International Journal Dental and Medical Sciences Research (IJDMSR)
ISSN: 2393-073X Volume 3, Issue 4 (April- 2019), PP 01-13
www.ijdmsr.com

Comparing Different Markers of Insulin Resistance in Pediatric Obesity

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ABSTRACT: A prospective study was conducted at the pediatric outpatient department to assess insulin resistance (IR) using the derived indices namely, homeostasis model assessment of insulin resistance(HOMA-IR), fasting insulin, fasting glucose –to-insulin ratio(FGIR) quantitative insulin-sensitivity check index(QUICKI) and McAuley index to define metabolic syndrome.Overweight and obese children between 10-18 years attending Pediatric outpatient department formed the study subjects. Cut-off point for indices of insulin resistance was assessed by fasting insulin, FGIR and other methods (HOMA model, QUICKI, McAuley index) to define metabolic syndrome.Among various parameters of insulin resistance (HOMA-IR, FGIR ,QUICKI and McAuley index), HOMA-IR≥2.5 had the highest sensitivity in diagnosing metabolic syndrome in overweight and obese children and adolescents .IFG had the highest specificity(99.3%). The ROC curve analysis using our study sample showed that the cut-off of **4.5** for HOMA-IR had 59.5 % sensitivity and 81%specificity. Among the derived indices, the area under the curve(AUC) was more for HOMA-IR(0.73) followed by QUICKI(0.265) as compared to FGIR(0.238) or McAuley index(0.145).HOMA-IR had emerged as a reliable diagnostic tool and it is found to be a stronger surrogate marker of IR when compared to FGIR,QUICKI and McAuley index in normoglycemic overweight and obese children.

Keywords:- Metabolic syndrome, HOMA-IR, FGIR,QUICKI , McAuley index

I. INTRODUCTION

Insulin resistance is characterized by a decreased capacity of insulin to stimulate glucose uptake in muscles and adipose tissue and suppress hepatic glucose production. Insulin resistance is found to play an important role in the development of metabolic syndrome(MetS) also known as syndrome X [1].Insulin resistance and concurrent fasting hyperinsulinemia short of type 2 diabetes mellitus are independently associated with metabolic syndrome(MetS) markers, including blood pressure elevation ,high triglycerides level and low high –density lipoprotein cholesterol(HDL-C)level [2],[3],[4],[5] and have also been linked to compromised brachial artery distensibility[6],hepatic steatosis[7] and polycystic ovary disease[8]. In youth with insulin resistance, fasting blood glucose levels often remain normal owing to compensatory hyperinsulinemia and adequate pancreatic beta-cell reserve. HOMA-IR has been validated against hyperinsulinemic euglycemic insulin clamp technique(gold standard) and against intravenous glucose tolerance tests in overweight youth and is also less time- consuming. The strength of the various indices in predicting IR to define metabolic syndrome was compared in our study.Other derived indices namely fasting insulin, fasting glucose-insulin ratio(FGIR), McAuley index and quantitative insulin sensitivity check index(QUICKI) have been frequently applied in screening populations[9],[10].Keeping in mind the increasing trend of pediatric obesity we estimated the prevalence of metabolic syndrome in a group of overweight and obese boys and girls attending our hospital, incorporating the derived indices of insulin resistance in the definition of metabolic syndrome to help in early diagnosis and intervention in the form of diet and lifestyle modification or pharmacological therapy.

II. METHODS AND MATERIALS

2.1. Study Design,Setting and Participants

It was a prospective study conducted between October 2012 and August 2014.The study participants included overweight and obese children between 10-18 years attending Pediatrics Outpatient Department.Cut-off point for indices of insulin resistance was assessed by fasting insulin, FGIR and other methods (HOMA model, QUICKI, McAuley index) to define metabolic syndrome. All overweight and obese children between 10-18 years attending the outpatient department, who underwent the medical screening for metabolic syndrome in childhood obesity were included in the study. The height and weight of all children was measured. Body mass index [BMI(calculated as weight in kilograms divided by height in meters squared)] adjusted for age and sex was plotted using the BMI-for –age charts 2007 WHO reference .Children with a BMI ≥85th percentile and <

95th percentile were classified as overweight and children with BMI ≥95th percentile were classified as obese[11].

2.2. Exclusion Criteria

2.2.1. Overweight and obese boys and girls between 10-18 years with any known metabolic disease (eg. Hypothyroidism, Diabetes mellitus).

2.2.2. Overweight and obese children between 10—18 years with weight gain associated with either any or all of the following including intake of antiseizure medications (eg.sodium valproate),intake of steroids (eg. cases of Nephrotic syndrome, malignancy, SLE),obesity in syndromic children eg. Down syndrome, Prader Willi syndrome, Lawrence Moon Biedl syndrome.

2.3. Anthropometric Measurements

Height was taken using the wall mounted measuring tape after removing the footwear with the subject standing erect with feet parallel:heel, buttocks, shoulders and occiput touching the wall, position of the head being comfortably erect with the lower border of orbit of the eye in the same horizontal plane as external ear canal and arms hanging loosely by the sides. Measurement was recorded to the nearest 0.5cm.Weight was recorded using the electronic weighing machine.Waist circumference for each child was measured with child standing ,without heavy outer garments and with empty pockets, using a non stretchable tape with an accuracy of 0.1cm.It was measured at the level midway between the lower rib margin and the iliac crest, at the umbilicus, with the child breathing out gently.

2.4. Blood Pressure Measurement

Blood pressure was measured using a standard mercury sphygmomanometer, after the subject had rested in the sitting position ,using the appropriate cuff size and phase 5 Korotkoff sounds were taken for diastolic blood pressure categorization. A minimum of 3 readings were taken and the lowest of the 3 readings was used for data analyses[12].

2.5. Metabolic Parameters

Venous blood samples were drawn after a 12-h fast and transported immediately to the laboratory where the serum was separated. Fasting blood glucose was measured using hexokinase method (Roche/Hitachi cobas C systems). Fasting insulin was assayed using electrochemiluminescence, "ECLIA" intended for use on Elecsys and cobase immunoassay analyzers. Total cholesterol, HDL-C, LDL-C and triglycerides levels were analyzed by enzymatic colorimetric assay using Roche/Hitachi cobas C systems which automatically calculate the analyte concentration of each sample. HOMA-IR was calculated as the fasting blood glucose level (in milligrams per deciliter) times the fasting insulin level (in microinternational units per milliliter), divided by 405[13].FGIR was calculated as fasting plasma glucose/serum insulin ratio.QUICKI was calculated as 1/[log fasting insulin(uIU/mL)+log fasting glucose(mg/dL)] .McAuley index was calculated as exp [2.63-0.28ln(fasting insulin in uU/mL)-0.31ln(fasting triglyceride in mmol/L)] (conversion factor for fasting triglyceride levels, mg/dL to mmol/L multiply by 0.01129)

2.6. Definitions

2.6.1. Parental Obesity

When either one or both the parents had a body mass index ≥30kg/m2 a positive history of parental obesity was considered[14].

