RESEARCH PAPER

# Evaluation of Surrogate Markers for Insulin Resistance for Defining Metabolic Syndrome in Urban Indian Adolescents

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**Objective:** To compare parameters of insulin resistance, with special reference to McAuley index, in urban Indian adolescents, and to establish their cut-off values for defining metabolic syndrome.

**Design:** Cross-sectional study.

**Setting:** Schools located in four different geographical zones of Delhi, India.

**Participants:** 695 apparently healthy adolescents grouped as normal weight (298), overweight (205) and obese (192).

**Outcome measures:** Cut-off point for indices of insulin resistance was assessed by fasting insulin, insulin glucose ratio, and other methods (HOMA model, QUICKI, McAuley index) to define metabolic syndrome.

**Results:** The McAuley index increased progressively from normal weight to obese adolescents in both sexes. McAuley index was significantly lower in adolescents with metabolic syndrome (5.36 ± 1.28 *vs.* 7.05 ± 1.88; *P*<0.001). McAuley index had the highest area under curve of receiver operator characteristics [0.82 (0.02)] as compared to other indices of insulin resistance. McAuley index of 6.23 had the highest specificity (88%) with sensitivity of 63.3% for diagnosing metabolic syndrome, whereas insulin glucose ratio had the highest sensitivity (79.7%) but low (55.5%) specificity. McAuley index was negatively correlated with height (r= -0.257, *P*=<0.001), weight (r= -0.537, *P*=<0.001), body mass index (r= -0.579, *P*<0.001), waist circumference (r= -0.542, p<0.001), and waist hip ratio (r= -0.268, *P*<0.001).

**Conclusions:** Among various parameters of insulin resistance, McAuley index had the highest specificity, and insulin glucose ratio had the highest sensitivity in diagnosing metabolic syndrome in urban Indian adolescents.

**Keywords:** *Diabetes, Hypertrigyceridemia, Insulin resistance, Waist circumference, Waist-hip ratio.*

Insulin resistance (IR) is characterized by a lack of physiological response of peripheral tissues to insulin action, leading to the metabolic and hemodynamic disturbances known as the Metabolic syndrome (MS). Obese children and adolescents, with IR, are at increased risk of metabolic syndrome, type 2 diabetes mellitus and cardiovascular diseases [1].

Tools used for quantifying insulin sensitivity and resistance include direct methods such as hyperinsulinemic euglycemic glucose clamp study, and insulin suppression test. For clinical studies, simpler indirect methods based on measuring plasma insulin levels during fasting or after glucose stimulus have been advocated [2]. These include fasting insulin levels, insulin-glucose ratio, Homeostasis model assessment (HOMA-IR) [3], Quantitative insulin sensitivity check index (QUICKI) [4], and McAuley index [5]. The utility of HOMA-IR in assessment of IR has been validated in children and adolescents. McAuley index, which uses fasting insulin and triglyceride values, provides a useful and simple tool to assess IR in population based studies as well as for clinical practice [6-10].

There is limited evidence validating McAuley index as a tool to identify and define MS in adolescent population [11]. We undertook this study to estimate and compare IR as estimated by various surrogate markers such as, fasting insulin, insulin-glucose ratio, HOMA-IR, QUICKI and McAuley index. In addition, we aimed to establish cut-off values of the various indices for defining MS in urban Indian adolescents.

## Methods

In this cross sectional study (conducted between 2004-2006), 900 randomly selected adolescents (300 each in obese, overweight and normal weight categories) in the age group of 10-17 years, from our earlier survey in schools located in four different geographical zones of Delhi [12] were invited. A total of 695 apparently healthy

adolescents, including 192 obese, 205 overweight and 298 subjects with normal body mass index (BMI), as defined by International Obesity Task Force (IOTF) criteria [13], consented to participate. These subjects underwent a detailed clinical and hormonal evaluation (thyroid function tests); and were found to be free of any systemic illness.

Ethical clearance was obtained from Institutional Ethical Committee of Institute of Nuclear Medicine and Allied Sciences, New Delhi. A prior consent for the study was taken from the school administration and from the parents/guardians. At the time of initiating the study, parents/guardians of each participant provided written informed consent for their ward's participation. Assent from children was also obtained before drawing blood samples.

