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Original Article

Internal Medicine Section

Comparison of Insulin Resistance in Lean and Obese Adults with Type 2 Diabetes Mellitus- A Cross-sectional Study

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ABSTRACT

Introduction: Insulin Resistance (IR) can develop into type 2 diabetes mellitus and is closely associated with obesity. However, the non-obese population has also shown a predisposition to the risk of IR due to genetics.

Aim: To assess the relationship between IR and obesity in Type 2 Diabetes Mellitus (T2DM) by comparing the proportion of subjects with IR in lean and obese T2DM and to identify the factors predicting IR in T2DM.

Materials and Methods: A cross-sectional, hospital-based study was done at Department of Medicine of RL Jalappa hospital, Kolar, Karnataka on 106 T2DM patients aged >18 years. The study population was grouped into lean (BMI <19 kg/m^2) and obese adults (BMI >30 kg/m^2). IR was calculated using Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) and was considered as primary outcome variable. Obesity was considered as primary explanatory variable. Age, Gender, fasting insulin, C-peptide, Fasting Blood Sugar, Glycated haemoglobin (GHB or HbA1c) were the other explanatory variables. Descriptive analysis was carried out using mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Chi-square test was used to test statistical significance between the groups. Univariate logistic regression analysis was done to identify the predictors of IR. IBM Statistical Package for Social Sciences (SPSS) version 22 was used for statistical analysis. The p-value <0.05 was considered to be statistically significant.

Results: The 106 subjects involved in the study had a mean age of 53.88±9.21 years. 44 subjects (41.5%) had IR. Obese to lean diabetic patients were in the ratio of 1:4. The proportion of obese diabetic subjects was (n=84, 79.2%) whereas lean diabetics were (n=22, 20.8%). The proportion of obese diabetic subjects with IR was 38.1% while the proportion of lean diabetic subjects with IR was 54.55%, but this difference was statistically not significant (p=0.163). On univariate logistic regression analysis, fasting insulin (odds ratio of 2.442 with 95% CI of 1.665 to 3.851, p<0.001**) and C-peptide (odds ratio of 1.446 with 95% CI of 1.123, p=0.004) were statistically significant factors attributing to IR.

Conclusion: There was no significant relationship between IR and obesity. IR was independently associated with Fasting insulin levels and C-peptide levels.

Keywords: Body mass index, C-peptide, Fasting insulin, Glycated haemoglobin, Homeostasis model assessment, Metabolic syndrome

INTRODUCTION

The DM is characterised by a pathological condition called IR in which cells fail to respond normally to the hormone insulin [1]. IR occurs due to an imbalance in the glucose metabolism causing less sensitivity of adipose, muscles, liver and other body tissues to insulin, in spite of blood insulin levels being normal or above in concentration [1]. The initial event of glucose-stimulated insulin secretion is glucose sensing. The glucose transporter 2 (GLUT2) and glucokinase (GK) are important regulatory molecules which modulate glucose homeostasis. Impairment in glucose sensing is associated with pancreatic beta cell dysfunction. Therefore, it is necessary to maintain adequate expression levels of GLUT2 and GK to ensure normal β-cell function [2]. The prime culprit of IR is obesity, which has reached epidemic proportions worldwide, because of improved life quality and ever-increasing inactive lifestyles, the prevalence of obesity increased dramatically over the past decade in India [3].

Globally, the epidemic of obesity has been assuming epidemic proportions. The prevalence of obesity has increased by 3 times compared to 1975 according to World Health Organisation (WHO) [4]. In adults aged more than 18 years, 39% were overweight and the prevalence of obesity was 13% according to WHO [4]. Lean type 2 diabetes is an emerging entity and it differs largely from classical obesity related T2DM [5]. The term "Lean diabetes" is used to describe Diabetic patients with Body Mass Index (BMI) value of less than 19 kg/m^2 or BMI in the normal range (lean diabetic patients) whereas those diabetic subjects with BMI more than 30 kg/m^2 are categorised as obese diabetic patients [5,6].

