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Beta Cell Dysfunction, Insulin Resistance and Impaired Insulin Sensitivity in Obese Adolescents

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Abstract

Introduction: *Changes in food consumption and health habits that have developed over the last three decades, the prevalence of obesity in children and adolescents has increased in both developed and developing countries. This has led to a striking worldwide increase in the rate of type 2 diabetes mellitus in the adolescent age group.*

Materials and Methods: *In the present study, a total of sixty seven subjects were studied comprising of 36 obese adolescents (15 males, 21 females) and 31 (16 males, 15 females) apparently healthy normal weight adolescents of age group between 17-19 years. In all the subjects BMI, waist circumference, hip circumference was measured, GTT was done, and the serum concentrations of fasting glucose, 2 hr glucose and fasting insulin were estimated. Further HOMA-IR, GF/IF, QUICKI, HOMA%B were calculated.*

Results: *Increased insulin concentrations was observed in obese individuals (18.18±1.29) when compared to non obese individuals (9.41±3.19). Significantly higher HOMA-IR (3.97±2.61 vs 1.97±0.69) ($p<0.001$) and HOMA%B (269.32±147.02 vs 173.07±92.94) ($P<0.01$) were observed in obese individuals when compared to non obese individuals. GF/IF (6.31±3.25 vs 10.26±4.18) ($p<0.001$) and QUICKI (0.32±0.02 vs 0.35±0.02) ($p<0.001$) were significantly lower in cases when compared to controls. BMI was positively correlated with insulin resistance ($r= 0.536$, $p<0.001$) and negatively correlated with insulin sensitivity ($r=-0.545$, $p<0.001$) and both were found to be statistically significant. The odds of developing insulin resistance and impaired insulin sensitivity is 6.86 and 5.33 times respectively more in obese when compared to non obese individuals.*

Conclusion: *The results demonstrate that both insulin resistance and insulin sensitivity predict conversion to diabetes in obese adolescents. Improving insulin resistance may be crucial for the prevention of both type 2 diabetes and premature cardiovascular diseases in this young population at risk. Lifestyle measures have to be taken to improve IR.*

Keywords: *Beta cell dysfunction, type 2 DM, obesity, insulin resistance, impaired insulin sensitivity.*

Introduction

Fuelled by changes in food consumption and health habits that have evolved over the last three decades, the prevalence of obesity in children and adolescents has reached epidemic proportions in both developed and developing countries[1–3]. This has led to a striking worldwide increase in the rate of type 2 diabetes mellitus in the adolescent age group [4–6]. Changes in lifestyle, such as lack of exercise and consumption of a high-calorie diet,

have increased the global prevalence not only of diabetes but also of obesity. About 60% to 90% of cases of type 2 diabetes are related to obesity[7].

Obesity has become a serious public health concern affecting a significant portion of the population in countries like the US. Overall, among adults aged at least 20 yr in 1999-2002, 65.1 per cent were overweight and 30.4 per cent were obese. Among children aged 6 through 19 yr in 1999-2002, 31.0 per cent were overweight and 16.0 per cent were obese[8]. Asian countries are not immune to this phenomenon. For example, in China, the prevalence of overweight and obesity among children aged 7-9 yr increased from 1-2 per cent in 1985 to 17 per cent among girls and 25 per cent among boys in 2000 [9]. In the SEARCH study[10] the incidence rate (per 100,000 person-year) of type 2 diabetes among children and adolescents varies greatly by ethnicity, with the highest rates observed among youths aged 15–19 years in minority populations. In particular, the reported incidence rate was 49.4 for Native Americans, 22.7 for Asian/Pacific Islanders, 19.4 for African Americans, 17 for Hispanics, and 5.6 for non-Hispanic whites. Most of the earlier studies done in children and adolescents in India have reported prevalence based on international cut-off points[11-19], with a meta-analysis estimating the prevalence of overweight as 12.6% and obesity as 3.4%[20].Another multi centric study reported an overall prevalence of overweight/ obesity as 18.2%.[18]