Height was measured to the nearest 0.1 cm using a stadiometer, and weight was measured to the nearest 0.1 kg, using standard methods [12]. Height and weight measurements were taken twice and the mean of two measurements was used to calculate BMI. The waist circumference and the hip circumference were measured as previously described [12].

The adolescents were given written instructions to fast for 12 hours and compliance was determined by interviewing the subjects and their parent(s) on the morning of the test. For the oral glucose tolerance test, the glucose load was calculated based on the body weight (1.75 g/kg). Air tight packets of calculated glucose load were prepared for each child on the day prior to the test.

After a 12-hour overnight fast, venous blood samples were drawn and the participants were given the glucose load. Two-hour post glucose load samples were taken for plasma glucose and serum insulin. During the interim period, the children stayed fasting in the examination hall and did not indulge in any strenuous physical activity. Fasting and post-glucose load plasma glucose was estimated the same day and the remaining aliquots were stored at – 20ºC until assayed.

Measurements of plasma glucose were done by glucose oxidase–peroxidase method (Trinder, Clonital, Italy). Fasting serum total cholesterol, HDL and triglycerides were estimated using automated analyzer (Hitachi-902; Roche, Manhiem, Germany) and their commercial kits. Serum insulin was measured using commercial kits and electrochemiluminiscence machine (Elicsys, Roche Diagnostics), with measurement range of 3.47-2083.5 pmol/L and normal value 14.58-152.8 pmol/L. Intra-assay and inter-assay coefficient of variation were 4.3% and 3.4%, respectively.

*Definitions*: Waist circumference cut-offs as proposed by Kurian, *et al*. [14] were used to identify children with a waist circumference >90th centile. Waist-hip-ratio (WHR) of 0.9 in boys and 0.8 girls was taken as cut-off. Hypertension was defined as systolic (SBP) and diastolic blood pressure (DBP) greater than 90th centile for age and sex [15].

MS in adolescents was defined by the International Diabetes Federation (IDF) criteria (waist circumference >90th percentile with any two of the parameters triglyceride ≥150 mg/dL, HDL <40 mg/dL, FPG >100 mg/dL and BP >130/85 mmHg) [16] and Adult Treatment Panel (ATP) III criteria (abnormality in any of three parameters namely waist circumference >90th percentile, dysglycemia, hypertension, hypertriglyceridemia and low HDL) [17]. Any degree of dysglycemia was defined by impaired fasting glucose (IFG) normal 101-125 mg/dL, impaired glucose tolerance (IGT) – 2-hour post 75 glucose load normal 141-199 mg/dL) or diabetes mellitus (fasting plasma glucose ≥126 mg/dL or post glucose plasma glucose ≥200 mg/dL) as per the definitions provided by the American Diabetic Association. We took adult cut-off points in MS-ATP definition (triglyceride >150 mg/dL, HDL <40 mg/dL), as recent Indian data have shown that 95th percentile for triglycerides in adolescents was above the adult limit of 150 mg/dL, and 5th percentile for HDL was lower than 40 mg/dL [18].

IR was assessed by fasting insulin levels, insulin glucose ratio (IGR) and calculating HOMA, QUICKI and McAuley indices using standard definitions [3-5].

*Statistical analysis* was carried out using SPSS version 20.0 (SPSS Inc. Chicago, USA). All parametric data were analyzed by independent student's t-test in categorical groups (2 groups) and ANOVA test (>2 groups). All non-parametric data were analyzed by Chi-squared test. Pearson's correlation coefficient was calculated to assess the strength of relationship between lipid HOMA-IR and other parametric variables. Receiver operator characteristic (ROC) curves were plotted using sensitivity and specificity of various indicesand presence or absence of metabolic abnormalities. Youden's index were calculated by sensitivity – (1-specificity), obtained from co-ordinates of curve. Highest value of Youden's index was used to identify cut-off value for various IR indexes. A $P$ value of $< 0.05$ was considered statistically significant.

## RESULTS

The basic characteristics of the study population are depicted in ***Table* I**. There were 192 (27.6%) obese (92 boys), 205 (29.5%) overweight (107 boys) and 298

(42.9%) normal weight (146 boys) adolescents. MS defined using modified ATP III criteria was present in 1%, 18.4%, and 49%, and by IDF criteria in 0.3%, 13.6% and 46.4%, respectively in normal BMI, overweight and obese adolescents.