Previous studies have also indicated that with subcutaneous fat, visceral fat accumulation, more pro-atherogenic and pro-inflammatory factors are released, leading to the exacerbation of IR and oxidative stress and henceforth contributing to Cardiovascular Diseases (CVD) [7,8]. Increased high fat accumulation is commonly related to an elevated risk of the development of diseases, such as hypertension, dyslipidaemia, and DM, arterial hypertension, hypercholesterolemia, obesity, and hypertriglyceridemia [9].

Developing countries like India are witnessing a gradual rise in the frequency of obesity in recent decades [10,11]. However, IR does not develop in all obese persons, and genetic background backs strongly to IR, even in non-obese persons [12,13]. IR is an important therapeutic target for oral anti-diabetic drugs. Hence, the present study was carried out to compare the proportion of subjects with IR in lean and obese T2DM and identify the factors significantly contributing to IR in T2DM.

MATERIALS AND METHODS

This was a cross-sectional, hospital-based study conducted in the Department of General Medicine at RL Jalappa hospital, Kolar, studied for a period of 1.5 years after obtaining Institutional Ethical Clearance (IEC no. SDUMC/KLR/IEC/12/2017-18 Dated: 29.11.2017). All lean and obese type 2 diabetic patients presenting to Medicine Department of RL Jalappa Hospital were considered

as study population. Prevalence of IR was assumed as 50% and an absolute error of 5 was taken. Z alpha value at 95% confidence interval is 1.96. From this calculation, a sample size of 106 was obtained and the ratio of lean and obese diabetic patients was taken as 1:4 for convenience based on the pilot study.

Inclusion criteria: Patients more than 18 years of age with T2DM and willing to sign the informed consent were included in the study.

Exclusion criteria: Known cases of thyroid, pituitary or adrenal disorders and on medication with beta agonists, thiazides, hydantoins and steroids were excluded from the study.

The participants were divided into age groups of <40, 41 to 50, 51 to 60 and above 60 years for distribution of subjects age-wise as the number of diabetic subjects aged less than 40 years were fewer. BMI was calculated by dividing weight in kilograms by height in meter square. WHO criteria was used for classifying BMI [14]. Height was measured with the help of stadiometer. Weight was measured with the help of digital weighing scale after removing all the outer clothing. All the measurements were taken twice, and the average was taken for data entry. Diabetic patients with BMI value of less than 19 kg/m^2 were categorised as group 1 (lean diabetic patients) and those with BMI more than 30 kg/m^2 were categorised as group 2 (obese diabetic patients) [5,6]. Laboratory investigations included glycated haemoglobin, fasting insulin level; fasting glucose level and C-peptide level in plasma were measured. IR of patients was calculated in both groups using HOMA-IR [15,16]. It is a simpler way to estimate insulin sensitivity. It is a simple mathematical model which can estimate individual's insulin sensitivity and beta cell function from simultaneous measurements of fasting insulin and fasting plasma glucose. HOMA-IR index is calculated by multiplying fasting insulin concentration with fasting glucose concentration and then dividing by 22.5 [17]. Based on a study by Gayoso-Diz P et al., the present HOMA cut-off point for diagnosis of IR was taken as 2.77 in this study [18]. Fasting C-peptide and fasting insulin levels were measured using chemiluminescence. Normal Fasting C-peptide levels were taken as 0.81 to 3.85 ng/mL [17]. Normal Fasting insulin levels were taken as 3 to 25 mU/L [19].