Type 2 diabetes develops over a long period, and most, if not all, patients initially have impaired glucose tolerance, which is an intermediate stage in the natural history of type 2 diabetes [21] and predicts the risk of the development of diabetes [22] and cardiovascular disease[23].With appropriate changes in lifestyle, progression from impaired glucose tolerance to frank diabetes can be delayed or prevented[24,25]. Thus, great emphasis has recently been placed on the early detection of glucose intolerance in adolescents. Impaired glucose tolerance (IGT) is a state of altered glucose homeostasis associated with a high risk of progression to type 2 diabetes in adults [22] and children[26]. Progression to diabetes can be viewed as having definable stages characterized by changes in various metabolic parameters and β-cell function. At the very beginning, fasting plasma glucose levels increase from perfectly normal values of ~4.5 mmol/l (80 mg/dl) to higher values of 5.0 mmol/l (89 mg/dl). This change in glycemia would not be recognized as being clinically abnormal because it would fail to reach the official category of impaired fasting glucose (IFG; glucose level ≥5.6 mmol/l or 100 mg/dl) or impaired glucose tolerance (IGT; 2-h post glucose level of ≥7.8 mmol/l or 140 mg/dl) [27]. Those destined to develop diabetes then progress to the IFG or IGT range, where they may remain for years before developing frank diabetes. Although this progression is mostly discussed in the context of type 2 diabetes, very similar changes occur as type 1 diabetes unfolds.

Aims and Objectives

Aim: To study the Beta-cell dysfunction in adolescent population.

Objectives

1. To compare fasting plasma glucose, Oral Glucose Tolerance Test, plasma insulin in normal adolescents, over weight and obese adolescents.
2. To study insulin resistance, insulin sensitivity and pancreatic β-cell function by homeostatic model assessment in normal adolescents, over weight and obese adolescents.

Materials and Methods

An observational, case control study, Adolescents (normal, over weight and obese) aged 17 to 19 years were studied. The study was conducted from December 2015 to June 2017. With the approval of the ethical committee of the college, the present study was carried out in Department of Bio-Chemistry, Mediciti Institute of Medical Sciences, Ghanpur, Medchal, R.R Dist, Telangana. The study comprised of total sixty subjects (31 normal

adolescents and 37 over weight and obese adolescents). Medical college students studying first year of MBBS were selected. The students were addressed one day before collecting the samples. They were explained about the study and advised to fast overnight for 12hrs and to come in the morning to give the fasting samples and again second sample after giving 75gms of glucose.

Controls

- **Inclusion Criteria:** Healthy Adolescents with normal BMI (19 to 22.9) aged 17-19 years not taking any medications, non-smokers.
- **Exclusion Criteria:** Smokers, taking medications for diabetes mellitus (metformin, glitazones), hypertension, cardiovascular diseases, hypothyroi-dism and on lipid lowering drugs.

Cases

- **Inclusion Criteria:** Adolescents with BMI values between 23 to 23.9 (over weight) and those with a BMI 24 and above (obese).
- **Exclusion Criteria:** Smokers, taking medications for diabetes mellitus (metformin, glitazones), hypertension, cardiovascular diseases, hypothyroidism and on lipid lowering drugs.

Table 1: Definition of Terms

Parameter	Reference level	Source
Fasting glucose level (mg/dl)	Normal=60-100mg/dl Impaired Fasting Glucose =101-125mg/dl Diabetic > 125mg/dl	IDF [28]
Arterial Blood pressure (mm Hg)	Normal<120/80mm Hg Pre Hyper tension 121-130/81-90mm Hg Hyper tension > 130/90mm Hg	NCEP ATP III [29]
BM(Kg/m2)	Lean<19 Normal=19-22.9 Over Weight=23-23.9 Obese ≥24	WHO [30]
Fasting plasma insulin(µIU/ml)	Normal = 2- 25 µ IU/ml	TIETZ [31]
75 gms Oral Glucose Tolerance Test(mg/dl)	Impaired Glucose Tolerance: Fasting Plasma Glucose < 126mg/dl 2hour plasma Glucose 140-200mg/dl Type II Diabetes : Fasting plasma Glucose ≥ 126mg/dl 2hour plasma Glucose > 200mg/dl	ADA.

Study Protocol

Those who gave informed consent were interviewed. A Pre-structured interview questionnaire were used to collect the information on socio-demographic, past medical history, physical activity and diet history of the subject. The patients satisfying both inclusion and exclusion criteria were included in the study. Adolescents aged 17 to 19 years were included in this study. National committee for laboratory standards (NCCLS) Guidelines was followed for sample collection, handling and processing [32, 33]. 5ml of 12hour fasting venous sample were collected from all the subjects.

