Insulin Resistance in Obese Adolescents in a Tertiary Care Hospital in Bangladesh

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Abstract

Background: Insulin resistance has evolved as an important metabolic alteration in obese children especially during adolescence. Emerging data suggest that insulin resistance in obesity play the key role in the pathogenesis of hypertension, dyslipidemia, impaired glucose tolerance, type 2 diabetes mellitus, non-alcoholic fatty liver disease and metabolic syndrome.

Objective: The aim of this study was to assess the insulin resistance status of Bangladeshi obese adolescents in hospital settings.

Methods: It was a cross sectional study done in children, aged 10 to 16 years, attending the paediatric endocrine clinic, paediatric outpatient and paediatric inpatient department, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka over a period of 15 months. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) value was obtained from fasting insulin & fasting blood glucose level to assess insulin resistance in obese and normal weight children.

Results: Among obese adolescents, 78.8% were insulin resistant in comparison to 16% in non-obese adolescent. Mean HOMA-IR level of obese group were significantly higher than non-obese group (4.46±1.82 Vs 1.98±1.26, p<0.001). Insulin resistance was observed in 73.8% and 84.2% among grade 1 obese and grade 2 obese adolescents respectively. HOMA-IR showed positive correlation with BMI and waist circumference. Insulin resistance showed significant association with central obesity, puberty and acanthosis nigricans (AN).

Conclusion: In this study, insulin resistance was observed in higher frequency among obese adolescents than normal weight adolescents. Obese adolescents with central obesity, acanthosis nigricans and puberty are at increased risk of insulin resistance.

Keyword: Obesity, Insulin resistance, HOMA-IR, Puberty

Introduction:

Obesity in children and adolescent is rising alarmingly and approaching an epidemic proportion in many countries.1 World Health Organization (WHO) considered childhood obesity as one of the most serious public heath challenges in 21st century.2 A systematic analysis of 1,769 reports representing 188 countries revealed that the worldwide prevalence of childhood overweight and obesity rose by nearly 50% over a span of three decades.3 In Bangladesh, the prevalence of obesity was found to be 3.5% among school aged children.4

In recent years, studies have shown that type 2 diabetes mellitus has increased dramatically in children and adolescents throughout the world.5 This increase in frequency of type 2 diabetes seems to parallel the increase in prevalence and severity of obesity in children and adolescents.6 Insulin resistance is considered a pre-diabetic condition characterised by imbalance of glucose metabolism, causing an increase in insulin production and a given amount of insulin producing a subnormal biological response.7 Adipose tissue seems to play a key role in the pathogenesis of insulin resistance through several released metabolites, hormones and adipocytokines that can affect different steps in insulin action.8 Excessive accumulation of body fat, especially abdominal fat, is associated with increased
levels of free fatty acids in the bloodstream, which in turn inhibit carbohydrate metabolism via substrate competition and impaired insulin signaling by lowering receptor sensitivity in cell membranes, creating the insulin resistance. Several Studies have emphasised that children with insulin resistance have a higher predisposition to the future development of hypertension, dyslipidemia, metabolic syndrome, type II diabetes mellitus and cardiovascular disease. Longitudinal Study also observed that cardiovascular risk factors dyslipidemia and hypertension decreased in obese children with any degree of decrease in insulin resistance, independently of changes in body weight. 

In adolescents, insulin sensitivity declines considerably during pubertal period of life. Multiple cross sectional studies showed the association of puberty and declined insulin sensitivity in adolescents. Longitudinal study also revealed that insulin sensitivity undergoes a decline of around 25–50% during puberty.

There is different method capable of estimating the degree of sensitivity of individual to insulin. The homeostatic model assessment method for insulin resistance (HOMA-IR) index is a widely used method in adults and has been validated in children and adolescents as an indicator of insulin resistance. HOMA-IR index increases with the increase in insulin resistance in individual. There is paucity of data in Bangladesh regarding insulin resistance in obese adolescent. Aim of this study was to assess insulin resistance in obese adolescents in a tertiary care hospital in Bangladesh.

Materials and Methods
It was a cross sectional study conducted in Department of Paediatrics (Paediatric Endocrinology clinic, paediatric outpatient and inpatient department), Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from March 2018 to July 2019. A total of 80 obese adolescents aged 10 to 16 years who attended hospital for evaluation of obesity were included in the study. Age and sex matched 50 adolescents without obesity or overweight were included in the study as control. The weight was measured by using electronic weighing machine, height was measured by stadiometer and waist Circumference (WC) was measured midway between the lowest rib and the superior border of the iliac crest.