STATISTICAL ANALYSIS

Descriptive data was expressed as mean and standard deviation for quantitative variables and frequency and proportion for categorical variables. IR was considered as the primary outcome variable. Obesity was considered as Primary explanatory variable. Age, Gender, fasting insulin, C-peptide, Fasting Blood Sugar and (GHB or HbA1c) were considered as other explanatory variables. The crosstabs procedure was used to create contingency tables to test the association between explanatory variables and categorical outcomes and compare percentages. Odds ratio along with 95% CI was presented. Chi square test was employed to determine statistical significance. The p-value <0.05 was considered statistically significant. Univariate logistic regression analysis was done to identify the statistically significant factors contributing independently to IR. Statistical analysis was carried out using IBM SPSS version 22. The test hypotheses stated that there is no significant difference in the proportion of subjects with IR between lean and obese T2DM; and obesity measured in terms of BMI, is an independent predictor of IR in T2DM.

RESULTS

The ratio of lean and obese diabetic patients was 1:4. The mean age was 53.88±9.21 years in the study population with a range of 32 to 70 years (95% CI 52.10 to 55.65 years). Among the study population, 65 (61.3%) were participants males and remaining 41 (38.7%) participants were females. The mean BMI was 29.27±5.84 kg/m^2 in the study population, with a range of 17.90 to 38 kg/m^2 [Table/Fig-1].

The mean GHB was 9.25±2.96 (mmol/mol) in the study population, ranged between 4.80 to 18.80 (95% CI 8.68 to 9.82). The mean

Parameter	Mean±SD or n (%)
Age (years)	53.88±9.21
BMI (kg/m^2)	29.27±5.84 (Range 17.9 to 38)
Gender	
Male	65 (61.3%)
Female	41 (38.7%)
Lean/Obese Diabetes	
Lean	22 (20.8%)
Obese	84 (79.2%)
Insulin Resistance (IR)	
Yes	44 (41.5%)
No	62 (58.5%)

[Table/Fig-1]: Descriptive analysis of lean/obese diabetes in the study population (N=106).

FBS was 8.58±2.22 mmol/L in the study population, ranged between 3.90 to 14.40 (95% CI 8.15 to 9.01). The mean fasting insulin was 7.34±7.26 (mIU/L) in the study population, ranged between 1 to 33.10 (95% CI 5.95 to 8.74). The mean C-peptide was 1.87±2.15 ng/mL in the study population, ranged between 0.05 to 14.40 (95% CI 1.46 to 2.28). The mean Homa-IR was 2.56±2.09 in the study population, ranged between 0.27 to 7.56 (95% CI 2.15 to 2.96) [Table/Fig-2].

Parameter	Mean±SD	Median	Minimum	Maximum	95% CI	
					Lower	Upper
GHB (mmol/mol)	9.25±2.96	8.40	4.80	18.80	8.68	9.82
FBS (mmol/L)	8.58±2.22	8.30	3.90	14.40	8.15	9.01
Fasting Insulin (mIU/L)	7.34±7.26	5.05	1.00	33.10	5.95	8.74
C-Peptide (ng/mL)	1.87±2.15	1.22	0.05	14.40	1.46	2.28
Homa-IR (index)	2.56±2.09	1.87	0.27	7.56	2.15	2.96

[Table/Fig-2]: Descriptive analysis of parameters in the study population (N=106). GHB: Glycated haemoglobin (HbA1c); FBS: Fasting blood sugar

The distribution of subjects in different age groups across lean and obese diabetes groups was statistically not significant with a p-value of 0.319. The gender distribution of subjects across lean and obese diabetes groups was statistically not significant with a p-value of 0.809. There was no significant difference in proportion of subjects with IR across lean and obese diabetes groups with a p-value of 0.163 [Table/Fig-3].

Parameter	Lean/Obese diabetes as n (%)		Chi-square	p-value
	Lean (N=22)	Obese (N=84)		
Age group (in years)				
≤40	4 (18.18%)	8 (9.52%)	3.513	0.319
41 To 50	4 (18.18%)	25 (29.76%)		
51 To 60	6 (27.27%)	31 (36.9%)		
>60	8 (36.36%)	20 (23.81%)		
Gender				
Male	13 (59.09%)	52 (61.9%)	0.058	0.809
Female	9 (40.91%)	32 (38.1%)		
Insulin Resistance (IR)				
Yes	12 (54.55%)	32 (38.1%)	1.943	0.163
No	10 (45.45%)	52 (61.9%)		

[Table/Fig-3]: Comparison of demographic characteristics and IR between lean/obese diabetes (N=106).