Blood sample handling: At the end of sample collection, 1ml of sample was immediately transferred in to sodium fluoride coated polystyrene tube and plasma was separated by centrifugation of the sample at ≥ 3000rpm for 3 min. Fasting plasma glucose was analysed in the sample within 2hrs. Remaining serum samples were allowed to clot adequately before centrifugation. Centrifugation of samples was done at ≥ 1000 xg for 15 to 20 minutes. Samples that have been stored at room temperature for longer than 8 hrs were not used. Separation of serum from the red blood cells before storage was done. The serum sample was appropriately

labelled and stored at -80 degree centigrade' s until batch analysis for insulin was done.

Measuring Parameters

Anthropometry: Height and weight was measured on the subjects in standing position. Height was measured using a stadiometer. Weight was recorded to the nearest 0.1 kg using a weighing scale. The weighing scales and the measuring tapes were calibrated periodically. BMI was calculated from the formula, BMI = weight (kg) / height^2 (m ^{2}). Waist and hip circumference was measured using a standard measuring tape to the nearest 0.1cm.

BP Measurement: Three measurements were taken at 3- 5 minute intervals with an oscillometric digital sphygmomanometer (model: Omron Hem 780 N3). The instrument was validated against trained examiners using a mercury sphygmomanometer [(34)]. Calibration was checked periodically. The first measurement was taken after sitting comfortably on a chair for > 5 min, with the left arm at the level of the heart resting on a table. The mean of the last two measurements was used for analysis. In case where the second and the third measurements did not coincide within 10mm Hg, a fourth measurement was taken and the mean of the two closest values was used for analysis.

Fasting Plasma Glucose: Glucose was assayed on Siemens Dimension Xpand plus clinical chemistry analyzer (automated analyzer) that employs the principle of Hexokinase- Glucose 6-phosphate Dehydrogenase method [(35)]. The inter assay coefficient of variation were 2.01% (level 1) and 4.13% (level 2) and were within acceptable limits.

Oral Glucose Tolerance Test: As per WHO recommendation the fasting and 2hour post glucose load samples of blood were collected for mini GTT. After collecting the fasting sample. Flavored glucose in a dose of 1.75 gm/kg of body weight (up to maximum of 75gm) was given orally and the blood sample was collected after 120 minutes for measurement of plasma glucose. Corresponding urine samples were collected.

Urine Glucose: Urine samples were tested for presence of glucose in urine by dipstick method (Siemens Multistix SG reagent strips for urine analysis).

Fasting Plasma Insulin: Insulin was assayed by using Insulin (IRI) kit manufactured by Siemens healthcare diagnostics on ADVIA centaur CP. The inter assay coefficient of variation were 4.3% (level2) and 7.2% (level 3) respectively. The intra assay coefficient of variation was 5.05% and were within acceptable limits.

Calculations: The gold standard methods for measuring insulin sensitivity and pancreatic β-cell function are the hyperinsulinemic–euglycemic clamp and hyperglycemic clamp, respectively [(36)]. However, because these procedures are invasive and labor-intensive, we used simple surrogate measures that have been shown to correlate with the clamp procedures [(37, 38)]. Insulin resistance was estimated by the homeostatic model assessment (HOMA-IR) [(39)], insulin sensitivity by the ratio of fasting glucose (GF) to fasting insulin (IF) (GF/IF), and the quantitative insulin sensitivity check index (QUICKI) [(40),] and pancreatic b-cell function by HOMA derived β-cell function (HOMA %B) [(39)].

All four values were derived from the fasting measurements. The calculations were as follows:

1) HOMA-IR=(fasting insulin (µU/ml)x fasting glucose (mmol/l)/22.5); insulin resistance was defined as HOMA-IR>2[(39)]
2) Insulin sensitivity: GF/IF in mg/dl for glucose and µU/ ml for insulin;
3) QUICKI = 1/[log (fasting insulin (µU/ ml)) + log (fasting glucose (mg/dl))]; impaired insulin sensitivity was defined as QUICKI< 0.339[(41)]
4) HOMA %B= 20xfasting insulin (µU/ml)/(fasting glucose (mmol/ L)-3.5); as reported by Matthews et al[(39).]

Data Analysis

i. The data was appropriately entered into MS - EXCEL sheet

ii. The data was checked for distribution; the means of parameters between the groups were compared and correlation was estimated between insulin resistance and other parameters on SPSS software (version 17.0).

iii. Descriptive statistics for all the parameters was computed. Unpaired student-t test to compare means that were distributed normally. ANOVA was done for comparison of more than two groups.

iv. A p – value <0.05 was considered statistically significant.

v. Multivariate logistic regression was performed using stata 12. Statistical software (stata, college station, Texas, USA)

Results

This case control study was done in the Dept of Biochemistry and the subjects included in the study were medical college students studying first year MBBS. A total of sixty seven subjects were registered in the study (thirty one males and thirty six females). Out of the sixty seven subjects, 36 were cases of overweight and obese adolescents (15 males, 21 females) and remaining 31(16 males, 15 females) were apparently healthy normal weight adolescents of age group between 17-19 years.