2.6.2. Hypertension

Hypertension was defined as average SBP and/or DBP that was ≥ the 95th percentile for sex, age, and height on three or more occasions.Prehypertension in children was said to be present when the average SBP or DBP levels were ≥ the 90th percentile, but less than the 95th percentile.Adolescents with BP levels ≥ 120/80 mmHg were considered prehypertensive.

2.6.3. Acanthosis Nigricans

It was characterized by thickened areas of hyper-pigmentation, with later development of hypertrophy and sometimes papillomatosis occurring in the intertriginous regions such as the base of neck, axillae, groin, antecubital and popliteal fossae, and umbilicus[15].

2.6.4. Sexual Maturity Rating or Tanner Staging

The resulting sequence of somatic and physiologic changes with the onset of puberty of the study participants was determined based on the classification for girls and boys respectively.

2.6.5. Metabolic Syndrome

Metabolic syndrome in adolescents was defined by the International Diabetes Federation (IDF) consensus definition criteria[16] as central adiposity (waist circumference at the 90th percentile or higher for age and sex).Alongwith any two of the following parameters,including hypertriglyceridemia which was said to be present when TG level was >95th percentiles of the reference population[17], low HDL-C levels- values less than 5th percentile of the reference population[17] were taken as low HDL-C,elevated blood pressure- a systolic or diastolic blood pressure exceeding the 90th percentile adjusted for age, sex, and height or ≥120/80mmHg, whichever is lower)[18] was said to be elevated, insulin resistance which was said to be present if the fasting blood glucose level was ≥100mg/dL[16] or HOMA-IR of 2.5 or higher as has been previously described in children.The definition of metabolic syndrome (MetS) where IFG level was the surrogate marker for insulin resistance was referred to as $MetS_{IFG}$ whereas the one with an elevated HOMA-IR as an alternate criterion for glucoregulatory component was referred as $MetS_{HOMA}$.

2.7. Statistical Methods

Anthropometric and metabolic variables were compared across BMI percentile groups. Data was analysed using SPSS version 16;SPSS, Inc. The difference in proportions among the groups was analysed applying Fisher's Exact test with statistical significance assumed with p value<0.05.The Mann-Whitney U test was used to compare medians of characteristic variables across the groups. Spearman rank correlation was used to test the correlations among the variables. Receiver operator characteristic curve (ROC)analysis was performed to study the strength of the derived indices in predicting IR.

