Comparison of Definitions of the Metabolic Syndrome in Adult Asian Indians

JS Wasir*, A Misra*, NK Vikram**, RM Pandey***, R Gupta****

Abstract
Objective: The optimum definition of the metabolic syndrome (MS) is not known. We compared international definitions of MS [recently proposed modified definition of National Cholesterol Education Programme, Adult Treatment Panel III (NCEP, ATP III) and International Diabetes Federation (IDF)] with two proposed candidate definitions in adult Asian Indians.

Design: Data from three previous cross-sectional studies carried out in North India were analyzed.

Subjects: The study included 2050 adult (mean age: 40 ± 18 years) Asian Indian subjects residing two metropolitan cities.

Measurements: Candidate definitions of MS were proposed by modifying the NCEP, ATP III and IDF definitions by including the following modified variables into two combinations (MS-ATP1 and MS-IDF1); waist circumference cut-off points as >90 cm in males and >80 cm in females, body mass index (BMI) cut-off point as >23 kg/m², impaired fasting glucose (IFG) cut-off point >100 mg/dl and waist circumference as an obligatory criterion.

Results: Maximum overall and gender-specific prevalence of the MS (49.2% overall; 41.4% in males; 55.3% in females) was observed using the definition which included modified cut-off points of WC (non-obligatory), BMI, and IFG (>100 mg/dl) in addition to other defining parameters. Compared to other definitions this proposed candidate definition maximally detected presence of MS in subjects with IFG and T2DM [Percentage prevalence: 78.1% (73.0-82.7) and 91.1% (84.2-95.6)]. Even in subjects without abdominal obesity, a high prevalence of other abnormal defining parameters of the metabolic syndrome; hypertension (≥ 130 or ≥ 85 mmHg), 35.7%; BMI > 23 kg/m², 15.3%; hypertriglyceridemia (>150 mg/dl), 20.2% and low levels of HDL-C (< 40 in males; <50 mg/dl in females), 55% were seen. Further, 10.5% of subjects who did not have abdominal obesity had presence of at least 3 risk variables of the metabolic syndrome. These data indicate that by making abdominal obesity a mandatory criterion would lead to missing of some cases of the metabolic syndrome.

Conclusion: By including BMI and making waist circumference as a non-obligatory criterion, more cases of the metabolic syndrome is detected. For Asian Indians, making waist circumference as mandatory variable in the definition of the metabolic syndrome lead to non-inclusion of nearly 11% cases who would otherwise be diagnosed as metabolic syndrome according to modified NCEP, ATP III definition.

INTRODUCTION
Insulin resistance has been implicated as the central process in pathogenesis of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). Keeping this concept centrally, the World Health Organization (WHO) in 1998 proposed the first formal definition for the insulin resistance syndrome. This definition required biochemical measurement of insulin resistance as an obligatory criterion. In 2001 the National Cholesterol Education Programme, Adult Treatment Panel III (NCEP, ATP III) introduced a clinical definition of the metabolic syndrome. The definition was based on the premise that clustering of ‘lipid and non-lipid’ parameters in an individual increased future risk of development of type T2DM and CVD. Further, other definitions of the metabolic syndrome have been formulated and evaluated for their adequacy for predicting presence of, or the future risk of T2DM and/or CVD.