The study participants were divided into two groups based on BMI. (Table:2)

Group I (Cases) - Obese and over weight (n = 36)

Group II (Controls) -Normal weight (n = 31)

The study participants were divided into four groups based on BMI and sex. (Table:3)

Group I- Male obese and over weight (n = 15)

Group II- Female obese and over weight (n = 21)

Group III-Male normal weight (n = 16)

Group IV-Female normal weight (n = 15).

Table 2 : Demographic characteristics and biochemical parameters of the study groups (Mean ±SD)

Variables	Case(n=36) (Obese)	Control(n=31) (Non Obese)	Student's t-Test p-value
Age (years)	18.11±0.57	18.13±0.56	0.898
BMI (kg/m^2)	27.36±2.97	20.88±1.41	0.000***
Mean SBP (mm Hg)	117.5±4.39	114.83±5.08	0.024*
Mean DBP (mm Hg)	75.83±5.54	73.22±5.40	0.056
Waist circum ference(cms)	89.92±7.87	77.36±5.81	0.000***
Hip circum ference(cms)	105.8±9.47	92.76±7.06	0.000***
W:H ratio	0.85±0.05	0.83±0.04	0.149
Glucose fasting(mg/dl)	87.27±4.55	84.67±6.36	0.056
Glucose 2 hr(mg/dl)	109.72±14.35	105.48±23	0.362
Insulin fasting (µU/ml)	18.18±1.29	9.41±3.19	0.000***
HOMA IR	3.97±2.61	1.97±0.69	0.000***
GF/IF Insulin Sensitivity	6.31±3.25	10.26±4.18	0.000***
QUICKI	0.32±0.02	0.35±0.02	0.000***
HOMA % B	269.32±147.02	173.07±92.94	0.002**
Note: (*)=P<0.05 , (**)=P<0.01, (***)=P<0.001			

Table 3 : Demographic characteristics and biochemical parameters of the study sub groups (Mean ±SD)

Variables	GroupI(Male obese) (n = 15)	Group II(Female obese) (n = 21)	Group III(Male non obese) (n = 16)	Group IV(Female non obese) (n = 15)	ANOVA p-value
Age (years)	18±0.6	18±0.5	18±0.7	18±0.5	0.940
BMI (kg/m^2)	27.4±3.4	27.3±3.7	20.7±1.3	20.9±1.4	0.000***
Mean SBP (mm Hg)	118±4.1	117±4.6	116±5	113±4.9	0.041*
Mean DBP (mm Hg)	78±4	74±6	73±5	73±6	0.053
Waist circum ference(cms)	90.8±9.4	89±6.6	75.2±5.5	79.6±5.3	0.000***

Hip circum Ference (cms)	104±12.4	106.9±6.7	89.6±6.6	96±6.1	0.000***
W:H ratio	0.88±0.06	0.83±0.04	0.84±0.06	0.83±0.03	0.024*
Glucose fasting(mg/dl)	88.4±4.4	86.4±4.5	83.6±6	85.7±6	0.118
Glucose 2 hr(mg/dl)	105±7.6	113±17	101±20	110±26	0.220
Insulin fasting (µU/ml)	23.2±14.2	14.5±6.9	8.5±2.6	10.3±3.5	0.000***
HOMA IR	5.1±3.2	3.1±1.6	1.7±0.5	2.2±0.78	0.000***
GF/IF Insulin Sensitivity	4.9±2.2	7.2±3.5	10.9±4.2	9.4±4	0.000***
QUICKI	0.3±0.02	0.32±0.02	0.35±0.02	0.34±0.02	0.000***
HOMA % B	331±183	225±96	171±108	175±77.4	0.001**
Note: (*)=P<0.05 , (**)=P<0.01, (***)=P<0.001					

Odds ratio: We analysed the data using multivariate logistic regression for calculating the odds ratio. The BMI, waist circumference, hip circumference, W:H ratio were taken as independent variables. We assessed the association between these variables and insulin resistance and impaired insulin sensitivity by including one covariate at a time in separate logistic regression model (table: 4). We performed multivariate logistic regression to determine the independent effects of BMI, waist circumference, hip circumference, W:H ratio on each of the insulin resistance and impaired insulin sensitivity out comes. All the independent and dependent variables were dichotomised using the following cut off values.