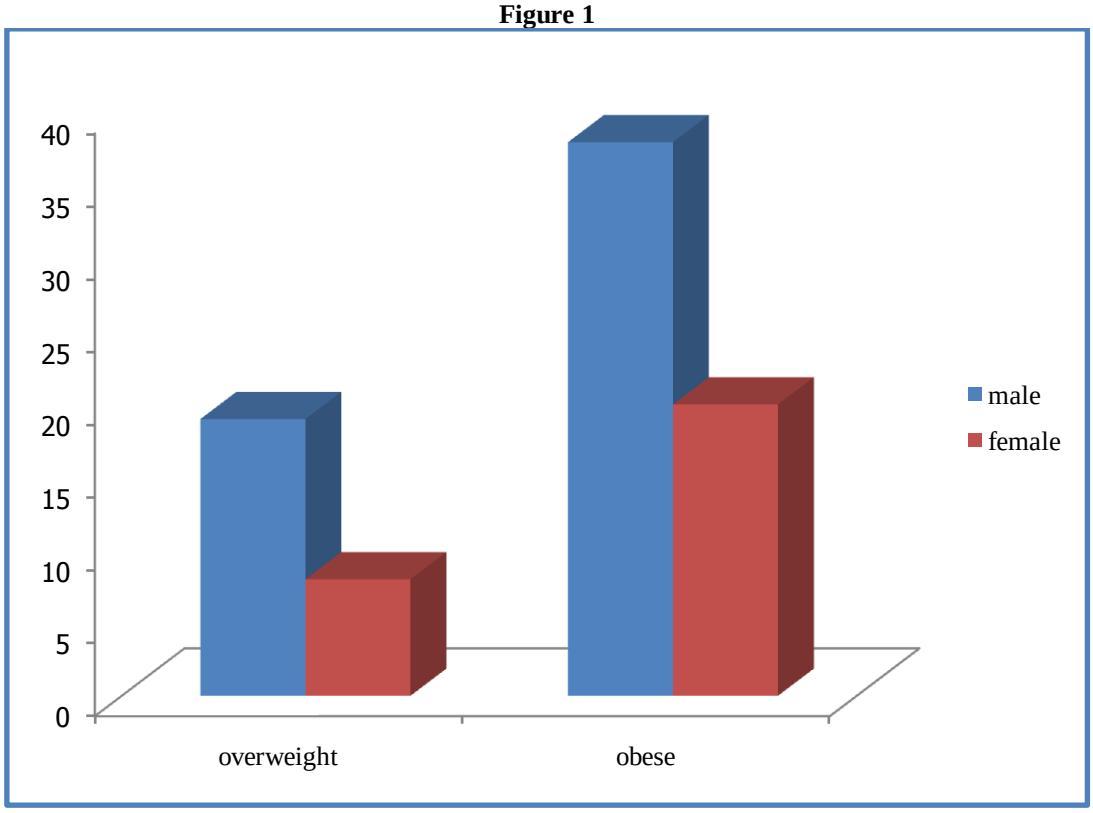
III. RESULTS AND DISCUSSION

Eighty-four participants who fulfilled the inclusion criteria were included in the study sample and data was analysed. Their mean (SD)decimal age was 12.8(2.01)years. The decimal age of the youngest child in the study was 10.00 years whereas the oldest was 17.98 years. As shown in Table 1,61.9%(52/84) of the children in the study were in the age group 10 to 13 years. As depicted in Figure 1,fifty seven subjects,67.86% (57/84) were obese.Males comprised 67.86% (57/84) of the cases. The proportion of obesity was 66.67% (38/57) in males and 70.37% (19/27) in females, which was comparable . All except 1 in the obese group, (98.25%) had central adiposity (defined by waist circumference ≥90th centile) as against (70.37%)in the overweight group which was statistically significant (p value <0.001)by Fischer's exact test. Majority in the study group were normotensive. Elevated blood pressure was observed in36.84 %(21/57) of obese children and 25.93% (7 /27) of overweight children. Hypertension was observed in 3 out of 7 overweight children with elevated blood pressure and 11 out of 21 obese children with elevated blood pressure. There were some obesity related complications observed among the participants in our study. Acanthosis Nigricans was present in 33.33% (28/84) participants. One girl at decimal age 15.53 years had excessive acne and hirsutism whereas two other girls at decimal age 16.85 years and 16.3 years presented with polycystic ovary syndrome(PCOS) and irregular menstrual cycles respectively and were being treated for the same. Fatty infiltration of the liver with hepatomegaly (on ultrasound) an incidental finding, was noted in 3 children who were included in the study. One boy had orthopaedic complications of slipped capital femoral epiphysis and Blount disease (tibia vera). Two children presented with asthma and were on treatment for the same. Other respiratory complications noted among study participants were obstructive sleep apnea characterized by snoring, adenotonsillar hypertrophy and periods of partial or complete airway obstruction while asleep, leading to recurrent hypoxia and sleep deprivation and wheezing episodes.Forty-six out of eighty-four children in the study were preadolescent (Tanner stage I).(vide Figure 3) The HOMA-IR index cut-off of 2.5 has been proven to be the best for prepubertal children with obesity and overweight from previous studies[19]. As majority of our study participants were preadolescent we chose the cut-off of 2.5 for HOMA-IR[19]. It has been stated in previous studies that insulin resistance increases during early teenage years until sexual development Tanner stage 3 and eventually normalizes by the completion of puberty[20],[21],[22].While comparing indirect indices of insulin resistance and pubertal status of overweight and obese children in our study we noted no or minimal variability except a small peak in fasting insulin at Tanner stage 3 which normalised by the completion of puberty.This to some extent defers the need to determine age appropriate cut offs for insulin resistance. There was no significant difference in the distribution of FBG, FI,HOMA-IR,LDL-C,HDL-C or TG across the two groups. Central adiposity was seen more in the obese than the overweight group and the difference was statistically significant. (p<0.001) The other components were almost similar in both the groups. Central adiposity was the most commonly observed abnormality in the obese group followed by HOMA-IR ≥2.5.HOMA-IR ≥2.5 was the most commonly observed abnormality in the overweight group followed by central adiposity.IFG and EBP were the least commonly observed abnormalities in the overweight group followed by L-HDL.IFG was the least commonly observed abnormality in the obese group followed by L-HDL . Only 16.67% (14/84) of total participants had an impaired fasting glucose whereas 78.57% (66/84) had a HOMA-IR ≥2.5. 74.07%(20/27) of

overweight and 80.70% (46/57) of obese participants had a HOMA-IR of 2.5 or higher.Impaired fasting glucose was present much less frequently than elevated HOMA-IR. The relative risk of central adiposity was 23.6 times more if one was obese than overweight.The relative risk of the other MetS components were comparable across the overweight and obese groups.The female gender had a 2.8 times relative risk of developing MetS defined by elevated HOMA-IR ($MetS_{HOMA}$) and is contrary to the findings of Cook S et al(n=2430), where males were predominantly affected (6.1% of males V/s 2.1% of females)[23]. Among various parameters of insulin resistance (HOMA-IR, FGIR ,QUICKI and McAuley index), HOMA-IR≥2.5 had the highest sensitivity in diagnosing metabolic syndrome in overweight and obese children and adolescents .IFG had the highest specificity(99.3%). The ROC curve analysis using our study sample showed that the cut-off of **4.5** for HOMA-IR had 59.5 % sensitivity and 81%specificity suggesting it to be a good test in diagnosing IR and thus helping in early diagnosis of MetS in overweight and obese children. A statistically significant correlation was observed between insulin and BMI, between BMI and all the derived indices and between the derived indices and insulin($p<0.001$).*Among the derived indices, the area under the curve(AUC) was more for HOMA-IR(0.73) followed by QUICKI(0.265) as compared to FGIR(0.238) or McAuley index(0.145). 40.48% (34/84) children in our study met the criteria for MetS using the cut-off of 4.355 for HOMA-IR. Using impaired fasting glucose alone, although highly specific (99.3%) would have resulted in a low sensitivity of 26.2% as compared to HOMA-IR ≥2.5 with a sensitivity of 88% and specificity of 36%. The high levels of sensitivity (88%)observed when using the HOMA-IR cut off of 2.5 as a MetS component suggests that for Indian children, insulin sensitivity should be used instead of glucose concentration to assess children for MetS. The MetS prevalence of 47.6% in the current sample, determined when using HOMA-IR≥2.5 is higher than the MetS prevalence of 30.95% when using IFG as a component suggesting that this population of children is seriously in the need of intervention in the form of diet modification and physical activity. A follow –up study is warranted to evaluate MetS prevalence in a larger and more diverse sample of Indian children. The optimal HOMA-IR cut off could also be confirmed in the larger sample.