Investigators have reported conflicting observations regarding aptness of various definitions of the metabolic syndrome to detect the presence of insulin resistance or to
correctly predict future risk of CVD or T2DM. Further, the applicability of NCEP, ATP III definition to various ethnic groups has been doubted particularly for south Asians who have comparatively lower body mass index (BMI), excess body fat, truncal and abdominal adiposity, lower waist circumference (WC), and reported to have higher magnitude of insulin resistance and risk for T2DM and CVD than white Caucasians. Specifically, waist circumference as defined by the NCEP, ATP III cut-off points underestimates prevalence of abdominal obesity in adult Asians, and recently we have further strengthened the data by providing waist circumference action levels for adult Asian Indians, which are lower than the presently accepted international accepted cut-off points for defining abdominal obesity. Further, we have recently shown that the NCEP, ATP III definition underestimates prevalence of the metabolic syndrome and, in particular, is poor in identification of the metabolic syndrome in adult Asian Indian subjects with T2DM. Moreover, we have proposed that a candidate definition of the metabolic syndrome which included, in addition to other NCEP, ATP III definition parameters, modified ethnic specific cut-off points for; body mass index (BMI), waist circumference and a measure of truncal subcutaneous fat (subscapular skinfold thickness), best identified the metabolic syndrome in subjects with impaired fasting glucose (IFG) and T2DM. In line with our observations and those from other investigators, the American Heart Association/National Heart, Lung, and Blood Institute in their latest scientific statement have recommended using the NCEP, ATP III definition with lower cut-off point for defining abdominal obesity for ethnic groups who are more insulin resistance and prone to develop T2DM and also lower cut-off point for diagnosis of IFG (>100 mg/dl) (termed as MS-ATP in the current study). The definition of the metabolic syndrome in adults, therefore, continues to be modified. Finally, according to results of our recent study, optimization of definition of the metabolic syndrome is also needed for adolescent Asian Indians.

Realizing the need for a universally acceptable and easy-to-use definition of the metabolic syndrome, which may be utilized for research and clinical purpose and also for international comparisons, the International Diabetes Federation (IDF) proposed a new definition of the metabolic syndrome. The changes in this definition as compared to NCEP, ATP III definition included; abdominal obesity is an obligatory criterion, ethnic-specific cut-off points of waist circumference, and a lower cut-off point (>100 mg/dl) of fasting blood glucose. Some perceived shortcomings of the NCEP, ATP III definition have been corrected by the IDF definition. However, the IDF definition has not been tested in epidemiological studies, compared against other definitions of the metabolic syndrome, and tested in various ethnic groups, specifically Asian Indians.

We hypothesized that in adult Asian Indians the IDF definition would identify the metabolic syndrome better in subjects with IFG and T2DM as compared to the NCEP, ATP III definition, and candidate definitions proposed by us. In present study, we tested the recently proposed modified definition of NCEP, ATP III, IDF definition, and two candidate definitions of the metabolic syndrome in an adult population sample from North India.

**Materials and Methods**

**Study design and sampling method**

For the current analysis data from three epidemiological, population-based studies carried out between 1998 to 2003 in two metropolitan cities in North India by two investigation teams, were analyzed. Approval was taken from respective institutional review boards. The methodology and field procedures are described in detail elsewhere. Briefly, two studies were conducted in New Delhi by our group (AM, NRV); the first on urban adult population the second on young subjects aged 14-25 years. The third study, Jaipur Heart Watch-2 (JHW-2) was conducted by another investigator (RG) in the city of Jaipur located in Northwest state of Rajasthan, nearly 250 kilometers from New Delhi. In these studies, random selection of subjects was carried out as described previously. An informed consent was obtained from all subjects. For the present study, data from the subjects older than 18 years of age have been analyzed.

**Clinical profile and measurements**

The data of blood pressure measurement and anthropometric parameters (height, weight, waist and hip circumferences) were available for all subjects. Field procedures including blood pressure measurement and anthropometry were the same in all the studies, and were carried out by a single trained observer at each site of study. Blood pressure was measured in the right arm with the subject seated and rested for 5 minutes using a standard mercury sphygmomanometer. At least two readings at 5-minute intervals were taken and if an abnormal value was obtained, then another reading was taken after 30 minutes of rest. Waist circumference was measured midway between the iliac crest and the lower most margin of the ribs with bare belly and at the end of normal expiration.

**Biochemical measurements**

Fasting blood glucose (FBG) levels and lipid profile [Total cholesterol (TC), serum triglycerides (TG) and high-density lipoprotein cholesterol (HDL-c)] were estimated within 48 hours of collection according to previously described methods. Low-density lipoprotein cholesterol (LDL-c) levels were calculated using the Friedewald’s formula.