Table 5: Cut off values

Parameter	Categorising levels
BMI (kg/m^2)	≥23
Waist circumference (cms)	>90 for males, >80 for females
Hip circumference (cms)	>105 for males, >108 for females
W:H ratio	>0.9 for males, >0.85 for females
HOMA-IRInsulin Resistance	>2
QUICKI-Impaired insulin sensitivity	<0.339

BMI: The odds of developing insulin resistance is 6.86 times more in obese individuals when compared to non obese individuals (P = 0.001). The odds of developing impaired insulin sensitivity is 5.33 times more in obese individuals when compared to non obese individuals (P =0.002).

Waist circumference: The odds of developing insulin resistance is 3.86, times more in obese individuals when compared to non obese individuals (P = 0.023) . The odds of developing impaired insulin sensitivity is 5.14times more in obese individuals when compared to non obese individuals (P =0.003).

Hip circumference: Hip circumference was not significant for insulin resistance (OR of 6.32, P =0.087) and was significant for impaired insulin sensitivity (OR of 5, P=0.047).

W: H ratio: W: H ratio was not significant for insulin resistance (OR of 1.088, P=0.889) and impaired insulin sensitivity (OR of 1.56, P=0.43).

Table 4: Results of multivariate logistic regression

	HOMA-IR Insulin Resistance		QUICKI Impaired insulin sensitivity	
	Odds ratio	P-value	Odds ratio	P-value
BMI (kg/m^2)	6.86	0.001	5.33	0.002
Waist circumference (cms)	3.86	0.023	5.14	0.003
Hip circumference (cms)	6.32	0.087	5	0.047
W:H Ratio	1.088	0.889	1.56	0.43

TABLE 6: Pearson's correlation coefficient (r value) of HOMA-IR with various parameters.		
Correlation of HOMA-IR with:	r- value	p-value
Age (years)	0.0137	P>0.05
BMI (kg/m^2)	0.536	P<0.001***
Waist circumference(cms)	0.459	P<0.001***
Hip circumference(cms)	0.383	P<0.01**
W;:H ratio	0.201	P>0.05
Mean SBP (mm Hg)	0.073	P>0.05
Mean DBP (mm Hg)	0.167	P>0.05
Glucose fasting(mg/dl)	0.408	P<0.001***
Glucose 2 hr(mg/dl)	0.058	P>0.05
Insulin fasting (µU/ml)	0.996	P<0.001***
GF/IF Insulin Sensitivity	-0.709	P<0.001***
QUICKI	-0.854	P<0.001***
HOMA % B	0.817	P<0.001***
Note: (*)=P<0.05 , (**)=P<0.01, (***)=P<0.001		

Table 7 : Pearson's correlation coefficient (r value) of INSULIN SENSITIVITY with various parameters		
Correlation of INSULIN SENSITIVITY with:	r- value	p-value
Age (years)	0.0984	P>0.05
BMI (kg/m^2)	-0.545	P<0.001***
Waist circumference(cms)	-0.475	P<0.001***
Hip circumference(cms)	-0.376	P<0.01**
W:H ratio	-0.232	P>0.05
Mean SBP (mm Hg)	-0.241	P<0.05*
Mean DBP (mm Hg)	-0.155	P>0.05
Glucose fasting(mg/dl)	-0.236	P>0.05
Glucose 2 hr(mg/dl)	-0.141	P>0.05
Insulin fasting (µU/ml)	-0.733	P<0.001***
HOMA IR	-0.709	P<0.001***
QUICKI	0.949	P<0.001***
HOMA % B	-0.737	P<0.001***
Note: (*)=P<0.05 , (**)=P<0.01, (***)=P<0.001		

Discussion

Obesity increases the risk of cardiovascular disease in adults and has been strongly associated with insulin resistance.[42,43] Several studies consistently demonstrated that hyperinsulinemia and insulin resistance are strong predictors of type 2 diabetes and are associated with adverse lipid and lipoprotein levels and prevalent atherosclerosis.[44] There is evidence that obesity in childhood increases the risk of onset of the metabolic syndrome in adulthood.[45]