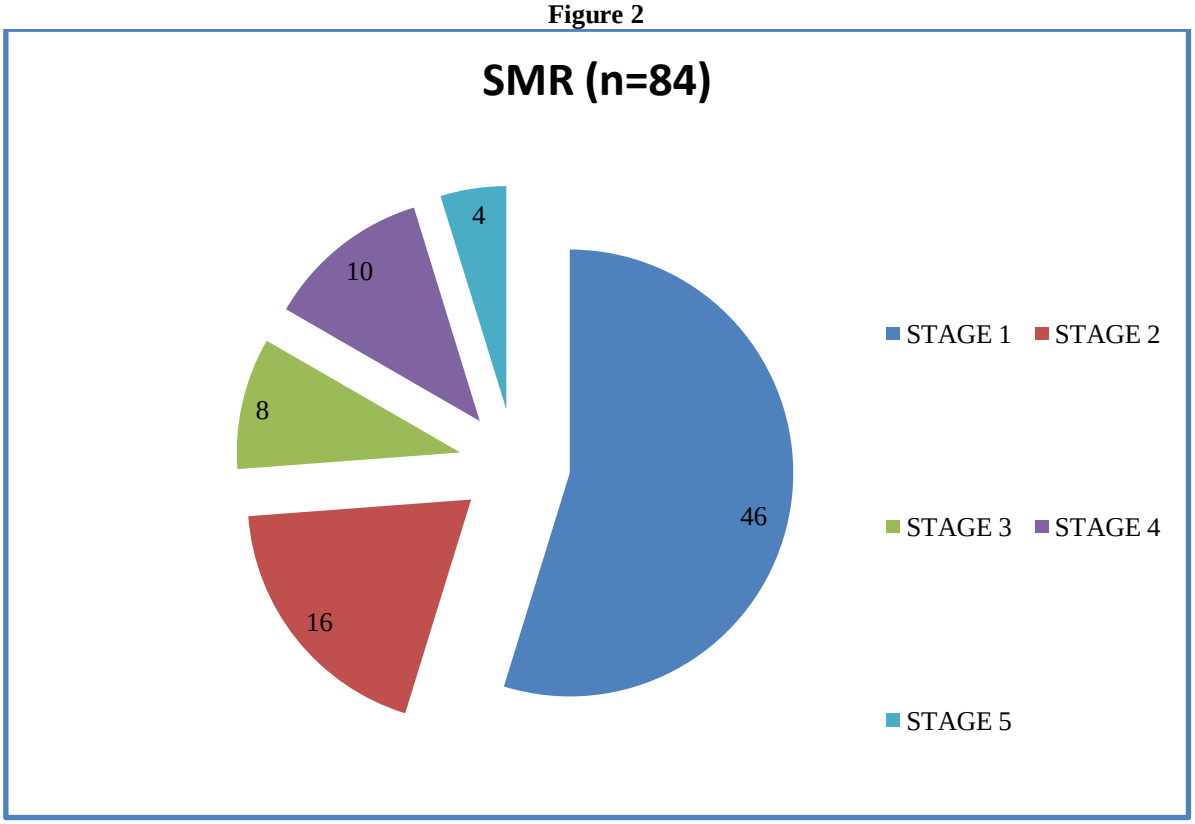
IV. FIGURES AND TABLES

Figure 1



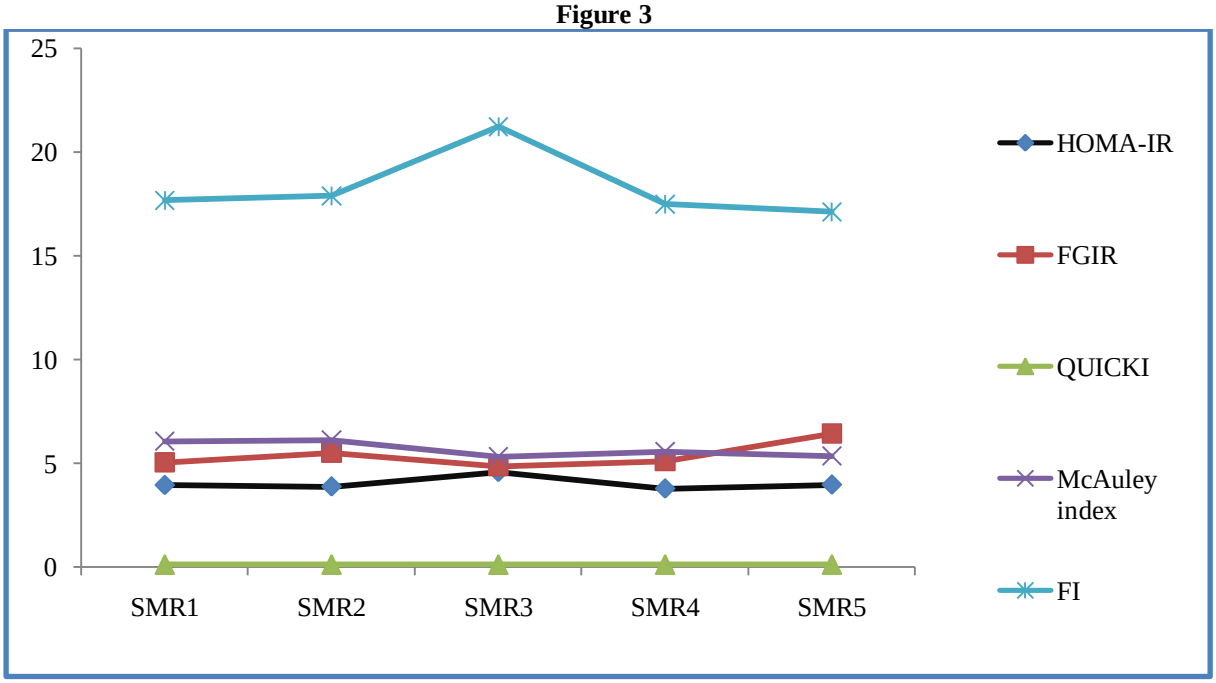
Sex Distribution

Figure 2