**Definitions**

A. Definitions of the metabolic syndrome: The
following is a brief description of the various definitions (see Table 1 for complete description):

1. Recently proposed modified definition of NCEP, ATP III\(^1\)(MS-ATP) and IDF (MS-IDF)\(^1\) definitions were set as reference for comparison.
2. MS-ATP definition was modified by incorporating BMI to generate a modified definition (MS-ATP1).
3. IDF (MS-IDF) definition was modified by addition of BMI as a defining parameter in addition to the proposed parameters to generate the definition MS-IDF1.
4. MS-ATP and MS-IDF definitions of the metabolic syndrome are similar to each other in all ways except one i.e. waist circumference is obligatory in the MS-IDF definition and non-obligatory in the MS-ATP definition.
5. The two candidate definitions proposed by us include BMI (>23 kg/m\(^2\)) as an additional defining parameter (MS-ATP1, and MS-IDF1).
6. The metabolic syndrome was identified according to the following:
a. Three or more defining parameters were abnormal (MS-ATP, MS-ATP1), or
b. Along with presence of abnormal obligatory criterion, presence of two other criteria (MS-IDF and MS-IDF1).

B. Blood glucose levels were classified as following:\(^1\)
1. Normoglycemia: <100 mg/dl
2. Impaired fasting glucose (IFG): 100 to 125 mg/dl
3. T2DM: \(^3\) 126 mg/dl

Statistical analysis

Data were recorded on a pre-designed performa and managed on MS Excel worksheet. The statistical analysis was done in three parts. First, we compared the recently proposed modification of the NCEP, ATP III (MS-ATP) and IDF (MS-IDF) definitions of the metabolic syndrome to determine if waist circumference should be used as an obligatory criterion. Secondly, the IDF (MS-IDF) and modified IDF (MS-IDF1) were used to determine the importance of BMI as a defining parameter of the metabolic syndrome. Finally, the two candidate definitions of the metabolic syndrome were compared with each other and also with MS-ATP and MS-IDF definition of the metabolic syndrome by computing the percentage prevalence and 95% confidence interval. Further, we applied all the definitions to three subgroups (normoglycemia, IFG and T2DM). The prevalence of the metabolic syndrome was compared overall and in subgroups. STATA 8.0 statistical software was used for data analysis.

RESULTS

The study included clinical and biochemical details of 2050 subjects. The mean age was 40 ± 18 years. The average values and prevalence of measures of obesity, and surrogate markers of insulin resistance are shown in Table 2. All the measures of obesity (except abnormal BMI) were more prevalent in females than males (Table 2). The prevalence of abdominal obesity (high waist circumference) increased by 21.7% (17.6% versus 39.3%) and 9.1% (39.3% vs. 48.4%) by decreasing the waist circumference cut-off points to >90cm and >80cm in males and females, respectively. Overall abdominal obesity was more prevalent in females (Table 2). The prevalence of IFG increased from 11.7% to 15.9% and 10.4% to 16.3% in males and females, respectively on using the recently proposed cut-point for IFG\(^1\) (Table 2).

Table 3 depicts the overall and gender-specific percentage prevalence of the metabolic syndrome using various definitions. The recently proposed modified definition of NCEP, ATP III (MS-ATP) detected the metabolic syndrome in 34.1% (31.9-36.3) [25.5% (22.5-28.6) and 40.7% (37.7-43.7) in males and females, respectively]. This definition (MS-ATP) in which waist

<table>
<thead>
<tr>
<th>Metabolic Syndrome Definitions (MS)</th>
<th>Blood pressure (mm Hg)</th>
<th>Triglycerides (mg/dl)</th>
<th>Fasting Blood Glucose (mg/dl)</th>
<th>HDL-C (mg/dl)</th>
<th>Waist circumference (cm)</th>
<th>Body mass index (kg/m(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ 130/≥ 85</td>
<td>≥ 150</td>
<td>≥ 100</td>
<td>M &lt;40 , F &lt;50</td>
<td>Males: &gt;90 Females: &gt;80</td>
<td>≥ 23</td>
</tr>
</tbody>
</table>

