Original Research Article

A cross sectional study of fasting and post prandial insulin level as a predictor of insulin resistance with hyperinsulinemia with HOMA-IR >2.5 among overweight and obese prepubertal children in a tertiary care Hospital of Bangalore, India

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ABSTRACT

Background: Overweight and obesity has reached epidemic proportions in developed countries and is rapidly increasing. The proportion of children in the general population who are overweight and obese has doubled over the past two decades in developed and developing countries including India and have a rising prevalence of diabetes. Insulin resistance if detected early, we can intervene early to slow or halt the progression of the associated co morbidities. Dynamic phase of juvenile obesity is initially characterized by an abnormal postprandial profile of plasma insulin, even when fasting insulin levels are still normal and insulin sensitivity is slightly increased. Objective of present study was to find out the occurrence of hyperinsulinemia and Insulin Resistance Markers among overweight and obese children between 7 to 11 years.
Methods: A cross sectional study was carried out in the Bangalore Baptist Hospital, Hebbal, Bangalore from September 2013 to May 2014. Children in the age group of 7 to 11 years who are overweight or obese admitted in the as per WHO Growth Charts were included in the study.A total of 51 Cases were included.
Results: In present study the 21 (41.2%) of the study subjects were classified as Overweight and 30 (58.8%) were Obese. The association between level of HOMA-IR and the study variables like age, weight, Height, BMI, FBS, PPBS were found to not significant statistically with p value being more than 0.5. The Pearson Corelation between HOMA-IR and Fasting Blood Glucose, Post Prandial Blood Glucose level, Fasting Basal Insulin Level and Post Prandial Basal Insulin Level were found to statistically significant.
Conclusions: Hyperinsulinism and insulin resistance is a concern not only in obese but also in overweight children as shown by the occurrence of insulin resistance.

Keywords: Adoloscents, Hyperinsulinemia, Insulin resistance, Obese, Overweight

INTRODUCTION

Overweight and obesity has reached epidemic proportions in developed countries and is rapidly increasing.[1] The proportion of children in the general population who are overweight and obese has doubled over the past two decades in developed and developing countries including India and have a rising prevalence of diabetes.[2-5]

Numerous health risks have been associated with adolescent overweight, including hypertension, respiratory disease, several orthopedic disorders, diabetes mellitus and elevated serum lipid concentrations.[6] Due to

the difficulty of curing obesity and over weight in adults and the many long-term adverse effects of childhood obesity, the prevention of child obesity has been recognized as a public health priority.[7] Increasing evidence shows that childhood obesity and overweight have a profound influence on morbidity and mortality in adult life.[8,9]

Dynamic phase of juvenile obesity is initially characterized by an abnormal postprandial profile of plasma insulin, even when fasting insulin levels are still normal and insulin sensitivity is slightly increased. After 4-5 years of evolution, the metabolic dysfunctions become progressively comparable with those reported in established adult obesity: permanent hyperinsulinemia in the fasting as well as the fed states and decreased insulin sensitivity slowly develop.[10]

Childhood obesity frequently tracks into adulthood, hence represents a major contributor to the adult obesity epidemic and to the increased cardiovascular morbidity and mortality in adult life.[11]

Insulin resistant individuals who can compensate by hyperinsulinemia may escape diabetes initially, but are still prone to other complications, such as early atherosclerosis, progression of obesity (especially central type), acanthosis Nigerians, increased skin tags, hypertension, dyslipidemia, hyper coagulation, PCOS, fatty liver infiltration, focal segmental glomerulosclerosis, and an increased cancer rate as well. Thus, insulin resistance syndrome is not benign even when diabetes does not develop.[12]

Obese children with a similar BMI can differ on the basis of the degree of insulin resistance in the risk for complications. In fact, those with a more impaired insulin sensitivity show, for example, a greater risk for T2DM and cardiovascular disease.[13]

Objective of present study was to find out the occurrence of hyperinsulinemia and Insulin Resistance Markers among overweight and obese children between 7 to 11 years.

METHODS

A cross sectional study was carried out in the Bangalore Baptist Hospital, Hebbal, Bangalore from September 2013 to May 2014. Children in the age group of 7 to 11 years who are overweight or obese admitted in the as per WHO Growth Charts were included in the study. Sample size estimation was estimated with.

