## Original Article:

# Indices of insulin resistance in paediatric obesity

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## ABSTRACT

**Background:** Paediatric obesity is associated with insulin resistance (IR), which increases risk of type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD). Hyperinsulinaemic-euglycaemic clamp and minimal-model analysis frequently sampled intravenous glucose tolerance test (FSIVGTT) are used to assess IR, which are invasive, complex and expensive.

**Objective:** To assess IR using the derived indices namely, homeostasis model assessment of insulin resistance (HOMA-IR), fasting glucose-to-insulin ratio (FGIR), quantitative insulin-sensitivity check index (QUICKI), in obese children.

**Methods:** Fifty obese children (cases) and 50 apparently healthy age-and gender- matched non- obese children (controls) were studied. Obese children with body mass index (BMI; $Kg/m^2$) greater than $95^{th}$ percentile and non-obese children with BMI between $5^{th}$ to $95^{th}$ percentile were included in the study.

**Results:** Obese children had higher fasting insulin levels, HOMA-IR ($p<0.001$), FGIR ($p<0.001$) and QUICKI ($p<0.001$) when compared to controls; fasting blood glucose levels were comparable ($p=0.170$). A statistically significant correlation was observed between serum insulin and BMI, between insulin and all the derived indices and between the derived indices and BMI ($p<0.001$). HOMA-IR had more area under the curve (0.760) followed by FGIR (0.721) when compared to QUICKI (0.240).

**Conclusions**: Obese children were normoglycaemic with IR. HOMA-IR was found to be a stronger predictor of IR when compared to FGIR and QUICKI in obese children.

**Key Words:** *Insulin resistance, Homeostasis model assessment of insulin resistance, Fasting glucose-to-insulin ratio, Quantitative insulin-sensitivity check index, Paediatric obesity*

**Chandrasekhar T, Suchitra MM, Sachan A, Bitla AR, Srinivasa Rao PVLN. Indices of insulin resistance in paediatric obesity. J Clin Sci Res 2014;3:7-13.**

## INTRODUCTION

A global increase in the prevalence of obesity in childhood is being reported.[1] Asian countries are not immune to this phenomenon. A recent study conducted in South India found an increase in the proportion of overweight children from 4.9% in 2003 to 6.6% in 2005.[2] Studies in children have established that increasing body mass index (BMI; $Kg/m^2$) is associated with an increase in insulin resistance (IR).[3,4]

IR characterized by a decreased capacity of insulin to stimulate glucose uptake in muscles and adipose tissue and in supression of hepatic glucose production. Obese adolescents are found to have IR which increases the risk for development of type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD).[5] IR is found to play an important role in the development of metabolic syndrome (MetS) also known as syndrome X.[6] IR may have a role in the development of early structural atherosclerotic vascular changes in children with obesity.[7] Hence measurement of insulin sensitivity in paediatric obesity is required to assess the IR.

Received: 26 March, 2013.

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There are various methods for assesssing insulin sensitivity, such as, the well accepted hyperinsulinaemic-euglycaemic clamp[8] and the minimal-model analysis frequently sampled intravenous glucose tolerance test (FSIVGTT).[9] Though these are accepted methods they are complex invasive and expensive. The reliability of oral glucose tolerance test has been reported to similar to FSIVGTT and clamp technique in assessing insulin sensitivity,[10] but its application in large populations is limited. A simpler and more practical method to measure insulin resistance, the homeostasis model assessment of IR (HOMA-IR) was, therefore, developed for application in large epidemiologic studies.[11] HOMA-IR is calculated from fasting plasma glucose and serum insulin levels, which is an estimate of IR and is used as a surrogate marker of IR. HOMA-IR in normoglycaemic children was found to have a significant correlation with hyperinsuliaemic-euglycaemic clamp or FSIVGTT measurement.[5,12-14] Quantitative insulin-sensitivity check index (QUICKI) is a derived index obtained by calculating the inverse of the sum of logarithmically expressed fasting glucose and insulin levels. It therefore expresses insulin sensitivity as an inverse of IR.[15] Fasting glucose-to-insulin ratio (FGIR) have also been proposed to be useful in assessing insulin sensitivity,[16] with FGIR having a strong significant positive correlation with insulin sensitivity in obese children and adolescents.[5] QUICKI along with HOMA-IR have been found to correlate with the clamp technique in a cohort of normal and overweight paediatric cases.[17] Hence the derived indices HOMA-IR, QUICKI and FGIR have been frequently applied in screening populations.[18-20]

As IR is the prime forerunner for various risk factors, its assessment by valid and reliable methods is required. HOMA-IR, FGIR and QUICKI indicate presence of IR. However the validity of these indices in paediatric obesity in Indian population needs to be evaluated. Hence the present study was taken up to assess IR using the derived indices HOMA-IR, QUICKI and FGIR and to compare the strength of these indices in predicting IR in obese children.