Body Mass Index (kg/m^2): In the present study, body mass index was found to be significantly higher in obese individuals than non obese individuals (27.36±2.97 vs 20.88±1.41) (P<0.001). We found a negative correlation between BMI and insulin sensitivity and was found to be statistically significant (r=-0.545, p<0.001) (table: 7). A positive correlation was found between BMI and insulin resistance and was found to be statistically significant (r= 0.536, p<0.001) (table: 6). Garg et al[46] reported the same that obese individuals exhibited more insulin resistance and less insulin sensitivity than controls. They concluded that as obesity increases, so does the prevalence of the MS. In obese persons, excess adipose tissue releases varieties of factors including nonesterified fatty acids that predispose to ectopic fat accumulation in liver, muscle, and visceral adipose tissue stores. Ectopic fat links closely to risk factors and adversely affects beta-cell function through lipotoxicity. S

Shalitin et al[47] also concluded that obese children and adolescents are associated with increased insulin resistance. In their study high insulin resistance and insulin sensitivity was seen in obese males. Ranjana Sinha MD et al[48] found increased insulin resistance in IGT individuals compared to NGT individuals. Abu Kholdum Al Mahmood et al[49] reported that there was a significantly negative correlation between insulin sensitivity and BMI in non obese normolipidemic subjects. They did not find significant correlation between HOMA%B and BMI.

Blood pressure (mm Hg): In the present study a negative correlation between blood pressure and insulin sensitivity was observed, which was statistically significant for SBP(r=-0.241, p<0.05) and not significant for DBP(r=-0.155, p>0.05) (table:7). A positive correlation was observed between blood pressure and insulin resistance, which was not statistically significant. S Shalitin et al[47] reported that insulin resistance have significant positive association with blood pressure. MK Garg et al[46] also reported that insulin resistance was positively associated with blood pressure and was statistically significant. A negative association between insulin sensitivity and blood pressure was observed, in the study done by MK Garg et al[46] which was not statistically significant.

Waist circumference (cms): In the present study positive correlation of insulin resistance was found with waist circumference which was statistically significant (r=0.459, p<0.001) and negative correlation of insulin sensitivity was found with waist circumference which was statistically significant (r=-0.475, p<0.001). Carlos Lorenzo et al[50] also reported that insulin sensitivity was negatively correlated with waist circumference and was statistically significant. They also concluded that converters had higher waist circumference compared to non converters which was statistically significant. Fida Bacha et al [51] reported that there was no significant difference in waist circumference among the five groups (NGT, IFG, IGT, IFG/IGT, T2DMs). Abu Kholdum Al Mahmood et al[49] also reported that there was a negative correlation between insulin sensitivity and waist circumference which was satistically insignificant. They did not find significant correlation between HOMA%B and waist circumference.

Hip circumference (cms): The mean hip circumference levels were increased in obese (105.8±9.47cms) compared to non obese (92.76±7.06 cms) (P<0.001)(table 2,3).The correlation of hip circumference with insulin sensitivity was found to be negative and statistically significant(r=-0.376, p<0.001). There was a positive correlation of hip circumference with insulin resistance and found to be statistically significant (r=0.383, p<0.001). None of the studies discussed about hip circumference.

Waist: Hip ratio: In the present study insulin sensitivity was negatively correlated (r=-0.232, p>0.05) (table:7) and insulin resistance was positively correlated (r=0.201, p>0.05) (table: 6) with waist hip ratio, which were not statistically significant. MK Garg et al [46]also concluded that waist hip ratio was negatively associated with insulin sensitivity and positively associated with insulin resistance which were statistically significant. Hui-Qi Qu et al [52] also concluded that insulin resistance was positively correlated with waist hip ratio. Waist hip ratio contributes an additional independent effect, which emphasizes the important role of central fat distribution in the risk of insulin resistance [52]. Otto Tschritter, MD et al [53] concluded that waist hip ratio was more in IGT subjects compared to NGT subjects which was statistically significant.

Fasting and 2hr blood glucose (mg/dl): In the present study fasting glucose was negatively correlated with insulin sensitivity, which was not significant statistically (r=-0.236, p>0.05) and fasting glucose was positively correlated with insulin resistance, which showed statistical significance (r=0.408, p<0.001). 2 hr glucose was not significant statistically. In the present study fasting glucose values were higher in cases compared to controls, which was not statistically