On univariate logistic regression analysis, the factors which showed statistically significant independent association with IR were fasting insulin and C-peptide levels [Table/Fig-4].

Factor	Unadjusted odds ratio	95 % CI of odds ratio		p-value
		Lower	Upper	
Age group (Base line ≥60)				
≤40	0.600	0.131	2.738	0.510
41 to 50	1.462	0.504	4.240	0.484
51 to 60	1.705	0.623	4.666	0.299
Lean (baseline=Obese)	1.950	0.756	5.031	0.167
Male (baseline=female)	1.653	0.736	3.712	0.223
GHB	1.036	0.909	1.181	0.594
FBS	1.049	0.881	1.249	0.592
Fasting insulin	2.442	1.665	3.581	**<0.001****
C-peptide	1.446	1.123	1.861	**0.004***

[Table/Fig-4]: Factors associated with IR in study population univariate logistic regression analysis.
p<0.05 *Statistically significant
p<0.001 **Statistically highly significant
GHB: Glycated haemoglobin (HbA1c); FBS: Fasting blood sugar; C-peptide: Connecting peptide; IR: Insulin resistance

DISCUSSION

In this era of global pandemic of DM, India has grown to be one of the major epicentres of DM. With development in technology and medicine, contributing to increased longevity and decreased physical activity, there is an alarming increase in the prevalence of DM over the past few decades [20,21]. In Asian Indians, there is an increasing trend of T2DM being characterised by an early onset at younger age groups and at relatively lower levels of BMI [22]. The major key abnormality in this group of patients seems to be the development of IR [23,24]. The present study was aimed to assess IR in lean and obese adults with T2DM. In this study, it was found that there was higher proportion of obese males compared to lean males and IR was seen predominantly in lean adults compared to obese adults. Till date, is has still not been clearly established whether hyperinsulinemia leads to insulin resistance, which is closely associated with the pathogenesis of obesity-associated type 2 diabetes, due to the complex regulatory mechanisms taking place in the peripheral systems and the brain [25].

The present study found a significant association of fasting insulin and C-peptide levels with IR, but among both lean and obese type 2 diabetic patients. In patients with T2DM, the major factor in maintaining optimal glycaemic control is residual β-cell function [26]. It was also observed by Anoop S et al., in their study that fasting insulin levels, C-peptide levels, IR levels were significantly higher in non-lean, non-obese diabetics compared to their controls. They also observed a significant correlation (r=0.4) between higher fasting levels of C-peptide and HOMA-IR (p<0.001) [27]. Gonzalez-Cantero J et al., in their study observed that compared to overweight subjects without Non-alcoholic Fatty Liver Disease (NAFLD), lean NAFLD subjects had higher HOMA-IR which was statistically significant (p<0.001) [28]. They also observed that IR was associated independently with NAFLD but there was no association with BMI [Table/Fig-5] [28].

Over the years, high levels of C-peptide has been studied as a useful marker for metabolic syndrome, death due to cardiovascular complications and IR among various races [29,30]. A study by Anoop S et al., was the first study which correlated C-peptide and fasting Insulin in non-obese and nonlean type 2 diabetic patients among North Indians [27]. They found high C-peptide levels in normal BMI patients with Type 2 diabetes among North Indian population. The present study has also found significant association of fasting insulin and C-peptide, but among both lean and obese type 2 diabetic patients. The C-peptide levels and fasting insulin showed no statistical difference among lean and obese groups. Further from past literature, the non-obese diabetics can be characterised based on BMI and can be grouped into lean with BMI <19 kg/m^2 and non-lean and non-obese with BMI >19 Kg/m^2 [Table/Fig-5] [27]. The pathophysiology of diabetes type-2 has known to be associated with obesity, perhaps in