## MATERIAL AND METHODS

Fifty obese children (cases) in the age group of 5-17 years attending the paediatric endocrinology out-patient clinic at Sri Venkateswara Institute of Medical Sciences, Tirupati, were studied. Fifty apparently healthy age- and gender-matched non-obese children served as control subjects. Informed consent for participating in the study was obtained from the parents / next responsible attendants. Obese children had a BMI of over 95$^{th}$ percentile for their age and gender as per the Centers for Disease Control and Prevention (CDC) growth charts 2000.[21] Apparently healthy non-obese children had a BMI between 5$^{th}$ to 95$^{th}$ percentile for their age and sex. Under weight children (BMI < 5$^{th}$ percentile for age and gender), children with other endocrine disorders such as hypothyroidism, Cushing's syndrome, type 1 diabetes mellitus, obesity syndromes, renal and liver diseases, active infection, those on medication and those who were unwilling to participate in the study were excluded from the study. The study was approved by the Institutional Ethics Committee. In all subjects, systolic, diastolic blood pressure and anthropometric measurements such as height (m), weight (Kg) were recorded and BMI (Kg/m$^2$) was calculated.

### Sample collection

Four mL of peripheral venous blood was collected from the subjects who were fasting for 8-12 hours. Two mL of blood was transferred into sodium fluoride and potassium oxalate anticoagulant containing bottle for

glucose estimation and two mL was transferred into additive free plain bottle for estimation of insulin. The plain samples were allowed to stand for 30 min and then centrifuged at 3000 rpm for 15 minutes. Serum was separated and stored at –80 $^{o}$C until analysis. Sodium fluoride/ potassium oxalate samples were centrifuged immediately and the plasma separated and analyzed for glucose on the same day. Glucose assay was performed by glucose oxidase peroxidase method using a commercial kit (Aspen Laboratories Pvt. Ltd., Delhi, India) on an autoanalyzer (Synchron CX9; Beckman Coulter, CA, USA). Insulin assay was performed by radioimmunoassay method using a commercial kit (Immunotech, Prague, Czech Republic) on automated gamma counter (Wallac, California, USA). The derived indices for IR namely, HOMA-IR [fasting glucose (mmol/L) × fasting insulin (μIU/mL)/22.5], QUICKI [(1/log fasting insulin (μIU/mL) + log fasting glucose (mg/dL)] and FGIR (fasting plasma glucose/ serum insulin ratio)[12] were calculated.

### Statistical Analysis

The distribution of continuous variables was tested using Kolmogorov-Smirnov test. Comparison of the mean values for the variables between the groups was done using unpaired student t-test for data with normal distribution. Mann-Whitney U-test was used for comparing variables which were not normally distributed. Spearman rank correlation was used to test the correlations among the variables. Receiver operater characteristic curve (ROC) analysis was performed to study the strength of the derived indices in predicting IR. A p-value of less than 0.05 was considered statistically significant. The statistical analysis was performed using statistical software, SPSS version 11.5 (SPSS, Inc., Chicago IL).

## RESULTS

Table 1 shows the baseline characteristics of the cases and controls. Table 2 shows comparison of the biochemical and derived indices between cases and controls. No

**Table 1: Baseline characteristics of cases and control subjects***

| Variable | Control subjects (n=50) | Cases (n=50) |
|---|---|---|
| Age (years) | 12.3±2.8 | 11.1±3.0 |
| BMI (Kg/m$^2$) | 17.15±3.18 | 27.51± 6.27 |
| Blood pressure (mm Hg) | | |
| Systolic | 95.8±12.2 | 99.7±9.6 |
| Diastolic | 65±7.2 | 67.1±6.7 |

*Data are presented as mean ±SD
BMI = body mass index; SD= standard deviation

**Table 2: Biochemical and derived indices in cases and control subjects***

| Parameter | Control (n=50) | Cases (n=50) | p-value |
|---|---|---|---|
| FBG (mg/dL) | 83.32±11.8 | 86.10±7.3 | 0.170 |
| Insulin (μIU/mL) | 6.98± 3.28 | 12.85± 7.51 | <0.001 |
| HOMA-IR | 1.68± 1.03 | 3.05± 2.62 | <0.001 |
| FGIR | 0.13±0.27 | 0.17±0.16 | <0.001 |
| QUICKI | 0.38±0.04 | 0.36±0.16 | <0.001 |