McAuley Index was significantly lower in boys when compared to girls in total study population (***Table* I**). Fasting insulin, IGR and HOMA-IR increased; and QUICKI and McAuley Index decreased progressively from normal weight to obese adolescent in both sexes. McAuley Index was significantly higher in normal weight boys compared to girls ($P$=0.002), but was comparable among adolescent boys and girls in overweight ($P$=0.117) and obese categories ($P$=0.867) (***Table* II**).

McAuley index was significantly lower in adolescents with MS defined either by IDF or ATP-III criteria. It was also significantly lower when individual components of the metabolic syndrome were analyzed separately (***Table* III**). Area under the curve of ROC was the highest for McAuley index, followed by HOMA-IR and QUICKI. The McAuley Index cutoff of 6.23 gave maximum specificity (88.%) with moderate sensitivity (63.3%). Fasting insulin levels of 15 mU/mL also had high specificity (78.2%) but low sensitivity (59.8%). Insulin glucose ratio, HOMA-IR, and QUICKI were sensitive but had low specificity (***Table* IV**).

McAuley index was negatively correlated with weight (r=–0.537, $P$<0.001), BMI (r=–0.579, $P$<0.0001), WC (r=–0.542, $P$<0.001), and WHR (r=–0.268, $P$<0.001). Log of McAuley index had negative linear correlation HOMA-IR ($r^2$=0.965) (***Fig.* 1**).

## DISCUSSION

In the present study, McAuley index was significantly higher in adolescents with MS compared to those without MS. McAuley index was also significantly higher in adolescents with individual parameters of MS except HDL cholesterol. McAuley index had the highest area under curve followed by HOMA-IR and QUICKI, while IGR had the lowest area under curve. IGR, QUICKI and HOMA-IR had almost similar sensitivity that was higher than McAuley index , but had low specificity.

Insulin resistance is a key contributor to the development of MS, which, in turn, predicts future risk of type-2 diabetes mellitus and cardiovascular disease. A measure of insulin resistance which can predict MS early, thereby providing an opportunity for instituting preventive measures, would have significant clinical

**TABLE I** BASIC CHARACTERISTICS OF STUDY POPULATION (N=695)

| *Parameters* | *Total* | *Boys (n=346)* | *Girls (n=349)* | *P value* |
|---|---|---|---|---|
| Age (y) | 13.3±1.9 | 13.3±1.9 | 13.5±1.9 | 0.159 |
| Height (cm) | 154.9±10.9 | 157.1±12.4 | 152.7±8.6 | <0.001 |
| Weight (kg) | 57.0±18.4 | 57.6±19.6 | 56.5±17.2 | 0.454 |
| BMI (kg/m$^2$) | 23.3±5.8 | 22.8±5.6 | 23.89±5.9 | 0.016 |
| Waist circumference(cm) | 74.9±15.1 | 78.2±16.4 | 71.6± 13.0 | <0.001 |
| Systolic BP (mm Hg) | 112±12 | 113±12 | 111±11 | 0.001 |
| Diastolic BP (mm Hg) | 75±8 | 76±8 | 74±8 | 0.004 |
| Triglycerides (mg/dL) | 137.9±52.6 | 133.9±55.8 | 142.0±49.0 | 0.043 |
| Total cholesterol (mg/dL) | 187.7±46.9 | 185.7±46.8 | 189.8±47.2 | 0.26 |
| HDL cholesterol (mg/dL) | 44.2±7.7 | 44.1±7.3 | 44.3±8.1 | 0.642 |
| LDL cholesterol(mg/dL) | 115.9±43.6 | 114.9±43.0 | 117.0±44.2 | 0.523 |
| Fasting plasma glucose (mg/dL) | 91±9 | 92±9 | 91±9 | 0.251 |
| *2-hour plasma glucose (mg/dL) | 101±18 | 101±19 | 102±18 | 0.697 |
| Fasting insulin (µU/mL) | 12.6±8.7 | 11.9±8.2 | 13.2±9.1 | 0.047 |
| IGR | 2.47±1.67 | 2.32±1.59 | 2.60±1.73 | 0.026 |
| QUICKI | 0.34±0.04 | 0.34±0.03 | 0.34±0.04 | 0.183 |
| HOMA-IR | 2.87±2.13 | 2.72±1.98 | 3.01±2.25 | 0.079 |
| McAuley index | 6.72±1.90 | 6.91±1.92 | 6.52±1.84 | 0.006 |