Definitions of the metabolic syndrome with obligatory waist circumference and non-obligatory BMI as an additional defining parameters
- MS-IDF\(^4\)\(^\psi\) + + + + + -
- MS-IDF1\(^\psi\) + + + + + -

Definitions of the metabolic syndrome with non-obligatory waist circumference and BMI as an additional defining parameters
- MS-ATP\(^1\) + + + + + -
- MS-ATP1\(^1\) + + + + + -

Candidate definitions of the metabolic syndrome: MS-ATP1 and MS-IDF1; \(^8\), International Diabetes Federation definition of the metabolic syndrome;\(^18\)\(^\psi\), Presence of abdominal obesity (waist circumference) is obligatory, and presence of two other abnormal criteria required for diagnosis of the metabolic syndrome\(^16\);\(^1\), Same as the newly proposed (AHA/NHLBI) modification of the NCEP, ATP III definition of the metabolic syndrome;\(^25\)\(^3\), Presence of three or more abnormal criteria required for diagnosis of the metabolic syndrome (waist circumference non-obligatory).
metabolic syndrome overall as well as in subgroups (40.3% (37.8-42.9), 78.1% (73.0-82.7) and 91.1% (84.2-95.6) in subjects with normoglycemia, IFG and T2DM, respectively. Importantly, 10.5% of subjects with normal waist circumference had three cardiovascular risk factors.

**DISCUSSION**

We present for the first time, comparison of recently proposed (NCEP, ATPIII and IDF) definitions, and two modified candidate definitions of the metabolic syndrome in adult Asian Indians. This analysis is important, since we are yet to determine the optimal definition of the metabolic syndrome, specifically for South Asians.

NCEP, ATP III definition provided, for the first time, simple criteria for detection of the metabolic syndrome which could be easily used in most settings, even in the developing countries. Although it was widely used, several lacunae have been pointed out.6,7 The most important lacuna, from point of view of South Asians, is cut-off points of the waist circumference.24,25 The IDF definition of the metabolic syndrome includes all the components of the NCEP, ATP III definition with some modifications.16 Although abdominal obesity is an important criterion of the metabolic syndrome, it is not clear why it should be made mandatory in the IDF definition. For example, insulin resistance and other components of the metabolic syndrome may occur in people who do not have abdominal obesity, or are non-obese (BMI < 25 kg/m²).26 Particularly in the developing countries, non-obese people or those without abdominal obesity may develop insulin resistance, IFG, and T2DM.26 To analyze whether obligatory criterion of abdominal obesity would make any significant

**Table 2 : Measures of obesity and prevalence of surrogate markers of the metabolic syndrome**

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>Males</th>
<th>n</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average measures of obesity: [Mean ± SD]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>866</td>
<td>85.6±15.3</td>
<td>1125</td>
<td>79.7±14.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>881</td>
<td>22.8±5.2</td>
<td>1165</td>
<td>23.0±5.7</td>
</tr>
<tr>
<td>Prevalence of measures of obesity: [% (95% confidence interval)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference (M: &gt;102 cm, F: &gt;88 cm)</td>
<td>866</td>
<td>17.6(15.1-20.3)</td>
<td>1125</td>
<td>28.9(26.3-31.6)</td>
</tr>
<tr>
<td>Modified waist circumference (M: &gt;90 cm, F: &gt;80 cm)</td>
<td>866</td>
<td>39.3(36.0-42.6)</td>
<td>1165</td>
<td>48.4(43.8-49.6)</td>
</tr>
<tr>
<td>Body mass index (&gt; 23 kg/m²)</td>
<td>881</td>
<td>47.0(43.7-50.3)</td>
<td>1165</td>
<td>44.0(41.2-46.9)</td>
</tr>
</tbody>
</table>