To assess obesity, BMI was categorised for particular age and sex according to Centers for disease control and prevention (CDC) criteria. Here, children having BMI for age and sex 5th to 85th percentile of reference population were classified as nonobese and children having BMI for age and sex ≥ 95th percentile of reference population were classified as obese. Obese group were further subdivided into 2 groups; grade 1 obese and grade 2 obese (severe obese) group. Grade 1 obese were defined as adolescents having BMI ≥95th percentile and <120% of 95th centile and grade II obese (Severe obese) were defined as adolescents having BMI ≥120% of 95th centile for age and sex, according to CDC growth chart 2000 or an absolute BMI ≥35 kg/m², whichever is lower based. Central obesity or raised waist circumference was defined as waist circumference ≥90th centile for age and sex, according to CDC (Anthropometric Reference Data for Children and Adults: United States), 2007–2010. Acanthosis nigricans and pubertal status of individual according to Tanner were assessed. Adolescents in tanner stage 1 were classified as prepubertal, adolescents in tanner stage 2,3,4 were classified as pubertal. Children who were taking systemic steroid for any cause or on any intervention for obesity like dietary restriction or taking any drug for impaired glucose homeostasis or suffering from genetic, endocrine (eg. Hypothyroidism, Cushing Syndrome, Hypothalamic disorder) and any neurological disease (Epilepsy getting Sodium valproate) that might lead to overweight or obesity were excluded from this study. We also excluded children having any known pancreatic disease or liver disease and children who were in pubertal stage 5 (postpubertal stage). The study protocol was approved by Institutional Review Board of BSMMU, Dhaka.

After considering inclusion and exclusion criteria, fasting blood glucose and fasting insulin level were measured in study participants. Blood glucose was assayed by hexokinase method and insulin levels was measured by chemiluminescent microparticle immunoassay method. HOMA-IR index was obtained by calculating the product of fasting insulin (microU/ml) and fasting blood glucose (mmol/L) divided by 22.5. HOMA-IR index was used to evaluate insulin resistance. Study subjects were defined as insulin resistant when HOMA-IR values were ≥3 and insulin sensitive when HOMA-IR values were < 3. Statistical analysis was performed by using SPSS

Qualitative data were analysed by chi-square test,
quantitative data were analyzed by unpaired t test and to evaluate correlation between two variables pearson correlation test and scattered diagram were applied. p value d’0.05 with 95.0% confidence interval was considered as the level of statistical significance.

Result

The study included 80 obese and 50 non-obese adolescents aged 10 to 16 years. Male were 49.23% and female were 50.76%. Mean age was about 11 years in both group, and age and sex of obese and non-obese adolescents showed no significant difference. Mean BMI was significantly higher in obese than non-obese adolescents (p<0.001) and waist circumference e’90th centile was more in obese group than nonobese group (66.3% vs 0%, p<0.001). Seventy percent of obese and 2% of non-obese adolescents had acanthosis nigricans, and it was significant (p<0.001). Most of the adolescents in both groups already entered puberty and no significant difference was found between two groups. (table I)

Among obese adolescents 78.8% were insulin resistant where as 16% non-obese adolescents were insulin resistant (p<0.001) and mean HOMA-IR value was significantly higher in obese than non-obese group (4.46±1.83 vs 1.98±1.26, p<0.001) (table II). Mean HOMA-IR level of grade II obese (severe obese) group was significantly higher than grade I obese group (5.06±1.89 VS 3.92±1.58, P<0.005). In 73.8% grade I obese adolescents and in 84.2% grade II obese adolescents had insulin resistant but on statistical analysis there was no significant difference (p=0.256) (table III). In insulin resistant obese adolescent 89% had acanthosis nigricans, 81% were in puberty and 75% had central obesity. On Chi-square analysis acanthosis nigricans (p<0.001), central obesity (p<0.03) and puberty (p=0.006) were significantly associated with insulin resistance in obese adolescents (table IV). Scatter diagram showed significant positive correlation of body mass index (BMI) with HOMA-IR (p<0.001) as HOMA-IR value was increased with increasing value of BMI in obese adolescents (figure 1).