significant (87.27±4.55 mg/dl vs 84.67±6.36 mg/dl) (P>0.05) (table:2). 2 hr glucose values were also higher in cases compared to controls but was not statistically significant. S Shalitin et al[47] observed that fasting glucose was high in IGT compared to NGT which was statistically significant. Our findings are, generally in concordance with many studies who similarly reported elevated glucose levels in obese individuals. Ranjana Sinha MD et al [48] concluded that fasting plasma glucose levels were similar in the children irrespective of whether their glucose tolerance was normal or impaired. In contrast, the adolescents with impaired glucose tolerance had higher fasting plasma glucose levels (90±1 mg per deciliter [5.0±0.06 mmol per liter]) than those with normal glucose tolerance (82±1 mg per deciliter [4.6±0.06 mmol per liter], P=0.03), and adolescents with type 2 diabetes had the highest fasting plasma glucose levels (118±6 mg per deciliter [6.6±0.33 mmol per liter], P<0.001). After the oral glucose-tolerance test, plasma glucose levels were higher in both children and adolescents with impaired glucose tolerance than in those with normal glucose tolerance and highest in subjects with frank diabetes (P<0.001).

Carlos Lorenzo et al[50]concluded that insulin sensitivity was negatively correlated to fasting and 2hr glucose, which was statistically significant. First phase insulin secretion (AIR) was also negatively correlated to fasting and 2hr glucose.

MK Garg et al [46] concluded that Subjects with IGT demonstrated more IR and had higher insulin than controls, but had similar insulin secretion. Subjects with T2DM had comparable insulin levels and higher HOMA-IR, but had significantly lower insulin secretion.

Insulin fasting (µU/ml): In the present study fasting insulin levels were higher in obese individuals compared to non obese individuals (18.18±1.29 vs 9.41±3.19), which was statistically significant (p<0.001). Our findings are in agreement with many studies who similarly reported increased fasting insulin levels in obese subjects. Our results are in consistent with MK Garg et al [46]who observed increased fasting insulin levels in obese cases compared to non obese controls. S Shalitin et al [47]who studied obese children and adolescents, reported increased insulin in IGT compared to NGT, which was not significant statistically. Ranjana Sinha MD et al [48] showed that in IGT children and adolescents fasting insulin levels were elevated compared to NGT children and adolescents, which was statistically significant. Carlos Lorenzo et al [50] concluded that fasting insulin levels were high in converters compared to non converters which was statistically significant.

HOMA IR (Insulin resistance): In the present study a negative correlation was observed with insulin resistance and insulin sensitivity which was statistically significant (r=-0.709 , p<0.001). In the present study the mean insulin resistance were increased in obese cases compared to non obese controls, which was statistically significant (3.97±2.61 vs 1.97±0.69) (p<0.001). The mean insulin resistance was comparatively higher in obese males compared to obese females, not much of difference was found in non obese groups. S Shalitin et al [47] concluded that insulin resistance was more in IGT compared to NGT subjects which was not significant statistically. They reported that patients with insulin resistance or impaired insulin sensitivity had a significantly higher prevalence of obesity complications than those with normal insulin resistance indexes. There did not find any difference for this factor by gender. The prevalence of insulin resistance was significantly higher in the patients in Tanner stages IV–V and II–III than in Tanner stage I for both genders. The HOMA-IR index did not show a significant increase during puberty. Accordingly, the subjects with insulin resistance were significantly older than those with HOMAIR ≤2, and they had a significantly higher BMI-SDS and significantly higher blood glucose and insulin levels after OGTT. They did not find a significant difference in HOMA-IR between the adolescent girls with and without PCO.

Ranjana Sinha MD et al[48] concluded that insulin resistance is increased in IGT children and adolescents compared to NGT children and adolescents, which was statistically significant. Studies have shown that insulin resistance increases with age. Abu Kholdum Al Mahmood et al[49] found that insulin resistance decreases with age. This study observed higher insulin resistance in yonger age group and decreases as age increases. This is not in concordance with other studies. MK Garg et al[46] concluded that subjects with MS exhibited more IR and secreted less insulin than controls, although plasma insulin levels were comparable in both groups. This further support the hypothesis that decrease in beta-cell function on the background of increased IR is the main determinant of progression to T2DM. Similar to our study, Ajjan et al[45]reported significantly higher HOMA-IR in 95 South Asian individuals with MS compared with controls. IR increased with increasing number of metabolic abnormalities. MK Garg et al[46] also reported that in univariate regression analysis, HOMA-IR was positively associated with BMI, body fat mass, and PBF, and negatively with basal metabolic rate, which was similar to reported by Snehlata et al in Indian young teenagers. Yiqing Song MD et al[54] concluded that women with diabetes had significantly higher levels of baseline fasting insulin, glucose, and HOMA-IR and lower HOMA-B than their matched control subjects.