*All values in mean±SD. BMI-body mass index, BP-blood pressure, HDL-high density lipoprotein, LDL-low density lipoprotein, P-plasma, IGR-insulin glucose ratio, QUICKI-quantitative insulin sensitivity check index, HOMA-IR- homeostatic model analysis for insulin resistance, *2-hour post-glocose level.*

**TABLE II** COMPARISON OF INSULIN RESISTANCE INDICES IN NORMAL, OVERWEIGHT AND OBESE ADOLESCENTS

| *Parameter* | *Normal (n= 298)* | *Overweight (n=205)* | *Obese (n=192)* |
|---|---|---|---|
| Fasting insulin | 8.30±3.63 | 12.87±7.40 | 18.80±9.48 |
| IGR | 1.66±1.22 | 2.52±1.46 | 3.65±1.76 |
| QUICKI | 0.36±0.04 | 0.33±0.03 | 0.32±0.03 |
| HOMA-IR | 1.86±1.46 | 2.93±1.76 | 4.36±2.44 |
| McAuley Index | 7.84±1.95 | 6.33±1.32 | 5.40±1.23 |
| *Boys (number)* | 147 | 107 | 92 |
| Fasting Insulin | 7.62±6.28 | 11.80±6.08 | 18.78±8.58 |
| IGR | 1.53±1.24 | 2.31±1.25 | 3.60±1.65 |
| QUICKI | 0.37±0.03 | 0.34±0.03 | 0.32±0.04 |
| HOMA-IR | 1.85 | 2.93 | 4.36 |
| McAuley Index | 8.19±1.82 | 6.47±1.23 | 5.41±1.38 |
| *Girls (number)* | 151 | 98 | 100 |
| Fasting Insulin | 8.95±6.19 | 14.03±8.44 | 18.82±10.28 |
| IGR | 1.79±1.20 | 2.75±1.65 | 3.70±1.85 |
| QUICKI | 0.36±0.05 | 0.33±0.03 | 0.32±0.03 |
| HOMA-IR | 2.01±1.46 | 3.22±2.05 | 4.32±2.69 |
| McAuley Index | 7.50±2.01 | 6.18±1.39 | 5.38±1.07 |

*All values in mean±SD. *P values calculated with ANOVA test were <0.001 for all parameters in both boys and girls. IGR-insulin glucose ratio, QUICKI-quantitative insulin sensitivity check index, HOMA-IR- homeostatic model analysis for insulin resistance.*

utility. Previously, we found that a HOMA-IR value of 2.5 defines MS (unpublished observation). A cross sectional study from Spain reported a robust correlation of McAuley index with Framingham risk score [19]. Another study identified that McAuley index was a more accurate measurement to detect IR than other indices [20]. McAuley index has been shown to have better reproducibility in comparison with other indices [21]. Mean McAuley index in this population was 6.72 with highest in obese and lowest in normal weight adolescents.

**TABLE III** MCAULEY INDEX ACCORDING TO PRESENCE OR ABSENCE OF COMPONENTS OF METABOLIC SYNDROME

| *Parameter* | *Present* | *Absent* | *P Value* |
|---|---|---|---|
| High waist circumference | 5.73± 1.29 | 7.36± 1.96 | <0.001 |
| Hypertension | 5.66± 1.47 | 6.89± 1.91 | <0.001 |
| Hypertriglyceridemia | 5.41± 1.04 | 7.49± 1.89 | <0.001 |
| Low HDL | 6.61± 2.25 | 6.76± 1.75 | 0.10 |
| Dysglycemia | 5.68± 1.33 | 6.88± 1.96 | <0.001 |
| MS-IDF | 5.30± 1.30 | 7.01± 1.87 | <0.001 |
| MS-ATP | 5.36± 1.28 | 7.05± 1.88 | <0.001 |

*HDL-high density lipoprotein, MS-IDF-metabolic syndrome-International Diabetes Federation, MS-ATP-metabolic syndrome-Adult Treatment Panel.*