| Table I: Clinical characteristics of study subjects in obese and non obese group (n=80+50) |
|-----------------------------------------------|-----------------|-----------------|----------|
| Clinical characteristics                      | Obese (n=80)    | Non obese (n=50)| p-value  |
| Age (Years) Mean ±SD                          | 11.84±1.63      | 11.90±1.17      | 0.832    |
| Sex n(%)                                       | Male 42(52.5%)  | 24(48%)         | 0.618    |
|                                               | Female 38(47.5%)| 26(52%)         |          |
| BMI (kg/m²) Mean±SD                            | 28.70±4.02      | 18.46±1.62      | <0.001   |
| Waist Circumference n(%)                       | e’90 th centile | 55(68.75%)      | <0.001   |
|                                               | <90 th centile  | 25(31.25%)      |          |
| Acanthosis Nigricans n(%)                      | Present 56(70.0%)| 1(2.0%)         | <0.001   |
|                                               | Absent 24(30.0%)| 49(98.0%)       |          |
| Pubertal status n(%)                           | Prepubertal 22(27.5%)| 16(32.0%)  | 0.583    |
|                                               | Pubertal 58(72.5%)| 34(68%)        |          |

| Table II: Comparison of insulin resistance status and mean HOMA-IR value between obese and non-obese adolescents (n=130) |
|-----------------------------------------------------------|-----------------|-----------------|----------|
| Insulin resistance status n(%)                            | Obese n=80      | Non-obese n=50  | P-value  |
| Insulin resistant                                         | 63(78.8%)       | 8(16.0%)        | <0.001   |
| Insulin sensitive                                         | 17(21.3%)       | 42(84.0%)       |          |
| HOMA-IR value (mean ±SD )                                 | 4.46±1.82       | 1.98±1.26       | <0.001   |
Insulin resistance is thought to be the key morbidity, which acts as a link between obesity and metabolic and cardiovascular diseases. Obesity causes insulin resistance by a number of mechanisms, including impaired insulin signaling, defects in glucose transport, defective insulin clearance and elevated intra portal free fatty acids with increased systemic adipocyte cytokines.

The exact prevalence of insulin resistance is not well established in adolescents. Prevalence of insulin resistance in obese children and adolescents vary greatly in different studies depending on different age group, ethnicity, methods used for determination of insulin resistance and also use of different definition of insulin resistance.

In present study, frequency of insulin resistance and mean HOMA-IR value was significantly higher in obese group in comparison to non-obese adolescents. In obese group, 78% adolescents were insulin resistant. These findings of our study match with the results of recent studies. Singh et al. found that prevalence of IR was 77.0% in obese adolescents and 19.7% in non-obese adolescents in their study. In another study done on US adolescents also revealed that mean HOMA-IR value was significantly higher in obese adolescents than non-obese adolescent (4.93 vs. 2.30).

**Table III:** Association of insulin resistance with severity of obesity and comparison of mean HOMA-IR value between grade I and grade II obese adolescents (n=80)

|                  | Grade I Obese n= 42 | Grade II Obese n= 38 | p-value |
|------------------|---------------------|----------------------|---------|
| Insulin resistance status |                     |                      |         |
| Insulin resistant  | 31(73.8%)           | 32(84.2%)            | 0.256   |
| Insulin sensitive  | 11(26.2%)           | 6(15.8%)             |         |
| HOMA-IR value     | Mean ±SD            |                      |         |
|                  | 3.92±1.58           | 5.06±1.89            | 0.005   |

**Table IV:** Association of acanthosis nigricans, puberty and central obesity with insulin resistance in obese adolescents(n=80)

|                                      | Insulin resistant, n=63 | Insulin sensitive, n=17 | p value |
|--------------------------------------|-------------------------|-------------------------|---------|
| Acanthosis nigricans                  |                         |                         |         |
| Present                              | 56 (89%)                | 0(0%)                   | <0.001  |
| Absent                               | 7(11%)                  | 17(100%)                |         |
| Pubertal stage                        |                         |                         |         |
| Pubertal                             | 51(81%)                 | 7(41%)                  | 0.006   |
| Prepubertal                          | 12(19%)                 | 10(59%)                 |         |
| Central obesity                      |                         |                         |         |
| Present                              | 47(75%)                 | 8(47%)                  | <0.03   |
| Absent                               | 16(25%)                 | 9(53%)                  |         |

**Figure 1:** Correlation of BMI with HOMA-IR value in obese adolescents (n=80) 

$r=+.469$, $p<0.001$ (Pearson correlation coefficient)

**Discussion**

Insulin resistance is thought to be the key morbidity, which acts as a link between obesity and metabolic and cardiovascular diseases. Obesity causes insulin resistance by a number of mechanisms, including impaired insulin signaling, defects in glucose transport, defective insulin clearance and elevated intra portal free fatty acids with increased systemic adipocyte cytokines. The exact prevalence of insulin resistance is not well established in adolescents. Prevalence of insulin resistance in obese children and adolescents vary greatly in different studies depending on different age group, ethnicity, methods used for determination of insulin resistance and also use of different definition of insulin resistance.

