]. It has been shown to be very common (>50 %) in type 2 diabetes and is linked to hepatic IR [6].

Increase in BMI or waist circumference are linked to IR and risk for T2DM, a number of adipose derived factors have influence in determining IR. In contrast to other adipocyte hormones, its concentration declines with increasing obesity. There are more evidence in human that have shown that low adiponectin is more likely to be a downstream signal of hyperinsulinemia, than a casual upstream determinant of IR [7].

Dyslipidemia, dysglycemia, high blood pressure (BP), inflammation, thrombic pathways and endothelial dysfunction may have suggested that IR must be a strong cardiovascular risk factor. Three out of five criteria are now required to be identified as having metabolic syndrome. The optimal BMI cut-off score for prediction of IR in Non-DM participants diagnosed using a glucose clamp was 22.7 [8]. The American Diabetes Association recently recommended that testing for diabetes should be considered for all Asian American adults who present with a BMI of 23 [9].

The most precise method for assessing IR is the hyperinsulinemic-euglycemic clamp test; however, this test is very complicated [10]. Instead, the homeostasis model assessment for insulin resistance (HOMA-IR) is widely used in clinical practice and in clinical studies [11]. However, the reliability of HOMA-IR is limited in the patients with low BMI values, decreased β cell function, and/or high fasting glucose levels [12]. Since Asian and Japanese patients often have decreased beta-cell function, a clamp study is required for accurate evaluation of IR in these populations [13].

Several cross-sectional studies documented an independent association between the IR and subclinical or clinical cardiovascular disease (CVD) in both nondiabetic [14, 15] and the diabetic subjects [16, 17]. The role of IR in the onset of hypertension remains controversial. Nonetheless, it has been postulated that a resistant state may lead to hypertension due to the failure of the nitric oxide-mediated vasodilator activity of the insulin hormone on endothelial cells [18]. The severity of IR might differ between Japanese and Caucasians, and heterogeneity in ethnicity might contribute to difference in the degree of IR in many ethnic groups. One of the reasons might be the difference in BMI among the study groups. It is not justifiable to directly compare these studies when HOMA-IR reference limits are not determined by a standardized procedure. In Japanese subjects, HOMA-IR $\geq$ 2.5 can be considered a reasonable indicator of IR [19].

South Asian children are 14 times more riskier for T2DM than in white European children and boys are less affected than girls [20, 21]. South Asian adults are at increased risk of developing T2DM as well as are more insulin resistant. They have an increased level of body fat and visceral fat deposition [22, 24]. However, the relationship between IR and fat distribution in childhood and adolescence is not clear. In obese children and adolescents but not in lean adolescents, a strong relationship between IR and visceral fat has been demonstrated in whom subcutaneous (SC) fat may be more important [25, 26]. The Early Bird study of pre-pubertal white European children found that 5-year-old girls were more insulin resistant than boys, but it is unclear what role adiposity plays at this age [27]. In adults, male body fat pattern with greater central and upper body fat is associated with greater metabolic risk, whereas a female fat distribution with relatively more fat in the hip and thigh regions is associated with lower metabolic risk [28]. Sex differences in body fat distribution has been established in pre-pubertal children in different ethnicities, highlighting the importance of ethnic-specific studies. Whether Ethnic and sex differences in body composition play a role in determining IR and metabolic risk in childhood is still not well established [22, 29, 30].

In obese, insulin resistant or T2DM patients protein and amino acid metabolism are dysregulated [31, 33], however, the extent to which this contributes to IR in normal-weight individuals is not fully elucidated. A number of circulating hormones, lipids, amino acids and inflammatory directly contribute to IR in these cases [34].

Though the robust tool for assessment of IR is the 'Homeostasis Model Assessment of Insulin Resistance' (HOMA-IR) [35, 36], there is great variability in the threshold HOMA-IR levels to define IR. Establishing cut-off values of HOMA-IR for the diagnosis of IR had been studied in different geographic areas [37, 43].

IR at any given degree of obesity accentuates the risk of CHD and type 2 diabetes [44]. BMI in proportionate to abdominal fat [45] is one of the main risk factors for T2DM and prediabetes [46]. β cell dysfunction is evident in T2DM East Asians, immediately after ingestion of glucose or mixed meals even though they are less obese compared to Caucasians. Insulin sensitivity is more in South Asian adolescents with higher fasting insulin levels than European adolescents. Measurement of HOMA, being, simpler, quicker, cost effective and more acceptable to children, making it ideal for larger studies [47, 48].

For several medical conditions, including IR and metabolic disease obesity is a significant risk factor [49]. Lim *et al*. in a recent paper showed that obesity, measured either by BMI or body fat percentage, is significantly correlated with IR, when calculated using homeostatic model assessment (HOMA-IR) levels [50]. BMI as a risk factor for the development of type 2 diabetes has a linear relationship [51].