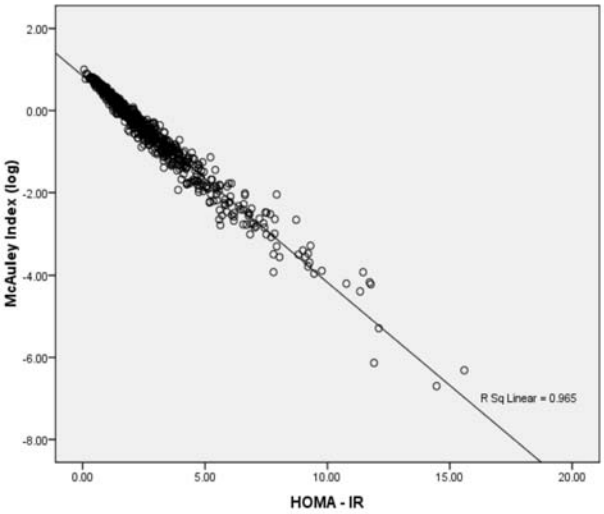


**FIG. 1** *Regression plot of log of McAuley index and HOMA-IR.*

A similar pattern of McAuley index has also been reported in adolescents from New Zealand [22]. Other studies in adults reported a similar value of McAuley index in other populations [6,8,23-25].

**TABLE IV** ROC CURVE ANALYSIS FOR VARIOUS INSULIN RESISTANCE INDEXES TO DIAGNOSE METABOLIC SYNDROME

| *Index* | *AUC±SE* | *95% CI* | *P value* | *Cut-off* | *Sensitivity* | *Specificity* |
|---|---|---|---|---|---|---|
| McAuley Index | 0.82±0.020 | 0.78-0.856 | <0.001 | 6.23 | 63.3% | 88.0% |
| HOMA-IR | 0.76±0.02 | 0.71-0.81 | <0.001 | 2.55 | 72.8% | 62.1% |
| QUICKI | 0.76±0.02 | 0.71-0.81 | <0.001 | 0.32 | 76.8% | 59.0% |
| IGR | 0.73±0.02 | 0.68-0.78 | <0.001 | 2.0 | 79.7% | 55.5% |
| Fasting Insulin | 0.75±0.02 | 0.71-0.809 | <0.0001 | 15.0 | 59.8% | 78.2% |

*ROC-Receiver operator characteristics, AUC±SE- area under curve ± standard error, CI-confidence interval, IGR-insulin glucose ratio, QUICKI-quantitative insulin sensitivity check index, HOMA-IR- homeostatic model analysis for insulin resistance.*

**WHAT IS ALREADY KNOWN?**

- Insulin resistance can be measured by various indices like plasma insulin, insulin glucose ratio, HOMA-IR, QUICKI and McAuley index.

**WHAT THIS STUDY ADDS?**

- McAuley index is superior to other indices of insulin resistance for the diagnosis of MS in urban Indian adolescents.
- A cut-off value of 6.23 of McAuley index has high specificity and sensitivity to diagnose MS in Indian urban adolescents.

A study from Belgium analyzed various indices of IR and compared them with M value obtained from hyperinsulinemic euglycemic clamp study from a large database. McAuley index had area under curve of (0.83), which was similar to our study, but area under curve for HOMA-IR (0.90) was higher than McAuley index [7]. Another study among non-diabetic offsprings of diabetic individuals reported the highest area under the curve to detect MS with McAuley index (0.895) [11].

A study among newly diagnosed subjects with type-2 diabetes compared fasting insulin and McAuley index to identify MS (ATP-III criteria). Fasting insulin and McAuley index (5.8) had high specificity (70% and 80% respectively) but low sensitivity, similar to that reported in the present study [22]. Another study compared QUICKI and McAuley index with the S(i) index, and found that McAuley index (5.8) was more specific (91.0%) and sensitive (75%) compared to QUICKI [6]. This suggests that McAuley index has better specificity and predictive value for MS in our population, which has traditionally been shown to have high prevalence of hypertriglyceridemia [18,26].

Among various parameters of insulin resistance, McAuley index had the highest specificity, in contrast to IGR which had the highest sensitivity in diagnosing MS in urban Indian adolescents. Since IR has been implicated in causation of MS, it may imply that metabolic abnormalities associated with MS are the end result of long term IR. These indices can be used to estimate underlying IR and thereby the risk of MS. This information can be of utility in the early diagnosis of MS and institution of appropriate management.

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