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and prevalence of insulin resistance was 52.1% in obese adolescents.\(^{22}\)

In this study mean HOMA-IR value of grade 2 obese adolescents were significantly higher than grade 1 obese adolescents (\(p=0.005\)). No significant difference was found when frequency of insulin resistance was compared between grade 1 and grade 2 obese adolescents (73.8% vs 84.2%, \(p=0.256\)). Scatter diagram and Pearson correlation efficient test showed positive correlation of BMI with HOMA-IR level. Other recent studies done in different countries observed almost similar findings in their study where HOMA-IR value increased with increasing BMI.\(^{23,25,26}\)

In pathogenesis of insulin resistance, fat distribution in body is more important than the total body fat. Visceral fat has a better correlation with insulin resistance than s.c. or total body fat.\(^{27}\) Excessive fatty-acid release from abdominal visceral adipose tissue into the portal circulation has an important influence on hepatic metabolism and islet cell function.\(^{28}\) Visceral fat also secretes higher levels of inflammatory adipokines than subcutaneous fat, which hamper insulin action.\(^{29}\) However, BMI value can not indicate body fat distribution and magnitude of visceral adiposity. Waist circumference (WC) are the measurements most commonly used to estimate abdominal fat because they have a positive, significant correlation to the amount of intra-abdominal fat as assessed by imaging studies both in adults and children.\(^{30}\) Our study finding also support the role of visceral adiposity in insulin resistance. Among obese group, waist circumference \(\geq\) 90th percentile was significantly associated with insulin resistance (\(p<0.03\)). This finding were similar to the findings observed by other studies.\(^{12,23,25,26}\)

In this study, we found significant association of acanthosis nigricans with insulin resistance in obese adolescents (\(p<0.001\)) which was consistent with the result of other studies done by Li et al. and Yamazaki et al.\(^{31,32}\) Acanthosis nigricans is a skin disorder which has been formally established as a clinical marker of insulin resistance in type 2 diabetes by American diabetic association.\(^{33}\) The theory is that high concentrations of insulin can stimulate epidermal keratinocyte and dermal fibroblast proliferation through high affinity binding to insulin-like growth factor 1 (IGF-1) receptors and elevated IGF-1 levels in obese patients.\(^{34}\)

Although the phenomenon of pubertal insulin resistance is well documented, the mechanism has not been clearly determined. However, some studies have hypothesized that the effect may be due to rapid acceleration of body fat during puberty.\(^{35,36}\) Alternatively, it has been hypothesized that the fall in insulin sensitivity may be driven by elevated level of sex hormones and transient changes in growth hormone levels in puberty. However insulin sensitivity again increases after puberty where sex hormones remain elevated in postpubertal period.\(^{37}\) In our study, among pubertal obese patients 87.93% were insulin resistant, which was significantly higher (\(p=0.006\)) in comparison to prepubertal obese subjects (54%). These findings of our study were comparable to result of the study done by Romualdo et al and Kurtoglu et al.\(^{12,14}\)

The present study has certain limitations. It was a cross sectional, hospital based study and family history of insulin resistance or diabetes mellitus was not evaluated in this study.

Present study showed high prevalence of insulin resistance in obese adolescents and higher BMI is associated with higher HOMA-IR value. Insulin resistance is associated with metabolic and cardiovascular complication suggested by multiple studies. So, prevention, timely diagnosis and appropriate management of obesity as well as insulin resistance is important to reduce the associated risk of metabolic and cardiovascular diseases in young population.

**Conclusion**

In this study, prevalence of insulin resistance in obese adolescents was 78.8%. Mean HOMA-IR level was significantly higher in obese adolescents. Insulin resistance in obese adolescents were associated with central obesity, acanthosis nigricans and puberty. Though high frequency of insulin resistance was found in both grade I and grade II obese adolescents, HOMA-IR level were significantly higher in grade II obese adolescents. However, further study with large sample size is suggested to confirm the findings.

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