Expected prevalence (p)= 15%, Q= 100-15= 85%, D= 90% confidence interval= 10

4 pq÷d×d = 4×15×85÷100 = 51.

A total of 51 study subjects who were aged between 7 to 11 years with overweight and obese children were included in the study.

Inclusion criteria

- Age 7 to 11 years.
- BMI more than or equal to 85th percentile for age.

Exclusion criteria

- Children who are already diagnosed with diabetes. (in these children both the fasting and post prandial insulin levels are expected to be high).
- Fasting blood glucose more than 126 mg/dl.
- Endogenous obesity. (endogenous obesity is caused due to other systemic illness like endocrinopathies. in these children there is no indication of measuring the insulin levels).

WHO growth charts are used to determine the corresponding BMI for age and sex percentile. For children and adolescents.[14]

Overweight is defined as BMI at or above the 85th percentile and lower than the 95th percentile for children of the same age and sex.[15]

Obesity is defined as a BMI at or above the 95th percentile for children of the same age and sex.

The who definition for adults is:

- BMI greater than or equal to 25 is overweight.
- BMI greater than or equal to 30 is obesity.[15]

The serum insulin level estimations are done at an NABL accredited laboratory using the chemiluminescence immunoassay (CLIA) method, which is validated by repetition of tests number of times, comparing with other NABL accredited lab. The lab adheres to the ISO 15189 standards.

Fasting levels of insulin greater than 15 mcu/ml, or insulin Peak (post-OGTT) levels of more than 150 mcu/ml and/or More than 75 mcu/ml at 120 min of OGTT are hyperinsulinemia levels, which infer insulin resistance.[16]

The following surrogate index for insulin resistance will be determined: HOMA-IR (homeostasis model assessment), Matsuda Index and QUICKI (quantitative insulin sensitivity check index).[17,18]

$$HOMA1\text{-}IR = (FBI \times FBS) / 22.5$$

$$QUICKI = 1 / [\log(FPI) + \log(FBS)]$$

$$Matsuda = 10{,}000 / \sqrt{(FBS \times FBI \times PPBS \times PPBI)}$$

In present study HOMA-IR >2.5 will be considered as insulin resistance.

Insulin resistance based on the surrogate markers are defined as:[19-21]

- HOMA-IR >2.5.
- QUICKI <0.34.
- Matsuda <3.

Statistical analysis

The data collected was tabulated in a Microsoft excel sheet and analysed. Analysis was done with SPSS statistical software version 16. A p value of less than 0.05 was considered a statistically significant level of difference.

RESULTS

Out of 51 study subjects in present study 29 (56.9%) male and 22 (43.1%) female was present. The mean weight of children in present study was 39.55±7.7, mean height was 133.45±11.78. The Mean age was 9.49 years with 1.9 Standard Deviation. The Average BMI was 22.57±2.29.

Table 1: Occurrence of hyperinsulinemia based on insulin resistance markers.

Hyperinsulinemia based on		Overweight (BMI>85th, ≤95th centile)	Obese (BMI>95th centile)	Both Overweight and obese (BMI>85th centile)
HOMA-IR	HOMA-IR >2.5	15 (71.4%)	19 (63.33%)	34 (66.66%)
	HOMA-IR≤2.5	6 (28.6%)	11 (36.66%)	17 (33.33%)
MATSUDA	Matsuda <3	10 (47.62%)	8 (36.37%)	18 (35.3%)
	Matsuda ≥3	11 (52.38%)	22 (73.33%)	33 (64.7%)
Quicki	QUICKI <0.34	10 (47.62%)	8 (36.37%)	18 (35.3%)
	QUICKI ≥0.34	11 (52.38%)	22 (73.33%)	33 (64.7%)
Absolute insulin values	FBI>15 and/or PPBI>75	12 (57.14%)	16 (53.33%)	28 (54.9%)
	FBI≤15 and PPBI≤7!	9 (42.86%)	14 (46.67%)	23 (45.1%)

In present study the 21 (41.2%) of the study subjects were classified as Overweight and 30 (58.8%) were Obese.