**Surrogate markers of insulin resistance: [% (n)]**

<table>
<thead>
<tr>
<th>Surrogate markers of insulin resistance</th>
<th>n</th>
<th>Males</th>
<th>n</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired fasting glucose (FBG ≥ 110 mg/dl &lt;126 mg/dl)*</td>
<td>847</td>
<td>11.7(99)</td>
<td>1156</td>
<td>10.4(120)</td>
</tr>
<tr>
<td>Impaired fasting glucose (FBG ≥ 100 mg/dl &lt; 126 mg/dl)**</td>
<td>847</td>
<td>15.9(135)</td>
<td>1156</td>
<td>16.3(187)</td>
</tr>
<tr>
<td>Diabetes mellitus (FBG ≥ 126 mg/dl)</td>
<td>847</td>
<td>6.4(54)</td>
<td>1156</td>
<td>5.5(63)</td>
</tr>
<tr>
<td>High blood pressure (Blood pressure ≥ 130/≥ 85 mm Hg)</td>
<td>883</td>
<td>29.1(257)</td>
<td>1167</td>
<td>42.8(499)</td>
</tr>
<tr>
<td>Hypertriglyceridemia (Serum triglycerides ≥ 150 mg/dl)</td>
<td>879</td>
<td>28.9(254)</td>
<td>1134</td>
<td>25.5(289)</td>
</tr>
<tr>
<td>Low levels of HDL-C (M: &lt; 40 mg/dl, F: &lt; 50 mg/dl)</td>
<td>874</td>
<td>43.8(383)</td>
<td>1127</td>
<td>81.8(922)</td>
</tr>
</tbody>
</table>

**Table 3 : Overall and gender-specific percentage prevalence of the metabolic syndrome**

<table>
<thead>
<tr>
<th>Metabolic Syndrome Definitions (MS)</th>
<th>Overall</th>
<th>Males; % prevalence (95% CI)</th>
<th>Females; % prevalence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitions of the metabolic syndrome with obligatory waist circumference and non-obligatory BMI as an additional defining parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS-IDF†</td>
<td>2050;</td>
<td>25.3 (23.4-27.2)</td>
<td>883; 19.5 (16.9-22.2)</td>
</tr>
<tr>
<td>MS-IDF‡</td>
<td>2050;</td>
<td>41.4 (39.2-43.5)</td>
<td>883; 36.8 (33.6-40.1)</td>
</tr>
<tr>
<td>Definitions of the metabolic syndrome with obligatory waist circumference non-obligatory and BMI as an additional defining parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS-ATP†</td>
<td>1896;</td>
<td>34.1 (31.9-36.3)</td>
<td>821; 25.5 (22.5-28.6)</td>
</tr>
<tr>
<td>MS-ATP‡</td>
<td>1892;</td>
<td>49.2 (47.0-51.5)</td>
<td>819; 41.4 (38.0-44.9)</td>
</tr>
</tbody>
</table>

1 - IDF definition of the metabolic syndrome;16 † - recent modification NCEP, ATP III definition of the metabolic syndrome.13
The relative importance of BMI, or waist circumference or both as predictor(s) of cardiovascular risk factors, and whether one or both should be included in definition of the metabolic syndrome continue to be debatable issues. The BMI has been included in the WHO definition, and other modified definitions of the metabolic syndrome. Also, lower cut-off point of BMI (23 kg/m²) should be considered for Asians if it is included as a defining variable of the metabolic syndrome. In the present investigation we have demonstrated that by addition of BMI (MS-IDF1 and MS-ATP1) the percentage prevalence of the metabolic syndrome increased from 25.3% and 34.1% (MS-IDF/MS-ATP) to 41.4% and 49.2% (MS-IDF1/MS-ATP1). Hence it may be worthwhile including BMI as an additional defining parameter in the definition of the metabolic syndrome.