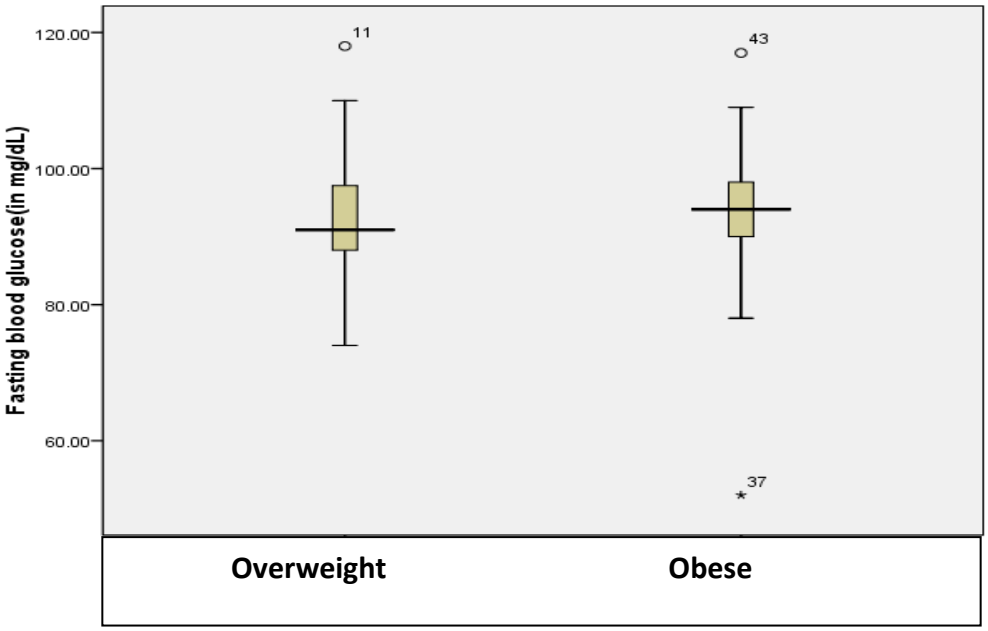
Tanner staging

Figure 3



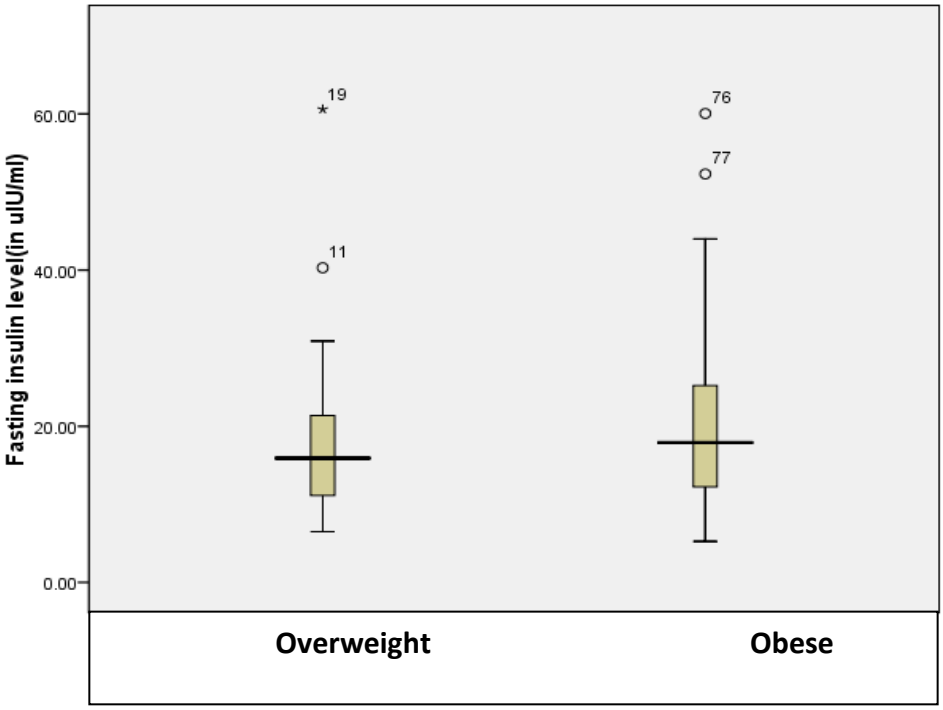
Line diagram depicting indices of Insulin Resistance across Pubertal Status