The level of HOMA-IR more than 2.5 was considered to be insulin resistance with hyperinsulinemia. Out of 21 overweight children 15 (71.4%) and 19 (63.3%) out of 30 Obese children had Hyperinsulinemia. Overall 34 (66.6%) of the children had Hyperinsulinemia as per HOMA-IR.

MATUSDA value of less than 3 was considered to be a marker of Hyperinsulinemia because of Insulin resistance. 18 (35.3%) of Overall children were classified as insulin resistance based on MATUSDA value. 10(47.6%) from Overweight and 8 (36.4%) from obese were considered insulin resistance.

Table 2: Comparison of insulin resistant children with non insulin resistant children (based on HOMA-IR).

Characteristic	HOMA-IR>2.5		HOMA-IR<2.5		P value
	Mean	Standard deviation	Mean	Standard deviation	
Age	9.15	1.184	8.41	1.372	0.890
Weight	39.66	6.922	38.95	9.5	0.077
Height	134.22	9.847	130.42	14.802	0.099
BMI	21.89	2.567	22.67	2.250	0.657
FBS	92.59	8.749	82.88	6.864	0.926
PPBS	110.24	13.987	103.47	13.139	0.265

QUICKI value of <0.34 was considered to be Hyperinsulinemia in present study as a marker of insulin Resistance. 34(66.7%) of the children were classified as insulin resistance and 15 (71.4%) of overweight and (63.3%) of obese were said to be Hyperinsulinemia. The children with FBI>15 and/or PPBI>75 Absolute Insulin

Level values were diagnosed to have insulin resistance. 28 (54.9%) of the study subjects, 12 (57.4%) of overweight and 16 (53.3%) of obese were resistance to insulin and considered as Hyperinsulinemia.

The association between level of HOMA-IR and the study variables like age, weight, Height, BMI, FBS, PPBS were found to not significant statistically with p value being more than 0.5.

Table 3: Sensitivity and specificity of fasting and post prandial absolute insulin levels with HOMA-IR.

		HOMA-IR > 2.5, N=34	HOMA-IR ≤ 2.5, N=17	Remarks
FBI	FBI >15	18 (100%)	0	Sensitivity= 53% Specificity= 100% Positive predictive value= 1 Negative predictive value= 0.52
	FBI ≤15	16 (48.48%)	17 (51.52%)	
PPBI	PPBI >75	15 (83.33%)	3 (16.67%)	Sensitivity= 44% Specificity= 82% Positive predictive value= 0.83 Negative predictive value= 0.42
	PPBI ≤75	19 (57.58%)	14 (42.42%)	

All the cases with absolute insulin levels in the fasting phase of >15 which was considered as hyperinsulinemia also had HOMA-IR level greater than 2.5. 16 (48.8%) of the cases with FBI level less than 15 had HOMA-IR level more than 2.5.

The sensitivity of the FBI in diagnosing Insulin resistance was 53 %, Specificity was 100%. The positive predictive value was 1 and negative predictive value was 0.52.

Among the post prandial absolute insulin level more than 75 which is a marker for insulin resistance had a sensitivity of 44%, specificity of 82%, positive predictive value of 0.83 and negative predictive value of 0.42. 15 (83.3%) had both PPBI >75 and HOMA-IR >2.5.

Table 4: Correlation between FBS, PPBS, FBI, PPBI and HOMA-IR.

	Correlation coefficient	P value
Pearson correlation between FBS and HOMA-IR	0.345	0.013
Pearson correlation between PPBS and HOMA-IR	0.365	0.008
Pearson correlation between FBI and HOMA-IR	0.944	0.000
Pearson correlation between PPBI and HOMA-IR	0.632	0.000

The pearson correlation between HOMA-IR and fasting blood glucose, post prandial blood glucose level, fasting basal insulin level and post prandial basal insulin level were found to statistically significant and all the variables had a positive association with HOMA-IR in determining the hyperinsulinemia status among obese and overweight children with insulin resistance.

DISCUSSION

The occurrence of Insulin resistance based on absolute insulin values was 57.14% in overweight, 53.33% in obese and overall occurrence was 54.9%.