*Data are presented as mean ±SD
FBG = fasting blood glucose; SD= standard deviation; HOMA-IR = homeostasis model assessment of insulin resistance; FGIR = fasting glucose-to-insulin ratio; QUICKI = quantitative insulin-sensitivity check index

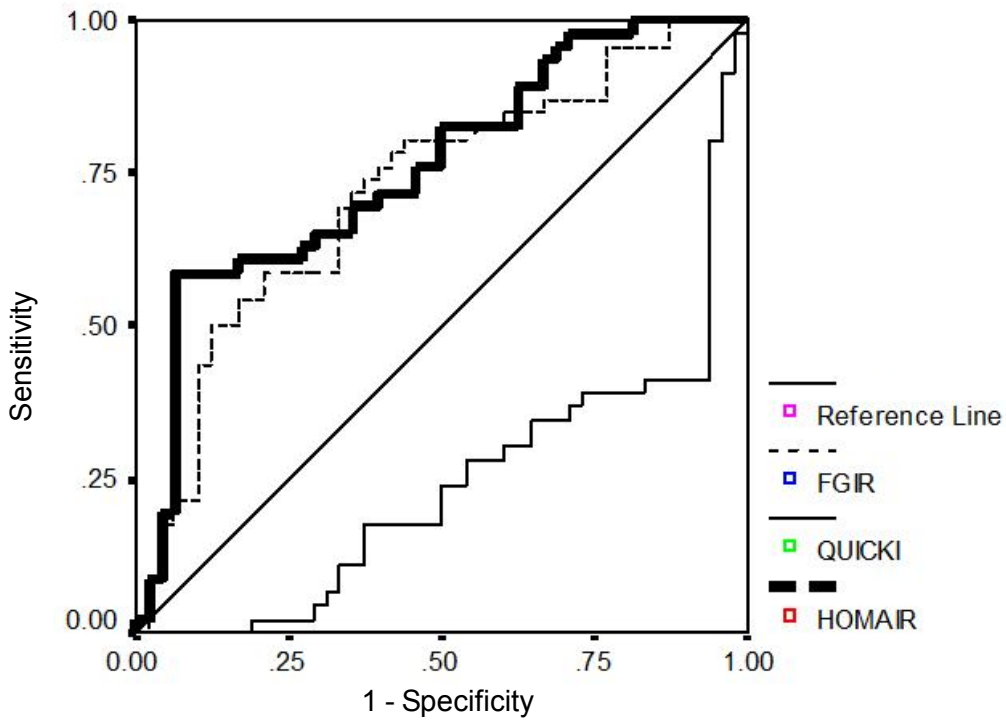


**Figure1:** ROC curves of IR indices studied

IR = insulin resistance ; HOMA IR = homeostasis model assessment of insulin resistance; FGIR = fasting glucose-to-insulin ratio; QUICKI = quantitative insulin-sensitivity check index

significant change in fasting blood glucose sugar was observed in cases when compared to controls (p=0.170). A significant higher fasting insulin levels were observed in obese children when compared to controls. The derived indices of IR, HOMA-IR, FGIR and QUICKI were significantly greater in cases when compared to controls.

Table 3 shows the association between Insulin, derived indices and BMI. A statistically significant correlation was observed between insulin and BMI, between insulin and all the derived indices and between the derived indices and BMI (p<0.0001).

Among the derived indices, the area under the curve (AUC) was more for HOMA-IR (0.760) followed by FGIR (0.721) when compared to QUICKI (0.240) (Figure 1, Table 4).

## DISCUSSION

Childhood obesity is associated with several metabolic changes such as IR, impaired glucose tolerance and T2DM.[22] Among these obesity is particularly associated with the presence of IR.[23] In obesity, IR increases the risk for development of hypertension, dyslipidaemia and metabolic syndrome. IR is also associated with the presence of systemic inflammation,

**Table 3: Association of anthropometry, biochemical and derived indices**

| | BMI | Insulin | HOMA-IR | FGIR | QUICKI |
|---|---|---|---|---|---|
| BMI | - | r = 0.519 (p<0.001) | r = 0.479 (p<0.001) | r = 0.428 (p<0.001) | r = –0.411 (p<0.001) |
| Insulin | - | - | r = 0.988 (p<0.001) | r = 0.975 (p<0.001) | r = –0.928 (p<0.001) |

r = correlation co-efficient; HOMA-IR = homeostasis model assessment of insulin resistance; FGIR = fasting glucose-to-insulin ratio: QUICKI = quantitative insulin-sensitivity check index