Figure 4



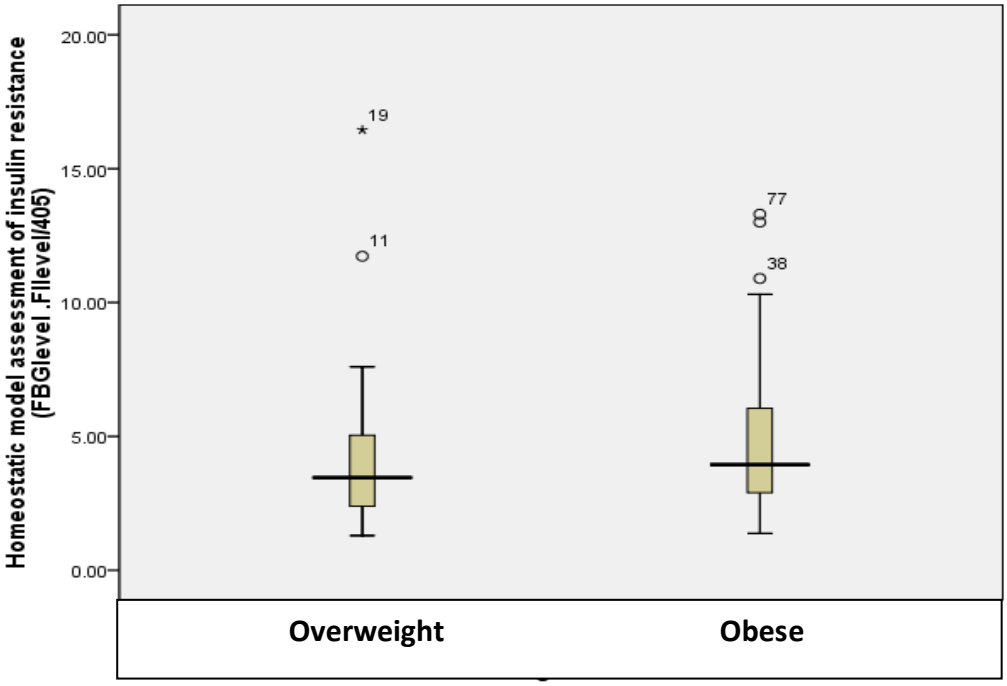
Box plot for Fasting blood glucose

Figure 5



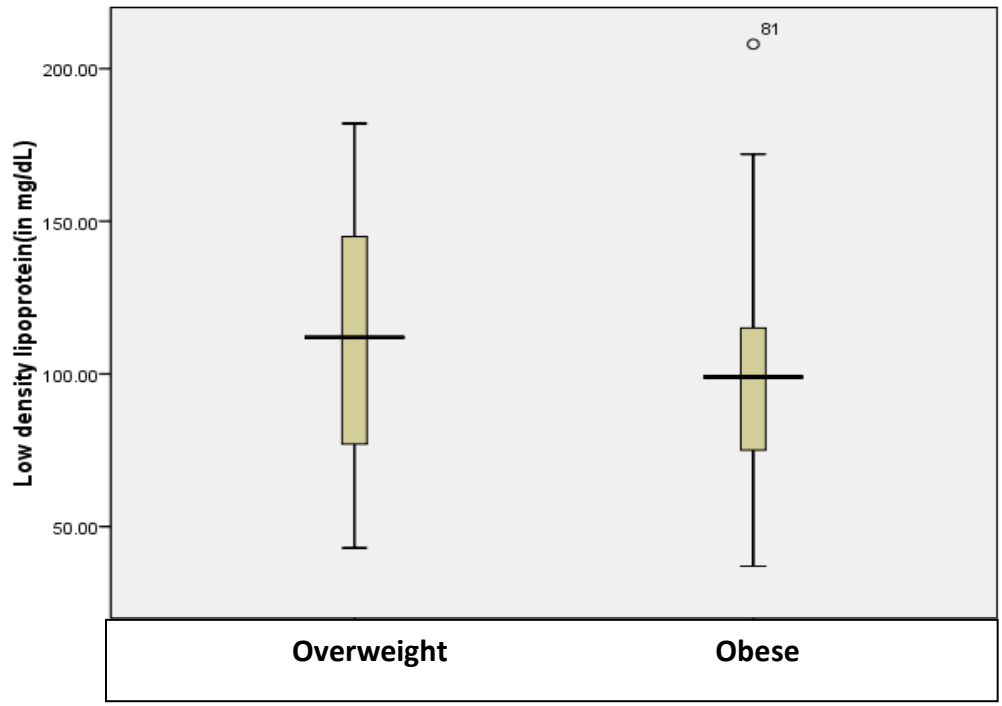
Box plot for Fasting Insulin

Figure6



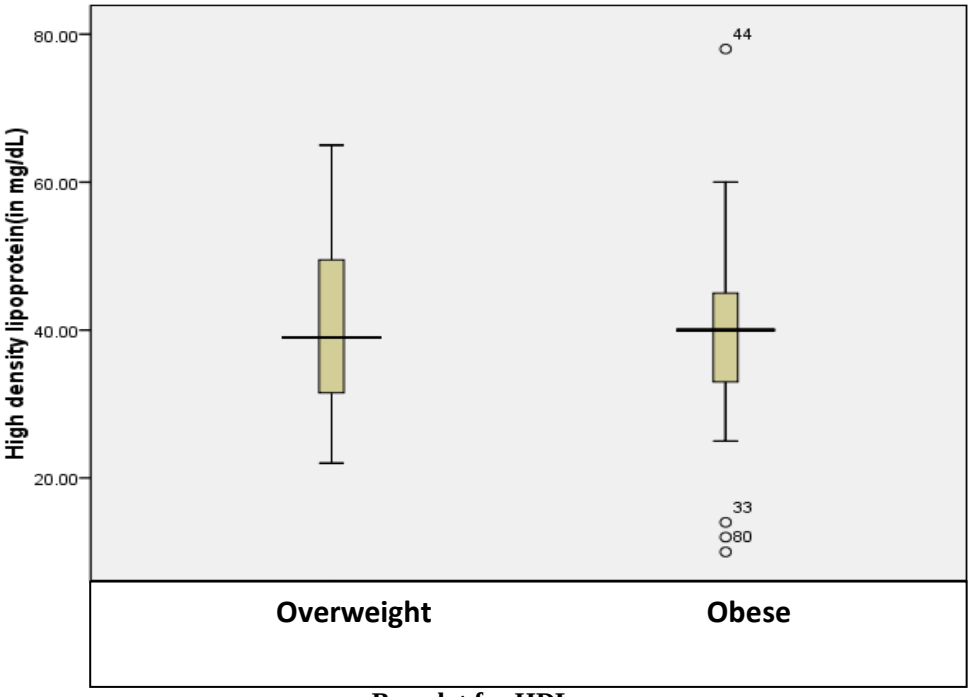
Box plot for HOMA-IR

Figure 7



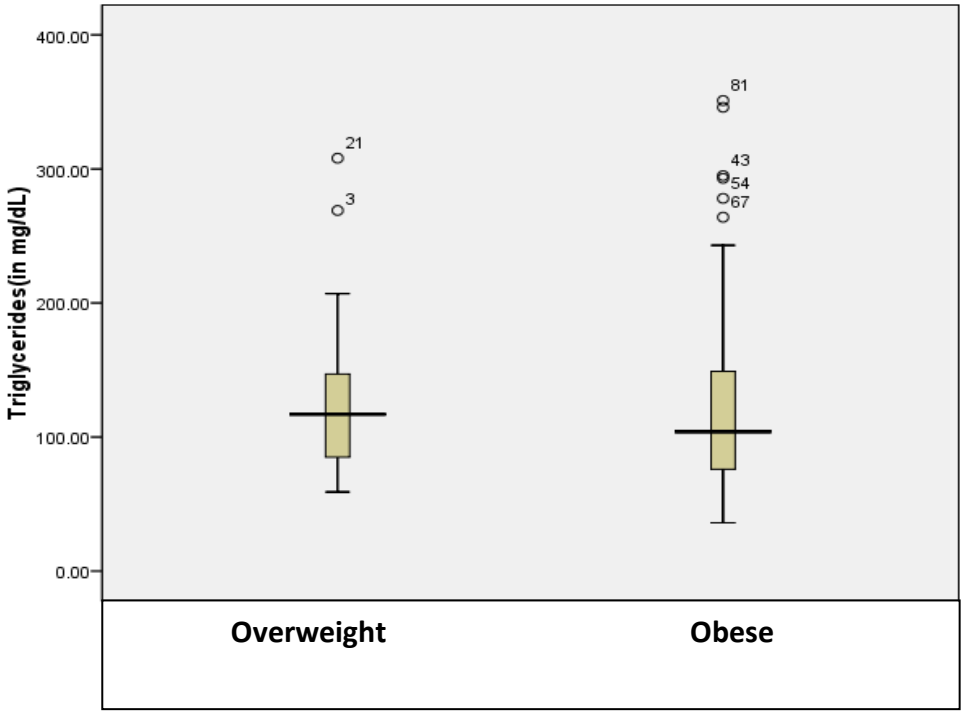
Box plot for LDL

Figure 8



Box plot for HDL

Figure 9



Box plot for TG

Figure10
MetS Components in Overweight and Obese group

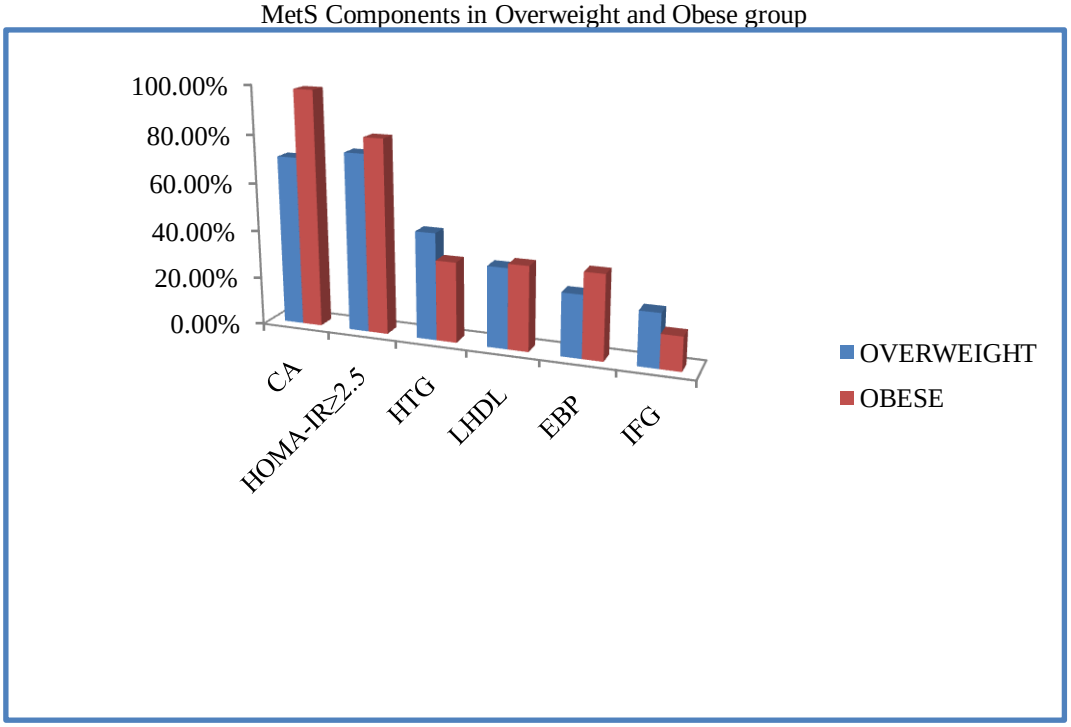
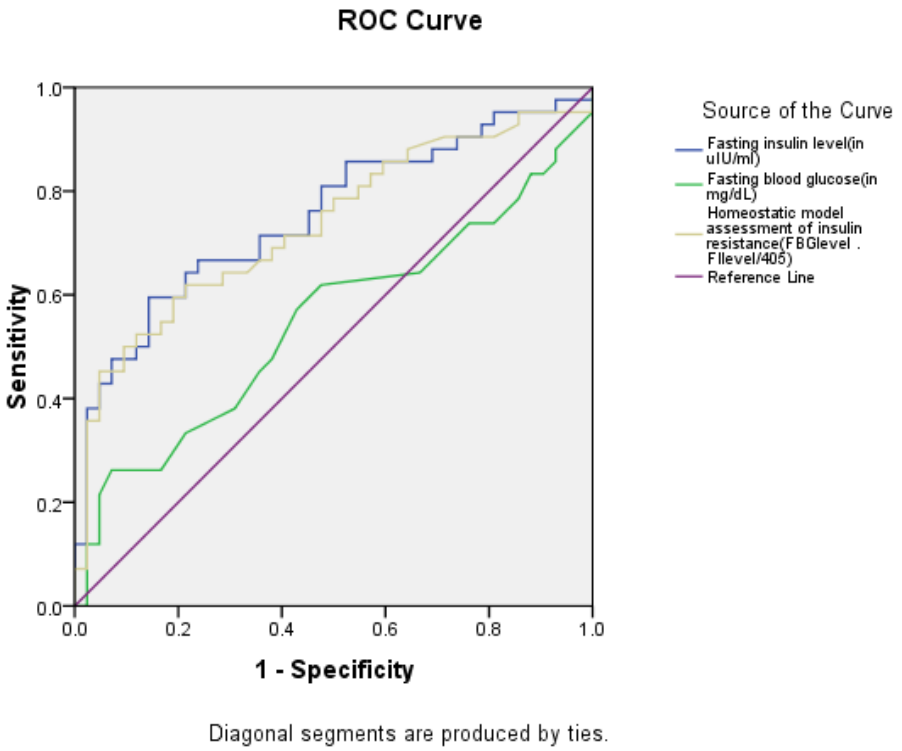
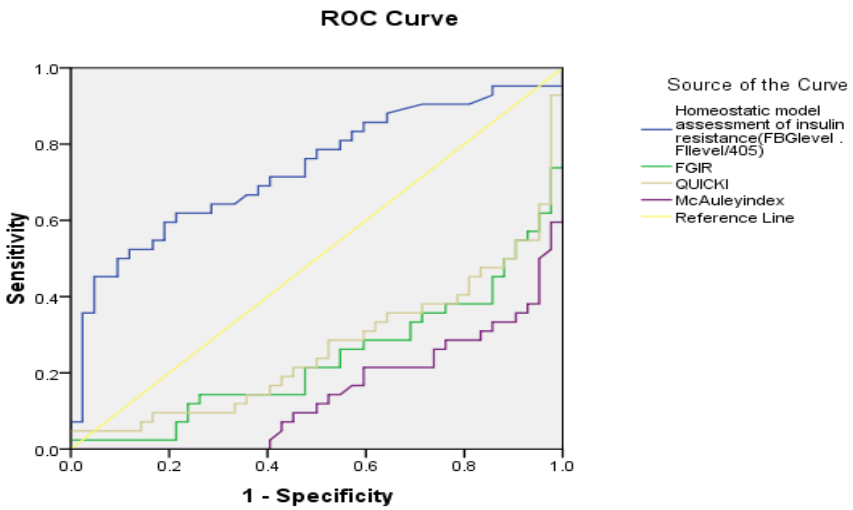


Figure 11



Comparison of AUC for HOMA-IR,FI and IFG to define metabolic syndrome

Figure 12



Comparison of AUC for HOMA-IR, FGIR, QUICKI and McAuley index to define metabolic syndrome

Table 1

AGE IN YEARS	MALE	FEMALE
10.00-12.99	**37**	**15**
13.00-15.99	**17**	**7**
16.00-18.00	**3**	**5**

Age Distribution

Table 2

	OVERWEIGHT (n=27)				**OBESE (n=57)**			
	Median	**IQR**	**Min**	**Max**	**Median**	**IQR**	**Min**	**Max**
BMI (kg/m2)	**23.84**	**22.4,25.2**	**19.9**	**29**	**26.6**	**23.9,29.73**	**20.7**	**39.9**
WC (cm)	**85**	**78,88**	**67**	**96**	**88**	**81,97**	**72**	**108**
SBP (mmHg)	**110**	**110,120**	**96**	**130**	**114**	**108,120**	**100**	**140**
DBP (mmHg)	**70**	**60,72**	**60**	**86**	**70**	**64,70**	**60**	**90**