Importantly, including ethnic-specific cut-off point of waist circumference and a lowered cut-off point of fasting blood glucose are evidence-based amendments. Furthermore, with these modifications, IDF definition appears to be applicable across most ethnic groups, particularly for Asian populations. However, despite these modifications, IDF definition detects the metabolic syndrome less in comparison to other candidate definitions for Asian Indians proposed by us in the current study (Table 3 and 4). Upon comparison of the various definitions, we observed that the candidate definition MS-ATP1 (included: modified cut-off points
for waist circumference and fasting blood glucose, modified cut-off point of BMI along with other criteria of NCEP, ATP III definition, all non-mandatory) identified presence of the metabolic syndrome in subjects with IFG and T2DM more than other definitions including the NCEP, ATP III and IDF definitions (Table 4). But, whether this candidate definition is optimal or can be applied easily to the general population including white Caucasians remains to be investigated.

The recent studies comparing the various definitions of the metabolic syndrome in Asians indicate a conflicting evidence of the NCEP, ATP III (modified for Asian Indians) and WHO definition when compared to the IDF definition. In a nationally representative sample of ~16,000 Chinese adults MS was detected in 16.5% and 23.3% (% agreement between the definitions, 93.2%) using the IDF and NCEP, ATP III definitions respectively. Further, when compared to IDF definition the ATP III definition detected aggregation of cardiovascular risk factors better. Further, in a multi-ethnic population including South Asians, agreement between the two definitions was gender specific with greater % agreement (~80%) in females as compared to males. When compared to the modified NCEP/ATP III definition the IDF definition is associated with the highest risk for detection of extensive CAD on angiography (OR 2.83; p = 0.0190). In another study, carotid atherosclerosis has been shown to be best associated with MS as defined by the WHO definition when compared with other definitions of MS including the IDF definition. Interestingly, in Caucasian subjects with T2DM the prognostic accuracy of the IDF definition for all cause mortality is markedly reduced when compared to the modified NCEP, ATP III definition. Finally, even though the IDF definition better detected prevalence of MS in Korean subjects, but when compared to the NCEP, ATP III definition the odds ratio for detection of CAD were lower (NCEP, ATP III V s IDF: 2.8 V s 3.5). On further analysis of a recently reported study on the metabolic syndrome by our group, we noted that ~80% of adolescent Asian Indian with normal BMI and waist circumference but increased subscapular skinfold thickness had fasting hyperinsulinemia. That subscapular adipose tissue is thicker, and more closely correlated with insulin resistance in Asian Indians was shown by several groups including ours. A new candidate definition of the metabolic syndrome for adult Asian Indians in which subscapular skinfold thickness (cut-off point: >18 mm) was included as a new defining parameter was shown by us to perform better than the NCEP, ATP III definition. Interestingly, on sub-group analysis of the present study data we found that 22.6% (n=196) of adult Asian Indians had increased subscapular skinfold thickness (> 18 mm) but normal BMI and waist circumference (results not shown). To summarize, though preliminary, these data suggest that subscapular subcutaneous skinfold thickness (or skinfold at other truncal sites) may be strongly correlated to insulin resistance in Asian Indians warranting inclusion of this parameter in any new definitions and risk scoring of the metabolic syndrome or T2DM.

Insulin resistance has been considered as the central factor and an important pathogenic mechanism for the metabolic syndrome. Further, the primary therapeutic intervention for the metabolic syndrome may also be directed towards control of insulin resistance. Doubts have been raised as to the adequacy of the NCEP, ATP III definition of the metabolic syndrome to detect presence of insulin resistance. Such evaluation for IDF definition remains to be done.

As yet, definitions of the metabolic syndrome are unsatisfactory, but encouragingly evolving. To determine a correct and universally applicable definition of the metabolic syndrome, the international agencies (NCEP, IDF, WHO and others) should initiate large, prospective studies involving several ethnic groups to test various candidate definitions against insulin resistance risk, CVD, T2DM and overall mortality.

Acknowledgments

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