**Table 4: Comparison of AUC for HOMA-IR, FGIR and QUICKI**

| Variable | AUC | 95%CI | p-value |
|---|---|---|---|
| HOMA-IR | 0.760 | 0.662-0.857 | <0.001 |
| FGIR | 0.721 | 0.617-0.825 | <0.001 |
| QUICKI | 0.240 | 0.143-0.338 | <0.001 |

AUC = area under curve; CI = confidence intervals; HOMA-IR = homeostasis model assessment of insulin resistance; FGIR = fasting glucose-to-insulin ratio: QUICKI = quantitative insulin-sensitivity check index

endothelial dysfunction and atherosclerosis, which contribute to the risk of CVD.[22] Hence it is necessary to measure insulin sensitivity in order to assess the presence of IR in obese children. The well accepted hyperinsulinaemic-euglycaemic clamp technique requires a steady intravenous infusion of insulin in one arm and a variable intravenous glucose infusion in the other arm with collection of a number of blood samples to monitor serum glucose levels. FSIVGTT is comparatively less labor intensive than clamp techniques, however, it also requires multiple blood samples over a prolonged period.[24] Hence these two techniques have been claimed as being invasive, labor intensive and expensive. The derived indices HOMA-IR, QUICKI and FGIR were found to correlate well with IR and HOMA-IR was described as being a practical alternative for detecting IR.[25] HOMA-IR was found to be greater in obese children when compared to healthy lean controls in the present study. The other measures FGIR and QUICKI were also found to be greater in the obese children when compared to controls.

A high fasting insulin concentration has been identified as an independent CVD risk factor and there is now considerable evidence demonstrating a link between obesity (particularly central obesity) and hyper-insulinemia in children.[26] A research in Singaporean adults has revealed a relationship between BMI, abdominal diameter and insulin resistance.[26,27] It has been reported that in children and adolescents the measurement of fasting insulin levels in the presence of normoglycaemia may be an indicator of IR, which is as good as HOMA-IR, FGIR and QUICKI.[22] However the variability of insulin measurements between laboratories makes it difficult in comparing the insulin levels obtained from different studies.[28] In the present study fasting insulin levels and HOMA-IR were found to be significantly higher in obese children when compared to controls and a positive significant correlation was observed between HOMA-IR and insulin. Similarly FGIR was also found to correlate positively with fasting insulin levels. QUICKI was found to have a significant negative correlation with insulin, indicating its inverse relation with IR.[15] However, no significant difference in the fasting blood glucose levels was observed between the cases and controls. Subjects with IR have hyperinsulinemia with normal or elevated blood glucose levels.[12] In this study the derived indices HOMA-IR, FGIR and QUICKI were found to significantly reflect IR in obese children who were normoglycemic.

In the present study, higher HOMA-IR levels represent greater degrees of insulin resistance as the ROC curve analysis revealed greater area under the curve for HOMA-IR when compared to FGIR and QUICKI. Similar findings were reported in a study wherein HOMA-IR was found to be more reliable than FGIR and QUICKI and HOMAIR cut-off point of 3.16 was reported to yield a sensitivity of 76% and a specificity of 66% for diagnosis of IR in the obese children.[12]

BMI is a simple index of adiposity and is generally found to correlate with the higher insulin levels in obses children.[29] In the present study also, a significant positive correlation between BMI and fasting insulin levels was observed. Similarly, the indices of IR, HOMA-IR and FGIR were found to have a positive significant correlation with BMI. These findings document the association between obesity and hyperinsulinaemia as well as the derived indices of IR in children.

Obesity and IR sets the stage for the risk of T2DM with its associated risk factors such as CVD and IR is observed in the paediatric obese population. Hence screening this group of obese children for the presence of IR is of prime importance in arresting the progression of these risk factors into adulthood. In the search for practical and reliable tests to assess IR, HOMA-IR has emerged as a reliable diagnostic tool which is comparable with the clamp techniques. HOMA-IR is found to be a stronger predictor of IR when compared to FGIR and QUICKI in normoglycemic obese children.

## ACKNOWLEDGEMENT

This study was funded by Indian Council of Medical Research (ICMR), New Delhi (3/2/ 2011-12/PG-thesis HRD-8) and "Sri Balaji Arogya Varaprasadini scheme of Sri Venkateswara Institute of Medical Sciences, Tirupati".

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