Author	Sample size	Predictors of insulin resistance (IR)
Present study	106-22 lean (BMI <19 kg/m^2) and 84 obese patients with T2DM (BMI >30 kg/m^2)	Fasting insulin (p<0.001) C-peptide (p=0.004)
Anoop S et al., [27]	87 Non-lean, non-obese (BMI >19 and <25 kg/m^2) Asian Indian patients with T2DM	Higher fasting C-peptide levels were correlated significantly with HOMA-IR (r=0.42, p<0.001)
Gonzalez-Cantero J et al., [28]	113 non-obese, nondiabetic individuals classified as overweight (BMI 25-29.9 kg/m^2) or lean (BMI 19.5-24.9 kg/m^2)	Hepatic triglycerides (p<0.01) NAFLD (p<0.05)

[Table/Fig-5]: Predictors of Insulin Resistance (HOMA-IR index) in various studies.
T2DM: Type 2 diabetes mellitus; BMI: Body mass index; C-peptide: Connecting peptide; HOMA-IR: Homeostatic model assessment-insulin resistance; NAFLD: Non-alcoholic fatty liver disease

lean and non-obese groups, the pathophysiology might differ. Several reasons for diabetes among lean population could be due to Late Onset of Auto Immune Diabetes (LADA), Maturity Onset Diabetes in Young (MODY), chronic calcific pancreatitis etc. A previous study on South Asian Indians showed that, lean type 2 diabetic population had normal levels of C-peptide, less serum insulin and were negative for autoimmune markers [10]. Lean individuals with type 2 diabetes especially among Indians have certain unique insulin kinetics, with different profile and enzymatic behaviour related to carbohydrate breakdown. Further these patients had less susceptibility for macrovascular disease [31]. A study by Misra A et al., witnessed increased body and abdominal fat in non-lean and non-obese Diabetic Indians [11]. Hence, these results reflect the disturbed metabolic condition in Indian racial group with BMI levels of non-obese group. Further the evidence was strengthened by Petersen KF et al., where they examined healthy young non-obese adults of five racial, which included Asian Indians too [32]. The authors found greater prevalence rate of IR among Indians compared to others. Other contributing factors such as triglycerides, pro-inflammatory markers were found higher among Asian Indians compared to the counterparts of the study [32]. Further when the results of studies by Petersen KF et al., and Tan VM et al., were observed, it was clearly evident that Asian Indians had greater resistance to insulin and inflammation of sub-clinical nature among non-obese Indians [32,33]. Although, Asian Indians had BMI levels of non-obese group, their body fat, waist circumference and triglycerides were higher. Non-obese Asian Indians are at more risk of developing diabetes compared to non-obese individuals from other races [34]. Other studies have shown greater volume of subcutaneous fat cells with IR and greater influx of free fatty acid among Indians with hyperactivity of genes related to inflammation [12,35]. The genetic association such as polymorphism in gene Palatin-Like Phospholipase-3 (PNPLA-3) and Peroxisome Proliferator-Activated Receptor Gamma (PPAR-g) has been found by few genetic studies [34].

Limitation(s)

The present study was limited by its descriptive design and cross-sectional nature. Causal association could not be established. The subjects were not chosen by random sampling and it was only a hospital-based study which could have contributed to the statistically inconclusive results. Other factors which define IR such as waist circumference, hepatic glycerides levels, NAFDL could not be included for the final analysis due to practical reasons. Further analytical large scale multi-centric studies are required to validate the results and make clinical recommendations.

CONCLUSION(S)

The IR is usually a precursor sign of T2DM. But there was no significant difference in proportion of subjects with respect to IR between lean and obese T2DM. Obesity measured in terms of BMI, is an independent predictor of IR in T2DM. But in this cross-sectional study on 106 subjects, during univariate logistic

regression analysis, the only independent predictors of IR were fasting insulin and C-peptide.

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