The BMI has high specificity for predicting high body fat percentage [52], however, several researchers have found that BMI has low sensitivity for predicting body fat percentage [53, 54]. To resolve issues associated with use of BMI to grade overweight and obesity, the concept of normal weight obesity (NWO), a condition in which individuals are classified as normal weight by BMI, but have excess body fat has been emerged. NWO, a good predictor of IR, has been associated with metabolic dysregulation [55]. physical impairment [56], and cardiovascular mortality [57], Romero-Corral *et al*. showed that adults with NWO have four-fold higher prevalence of metabolic syndrome and insulin sensitivity tends to decrease as body fat percentage increases [58, 60].

2. Materials and methods

The study was both retrospective and prospective which was conducted at Believers church medical college hospital, Thiruvalla. This study was approved by the Institutional Ethical Committee and patient consent was also taken. The study was

conducted in 72 subjects for a duration of 2 years (July 2017 to October 2019).

Inclusion Criteria

Patients with features of obesity and clinical features of IR acanthosis nigricans and reactive hypoglycemia. Impaired fasting glucose with HbA_{1c} more than 5.6 % of all age group of either sex were included in the study.

Exclusion Criteria

Diabetes patients on OHA and insulin were excluded from the study.

Demographic data was obtained from the computerized database. The HOMA IR and β cell (%) is calculated using the fasting insulin and fasting plasma glucose levels. The fasting insulin is measured using Chemiluminescence (CLIA) assay. (Snibe Maglumi 2000 plus, China). The fasting glucose is measured using the Hexokinase Enzymatic method (Beckman Coulter AU 480, USA). The calculated values are IR index and β cell (%).

The following equation is used:

$$HOMA\ IR = [glucose(mg/dL) * Insulin(\mu U/L)]/405$$

$$HOMA\ \beta\ Cell(\%) = 360 * insulin\ value(\mu U/L)/[glucose(mg/dL) - 63]$$

The groups were compared using the t test statistic and the Pearson correlation. A p value ≤0.05 is considered as statistically significant. Minitab 17 was used for statistical evaluation.

3. Results & Discussion

The study was conducted in 72 subjects, of which 28 (39%) were female and 44 (61%) were male. The average age of the female subjects were 38 years (38.3 ± 15.5) and male 44 years (44.1 ± 11.4). There was no difference in age between the two gender groups (t=-1.7, p=0.096) (Table 2)

Table 2: Comparison of mean of age between the male and female subjects

Gender	N (%)	Mean	StDev	SE Mean	t Value	p Value
FEMALE	28 (38.9)	38.3	15.5	2.9	-1.7	0.096
MALE	44 (61.1)	44.0	11.4	1.7		
Test used: t test, N: Total count, StDev: Standard deviation, SE: Standard error, p: Level of significance.						

The plot depicts there is negative correlation between the HOMA IR and BMI (r=-0.025, p=0.833) similarly insulin and BMI are negatively correlated(r=-0.048, p=0.688) and were not significant, in contrast there is a significant positive correlation between insulin and HOMA IR (r=0.285, p=0.015). β Cell percentage has a significant positive correlation with BMI (r=0.244, p=0.039), HOMA IR (r=0.501, p<0.01) and Insulin (r=0.219, p=0.065) (Table 3).

Table 3: Correlations of BMI, HOMA IR, Insulin and β cell mass (%)

Parameter 1	Parameter 2	Correlation	95% CI for ρ	P-Value
HOMA IR	BMI	-0.025	(-0.255, 0.208)	0.833
Insulin	BMI	-0.048	(-0.277, 0.186)	0.688
β cell Mass (%)	BMI	0.244	(0.013, 0.450)	0.039
Insulin	HOMA IR	0.285	(0.057, 0.485)	0.015
β cell Mass (%)	HOMA IR	0.501	(0.305, 0.656)	0.000
β cell Mass (%)	Insulin	0.219	(-0.014, 0.429)	0.065

The average height of female subjects was 158 cm (157.57 ± 6.12) and the average height of male subjects was found to be 170 cm (169.94 ± 7.54). The mean height was statistically different in the two gender groups (t=-7.63, *p*=<0.001). The average weight of female subjects was evaluated to be 75 kg (74.78 ± 12.03) whereas the average weight of male subjects was evaluated to be 84 kg (83.90 ±14.54) which was statistically different (t=-2.89, *p*=<0.01). The plot of BMI depicts the average BMI of female subjects to be 30 (30.11 ± 5.14) similarly the average BMI of male subjects was evaluated to be 29 (29.05 ± 3.68). There is no statistical difference between BMI of two gender groups (t=0.95, *p*=0.345) (Table 4).