None of the studies reported the odds ratio, in the present study the odds of developing insulin resistance is 6.86 times more in obese individuals when compared to non obese individuals(P = 0.001).

GF/IF (Insulin Sensitivity):

In the present study decreased levels of insulin sensitivity was observed in obese individuals (6.31±3.25) when compared to non obese (10.26±4.18), which was statistically significant (p<0.001). The correlation of insulin sensitivity with insulin resistance was found to be negative and statistically significant (r=-0.709 , p<0.001). Carlos Lorenzo et al[50] concluded that converters had decreased insulin sensitivity compared to non converters. They observed a negative correlation between insulin sensitivity and BMI which was in consistence with the present study. Abu Kholdum Al Mahmood et al[49] concluded that elderly can retain their insulin sensitivity if they maintain their BMI and lipid levels within limits.

Fida Bacha et al[51] concluded that for similar degrees of adiposity insulin sensitivity will not differ among the different prediabetic groups compared with youth with NGT but will be lower in youth with type 2 diabetes, whereas insulin secretion will be impaired in all categories of glucose dysregulation. Snehlata *et al* also found that insulin sensitivity was negatively associated with BMI, and positively with basal metabolic rate.

In the present study the odds of developing impaired insulin sensitivity is 5.33 times more in obese individuals when compared to non obese individuals (P =0.002).

There are few studies which have reported QUICKI and HOMA%B in obese adolescents.

QUICKI (Quantitative insulin sensitivity check index) :

In the present study decreased levels of QUICKI was observed in obese individuals (0.32±0.02) when compared to non obese individuals (0.35±0.02) (p<0.001). The correlation of QUICKI with insulin resistance was found to be negative and statistically significant(r=-0.854, p<0.001). There was a positive correlation of QUICKI with insulin sensitivity and found to be statistically significant(r=0.949, p<0.001). S Shalitin *et al*[47] concluded that decreased insulin sensitivity and impaired pancreatic b-cell function are the two main pathogenetic components of type 2 diabetes. In a cohort of obese children and adolescents, they found a high prevalence of insulin resistance, demonstrated by HOMA-IR or QUICKI. IGT was present in 13.5% of the patients.

HOMA % B (Pancreatic beta cell function):

In the present study increased level of HOMA%B was observed in obese (269.32±147.02) when compared to non obese (173.07±92.94) ($p<0.01$). The correlation of HOMA % B with insulin resistance was found to be positive and statistically significant($r=0.817$, $p<0.001$). There was a negative correlation of HOMA%B with insulin sensitivity and found to be statistically significant($r=-0.737$, $p<0.001$). HOMA%B was positively correlated to BMI, which was statistically significant this was in concordance with the work done by S Shalitin et al[47].

Conclusions

Insulin resistance is highly prevalent in obese children and adolescents. We found increased insulin levels and increased insulin resistance in obese males and females compared to non obese males and females. Our results of fasting insulin support the hypothesis that increased production of insulin is the primary compensatory mechanism for increased blood glucose levels in overweight and obese subjects.

I) Both fasting insulin and insulin resistance (HOMA-IR) was high in obese individuals compared to non obese individuals.

II) Insulin sensitivity (GF/IF) was decreased in obese individuals compared to non obese.

III) Impaired insulin sensitivity assessed by (QUICKI) was present in obese individuals compared to non obese.

IV) HOMA derived pancreatic beta cell function (HOMA %B) increased in obese individuals compared to non obese individuals.

V) The odds of developing insulin resistance is 6.86 times more in obese individuals when compared to non obese individuals.

VI) The odds of developing impaired insulin sensitivity is 5.33 times more in obese individuals when compared to non obese individuals.

In conclusion, this study suggests that insulin resistance, initially associated with hyperinsul-inemia, is the most important risk factor linked to the development of impaired glucose tolerance in obesity. In the presence of established diabetes, beta cell failure becomes fully manifest. Longitudinal studies are needed to identify the metabolic precursors and the natural history of the development of type 2 diabetes in these individuals.

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Abbreviations

S. No.	Serial number
S. ID.	Subjects identification
Yrs	Years
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
BMI	Body mass index
W:H	Wiast:Hip
Mm of Hg	Millimeters of mercury
mg/dl	Milligrams/deciliter
µU/ml	Micro units/milliliter
HOMA IR	Insulin resistance
GF/IF	Insulin sensitivity
QUICKI	Quantitative insulin sensitivity check index