BMI, WC & BP Distribution

Table 3

WC centile	**Overweight (n=27)**	**Obese (n=57)**
50 th-74 th centile	**1**	**0**
75th-89th centile	**7**	**1**
≥90th centile	**19**	**56**

Waist Circumference Centile Distribution

Table 4

	OVERWEIGHT (n=27)	**OBESE (n=57)**
NORMOTENSION	**20**	**36**
PREHYPERTENSION	**4**	**10**
HYPERTENSION	**3**	**11**

Blood Pressure in Children

Table 5

	Acanthosis Nigricans	
	Yes (n=28)	**No (n=56)**
Overweight (n=27)	**5**	**22**
Obese (n=57)	**23**	**34**

Acanthosis Nigricans and Obesity

Table 6

	OVERWEIGHT (n=27)		**OBESE (n=57)**		
	Median	**IQR**	**Median**	**IQR**	***p value***
FBG (mg/dL)	**91**	**88,98**	**94**	**90,98**	***0.390***
FI (uIU/ml)	**15.9**	**10.92,21.64**	**17.9**	**12.07,25.25**	***0.296***
HOMA-IR	**3.46**	**2.29,5.16**	**3.95**	**2.9,6.07**	***0.391***

*Mann- Whitney U test for comparing medians**,** FBG, FI and HOMA-IR Distribution

Table 7

	HOMA-IR	**FGIR**	**QUICKI**	**Mc Auley index**	**FI**
SMR1	3.95	5.04	0.1355	6.06	17.67
SMR2	3.88	5.53	0.1359	6.12	17.87
SMR3	4.58	4.87	0.1342	5.33	21.22
SMR4	3.78	5.11	0.1364	5.58	17.49
SMR5	3.97	6.44	0.1362	5.35	17.11

Mean values of Insulin resistance indices across Pubertal status

Table 8

	OVERWEIGHT (n=27)		OBESE (n=57)		
	Median	**IQR**	**Median**	**IQR**	***p value***
LDL (mg/dL)	**112**	**77,150**	**99**	**74,116.5**	***0.383***
HDL (mg/dL)	**39**	**30,51**	**40**	**33,45**	***0.996***
TG (mg/dL)	**117**	**83,150**	**104**	**75.5,153.5**	***0.281***

*Mann- Whitney U test for comparing medians .Lipid profile in Children

Table 9

MetS Component	OVERWEIGHT (n=27)	OBESE (n=57)	P value
1.Central adiposity	**19**	**56**	**<0.001**
2.Hypertriglyceridemia	**12**	**19**	**0.228**
3.Low-HDL	**9**	**20**	**0.539**
4.Impaired Fasting glucose	**6**	**8**	**0.261**
5.Elevated HOMA-IR ≥2.5	**20**	**46**	**0.336**
6.Elevated blood pressure	**7**	**20**	**0.281**

Proportion of Metabolic syndrome components

Table 10

Variable	AUC±SE	95%CI	*p-value*
HOMA-IR	**0.735±.055**	**0.626-0.843**	**<0.001**
FI	**0.752±.054**	**0.644-0.857**	**<0.001**
IFG	**0.548±0.064**	**0.422-0.674**	**0.456**

Comparison of AUC for IFG with HOMA-IR, FI to define metabolic syndrome

Table 11

Variable	AUC±SE	95%CI	*p-value*
HOMA-IR	**0.735±.055**	**0.625-0.843**	**<0.001**
FGIR	**0.238±.052**	**0.135-0.341**	**<0.001**
QUICKI	**0.265±.055**	**0.157-0.374**	**<0.001**
McAuley index	**0.145±.040**	**0.068-0.223**	**<0.001**

Comparison of AUC for HOMA-IR with FGIR, QUICKI and Mc Auley index to define metabolic syndrome

Table 12

Index	**Cut-off**	**Sensitivity**	**Specificity**
HOMA-IR	**2.5**	**88%**	**36%**
FGIR	**3.7**	**62%**	**4.8%**
FI	**15.42**	**71.4%**	**54.8%**
QUICKI	**0.13**	**54.8%**	**9.5%**
McAuley index	**5.16**	**50%**	**4.8%**
IFG	**100**	**26.2%**	**99.3%**

ROC Curve analysis for various insulin resistance indices to diagnose metabolic syndrome

Table13

	Insulin	**HOMA-IR**	**FGIR**	**QUICKI**	**McAuley index**
BMI	**r= 0.270**	**r= 0.278**	**r= -.261**	**r= -.279**	**r= -.213**
	p = 0.013	**p= 0.011**	**p= 0.016**	**p= 0.010**	**p= 0.052**
Insulin	**_**	**r= 0.982**	**r= -.976**	**r= -.982**	**r=-.641**
		p< 0.001	**p< 0.001**	**p< 0.001**	**p<0.001**

**-applying Spearman rank correlation* .Association of anthropometry, biochemical and derived indices

V. CONCLUSION

The mean decimal age of the study participants was 12.8 ±2.01years. The proportion of overweight and obesity was same in both the sexes, 33.3% (19/57) in males and 29.63% (8/27) in females and 66.67% (38/57) in males and 70.37% (19/27) in females respectively. The difference in proportions of central adiposity across the overweight and obese groups was statistically significant ($p \leq 0.001$). Acanthosis nigricans was present in 33.3% participants(28/84). Other co-morbidities observed were PCOS and Bronchial asthma (2/84 each). Majority in the study were pre-adolescent. Among children with central adiposity 57% of obese and 42% of over-weight had ≥2 risk factors for metabolic syndrome. Obese children were normoglycaemic with insulin resistance. HOMA-IR was found to be a strong predictor of IR to define metabolic syndrome. The cut-off of 4.5 for HOMA-IR had 59.5% sensitivity and 81%specificity suggesting it to be a good test in diagnosing IR and thus helping in early diagnosis of MetS in overweight and obese children. Among the derived indices for insulin resistance AUC was more for HOMA-IR (0.735) followed by QUICKI(0.265), FGIR (0.238), Mc Auley index (0.145). Using HOMA-IR as a marker of MetS has a sensitivity of 88% and a specificity of 36% as compared to IFG with a sensitivity of 26.2% and specificity of 99.3%. HOMA-IR had emerged as a reliable diagnostic tool and it is found to be a stronger predictor of IR when compared to FGIR,QUICKI and McAuley index in normoglycemic overweight and obese children.

Funding nil
Conflict of Interest nil

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