Table 4: Comparison of Height, Weight and BMI between female and male subjects

Variable	Sex:	Count	Percent	Mean	StDev	t test	p value
Height (cm)	FEMALE	28	38.89	157.57	6.12	-7.63	<0.001
	MALE	44	61.1	169.94	7.54		
Weight (Kg)	FEMALE	28	38.89	74.78	12.03	-2.89	<0.01
	MALE	44	61.1	83.90	14.54		
BMI	FEMALE	28	38.89	30.111	5.139	0.95	0.345
	MALE	44	61.1	29.048	3.682		
Test used; t test. N: number of subjects, SE: standard error: StDev: standard deviation.							

The average HOMA IR had no significant difference between the female 6.9 (6.86 ± 5.75) and male 6.5 (6.52 ± 5.22) subjects. The case was the same for Insulin among female subjects 34 (33.97 ± 46.24) and male subjects 28 (27.62 ± 29.86). Similar situation was noted in case of β cell mass (%) female subjects had an average value of 41 (41.42 ± 26.96) and in male subjects 39 (38.87 ± 20.62). (Table 5).

Table 5: Comparison of HOMA IR, Insulin and β cell mass (%) by gender.

Variable	Sex	Count	Percent	Mean	StDev	T test	P value
HOMA IR	FEMALE	28	38.9	6.86	5.75	0.025	0.8
	MALE	44	61.1	6.517	5.223		
Insulin	FEMALE	28	38.9	33.97	46.24	0.65	0.522
	MALE	44	61.1	27.62	29.86		
β Cell Mass (%)	FEMALE	28	38.9	41.42	26.96	0.43	0.672
	MALE	44	61.1	38.87	20.62		
Test used; T test. N: number of subjects, SE: standard error: StDev: standard deviation, P; level of Significance							

Results of studies done by Tsuyoshi Okura. *et al*, [8] Martinez K *et al*, [59] suggest that BMI is an important factor in determining IR. The points discussed in these studies were that the increase in the BMI is an important factor for the increasing IR. According to our results, the average BMI of female patients were found to be 30 whereas in male patients it was found to be 29. We could also find out that there is a negative correlation between the BMI and IR which is slightly contradictory to the traditional fact that BMI and IR have a positive correlation.

Apart from that we could also suggest that the visceral fat is a marker for the IR. Studies done by Banerji MA *et al*, [23] and Sarah Ehtisham *et al*, [24] points out that increase in the visceral fat leads to increase in the IR. They also found that two third of these non-obese men were Insulin resistant [23]. The points to be noted are that the visceral fat in lean BMI patients are found to be

increased that lead to increase in IR, which is slightly confusing to the fact that increase in BMI is the cause of increase in IR. HOMA of insulin sensitivity was linearly and inversely related with body fat percentage (r=-0.492, p<0.001).

Study conducted by Potts J *et al*, [22] draws our attention to the ground of waist/hip ratio and IR. This may be another factor that may suggest visceral fat can be the prime factor for IR in Type 2 DM patients. Study done by J. Gomez-Ambrosi *et al*, [54] notes that the relation between body fat percentage can be a more determinant factor than BMI for estimating IR. These studies support the fact that BMI is not related to IR and hence supports our study.

Madeira *et al*, [60] investigated NWO and its relationship with IR, found that the presence of NWO, was correlated with low insulin sensitivity compared to those of a normal weight with high body fat (OR=3.81, p=0.003).

Studies done by Lillioja S *et al*, [61] and Haffner SM *et al*, [62] reported that there is an inverse correlation between insulin secretion and IR which is not in agreement with our current findings. The results obtained in our study shows that the insulin secretion and HOMA IR have a significant positive correlation (r= 0.285, p=0.015)

Study conducted by Yoon. K.H *et al*, [63] shows a correlation between the volume of β cells and BMI in diabetic patients whereas a study conducted by Chung. O. K *et al*, [64] reports that the increase in the BMI may be positively correlated to the deterioration of the β cells. Our results show that BMI and β cell mass (%) are positively and significantly correlated (r=0.244, p=0.039). A comparison of β cell mass (%) between the female and male patients were also done, the values obtained were 41 and 38 respectively and was statistically not different.

A study conducted by Moller JB et. al,[48] reports that the IR may be associated with the defect in the β cell. According to our study reports there is a highly significant positive correlation between β cell mass (%) and HOMA IR, (r= 0.501, p<0.001) which was in accordance with findings of Moller JB *et al*.

4. Conclusions

In Asian population the earlier knowledge of correlation between BMI and IR could not be established in our study and this may be due to the relationship of IR with visceral fat and ethnicity. Further detailed studies may be required to evaluate the precise correlation between the β cell mass, BMI, insulin secretion and IR.

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