A study done in Department of Pediatrics and Department of biochemistry, Aristotle university of Thessaloniki, Greece also showed a similar result where 54% of obese prepubertal children had hyperinsulinemia.[22] They did a study on 26 prepubertal children and 20 obese adolescents by measuring fasting insulin, fasting glucose and fasting glucose to insulin ratio.

Though there are many studies on the prevalence of insulin resistance in obese adolescents and in children with metabolic syndrome there are hardly any study on prevalence or occurrence of insulin resistance in prepubertal overweight and obese children.

The occurrence of Insulin resistance based on HOMA-IR or QUICKI were the same, 71.4% in overweight, 63.33% in obese and overall occurrence was 66.66%. Based on Matsuda, insulin resistance was 47.62% in overweight, 36.37% in obese and overall occurrence was 35.3%.

HOMA –IR and QUICKI has been considered to be a good indicator of insulin resistance and is comparable to euglycemic clamp. QUICKI is a variation of HOMA equation and has a near perfect correlation with HOMA. Matsuda index derived from OGTT represents a composite of both hepatic and peripheral tissue sensitivity and few consider it better than HOMA-IR as it denotes whole body insulin sensitivity index.

The mean and standard deviations of anthropometric measurements in the insulin resistance and non resistant children did not show any significant difference (p value-0.890,0.077,0.099,0.657 for age, weight, height, BMI respectively) nor was the mean and SD difference in the fasting and post prandial blood sugars with p value-0.926 and 0.265 respectively. This emphasizes the need for using insulin levels to detect hyperinsulinemia and insulin resistance early in children and bring greater awareness of this condition.

A study was done by Singh B et al- Surrogate markers of insulin resistance and based on the study it was concluded that the use of surrogate markers to assess insulin resistance helps to use medical resources to fullest, while minimizing costs and inconvenient side effects.[23]

In a study done by Sinaiko A et al, Jornal de Pediatria, they mentioned that HOMA does not define insulin resistance in children with any greater accuracy than fasting insulin (the correlation between fasting insulin and HOMA was >0.95), because glucose is so tightly controlled, and its range is so narrow in children that its use in the HOMA formula does not discriminate among individuals.[24]

We had 100% of children with fasting nsulin >15 had insulin resistance (HOMA-IR >2.5) while 48.5% of children with normal fasting insulin levels had insulin resistance (p-0.000, sensitivity-53%, specificity-100%, PPV-1, NPV-0.52). This is significant as it shows the incomplete suppression of glucose at that particular normal insulin level.

On the other hand, 83.3% of children with high post prandial insulin were insulin resistant while 57.6% with normal PPBI had insulin resistance (p-0.073, sensitivity-44%, specificity-82%, PPV-0.83, NPV-0.42).

Present study findings support the usefulness of HOMA-IR as indicator of insulin resistance. In present study also, we found a significant positive correlation between insulin resistance as determined by HOMA-IR and fasting plasma insulin concentration (r=0.944, p=0.000).

Hanson et al reported that all indices based on fasting insulin concentrations, show significant correlation with IR (r approximately 0.60).[25]

Present study also showed a good inverse correlation between QUICKI (an index based on fasting insulin concentration) and insulin resistance determined by HOMA-IR (r = -0.865).

QUICKI is recognized as being a log derivative of HOMA-IR, which explains the inverse correlation with HOMA-IR.

Stunff CL et al conducted a study early changes in postprandial insulin secretion, not in insulin sensitivity, characterize juvenile obesity.[26]

CONCLUSION

Hyperinsulinism and insulin resistance is a concern not only in obese but also in overweight children as shown by the occurrence of insulin resistance. Post prandial hyperinsulinemia may not be an early feature of insulin resistance. Fasting parameters are sufficient to identify most cases of insulin resistance. Normal fasting and post prandial blood sugars alone does not help in assessing insulin resistance. Clinical and anthropometric measurements do not help much in detecting early insulin resistance in obese and overweight children. Fasting insulin and blood sugar and HOMA-IR index is a good indicator of insulin resistance but follow up studies are required to assess the incidence of metabolic syndrome. To do FBS and FBI for all overweight and obese children, preferably even PPBS and PPBI. They concluded that juvenile obesity is initially characterized by an abnormal postprandial profile of plasma insulin, whereas fasting insulin levels are still normal and insulin sensitivity is slightly increased.

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