

## The metabolic syndrome in South Asians: Continuing escalation & possible solutions

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**The metabolic syndrome is a crucial factor in causation of type 2 diabetes mellitus (T2DM) and coronary heart disease (CHD) in South Asians. Approximately 20-25 per cent of urban South Asians have evidence of the metabolic syndrome. Furthermore, insulin resistance was reported to be present in nearly 30 per cent of children and adolescents in India, more so in girls. At the same time many young individuals have clustering of other risk factors/conditions related to insulin resistance (e.g., non-alcoholic fatty liver disease, obstructive sleep apnoea, etc.). Rapid nutritional and lifestyle transition in urbanized areas in various countries in South Asia are prime reasons for increasing prevalence of obesity and the metabolic syndrome. It is particularly important to effectively implement and strengthen population-based primary prevention strategies for the prevention of 'epidemic' of obesity and the metabolic syndrome. The lifestyle factor modification to prevent the metabolic syndrome and T2DM in South Asians should start in early childhood. Finally, there is an urgent need to conduct research studies regarding the correct definitions of the metabolic syndrome and genetic and perinatal factors related to insulin resistance in South Asians.**

**Key words** Diabetes - India - metabolic syndrome - nutritional transition - South Asians

South Asians have an unusually high tendency to develop type 2 diabetes mellitus (T2DM) and coronary heart disease (CHD)<sup>1,2</sup>; important determinants of both non-communicable diseases (NCDs) are insulin resistance and clustering of other

proatherogenic factors. These diseases are escalating due to marked shift in lifestyle in South Asian countries caused by economic growth, affluence, urbanization and dietary westernization. Clustering of cardiovascular risk factors in South Asians was

initially reported from UK<sup>3,4</sup>. Since then a number of investigators have reported high prevalence of the metabolic syndrome in South Asian populations settled in many other countries. Prevalence of the metabolic syndrome as defined by National Cholesterol Education Program, Adult Treatment Panel III (NCEP, ATP III)<sup>5</sup> and other criteria ranges from about 11 to 41 per cent in different regions of India<sup>6-9</sup>. High prevalence of cardiovascular risk factors<sup>10,11</sup> and the metabolic syndrome (~12%) have been shown by our group in intra-country rural-to-urban migrant population belonging to low socio-economic stratum residing in urban slums. Further, certain communities in India (*e.g.*, Punjabi *Bhatia* community) have inordinately high tendency to develop obesity, T2DM, and the metabolic syndrome<sup>12</sup>. High prevalence of fasting hyperinsulinaemia (28%) has been reported by our group in the post-pubertal urban children and young adults, particularly in girls<sup>13</sup>. Prevalence of the metabolic syndrome in Sri Lankans appears to be inordinately high; 35 per cent in males and 51 per cent in females (n=16, 729, Wijesuriya M, unpublished observations). There is paucity of data regarding prevalence of insulin resistance and the metabolic syndrome from other south Asian countries; Pakistan, Bangladesh and Nepal. For detailed reviews on various aspects of insulin resistance and the metabolic syndrome in Asian Indians and South Asians, several recent review articles<sup>14-20</sup> are available. Various associations of insulin resistance in Asian Indians and South Asians are given in Table.

### Definitions of the metabolic syndrome

The NCEP, ATP III definition of the metabolic syndrome<sup>5</sup> is based on simple clinical and biochemical parameters, while other available definitions of the metabolic syndrome (*e.g.*, that by the WHO<sup>21</sup>) include measures which are expensive and difficult to measure in developing countries. There is increasing belief that NCEP, ATP III definition of the metabolic syndrome is not optimal for the identification of risks for T2DM or CHD, and does not identify the metabolic syndrome correctly in South Asians. Most important limitation is that the internationally accepted cut-off points of waist circumference (men >102 cm, and women, >88 cm) for diagnosis of abdominal obesity are not applicable for South Asians. This contention is supported by our recent data that show that waist circumference levels of >90 cm and >80 cm for men and women, respectively, were associated with high odds ratios for the presence of cardiovascular risk factor(s)<sup>22</sup>. We have also investigated several other candidate definitions of the metabolic syndrome devised by including three new parameters; modified waist circumference cut-off points (>90 cm in males and >80 cm in females), modified body mass index (BMI) cut-off point (>23 kg/m<sup>2</sup>), and subscapular skinfold thickness (>18 mm) in various combination with components of NCEP, ATP III definition, and reported that some of these definitions may work better for Asian Indians<sup>23</sup>. Recently, International Diabetes Federation (IDF)

**Table.** Associations of insulin resistance with other risk factors in South Asians

Factors with evidence of positive association	Factors with weak/no evidence of association	Poorly investigated factors
1. Excess body fat	1. C-reactive protein	1. Non-alcoholic fatty liver disease
2. Abdominal obesity	2. Intramyocellular triglycerides	2. Endothelial dysfunction
3. High truncal subcutaneous fat	3. Leptin	
4. Low birth weight		
5. High levels of procoagulant factors		

recommended a new definition of the metabolic syndrome. This definition included three major modifications as compared to NCEP, ATP III definition; (i) central obesity has been made a mandatory variable, (ii) the cut-offs of waist circumference have been lowered (male, 94 cm; female, 80 cm), and made ethnicity-specific (*e.g.*, for south Asians: male, 90 cm; female, 80 cm), and (iii) cut-off level for fasting plasma glucose has been lowered to 100 mg/dl<sup>24</sup>. Currently, we are testing utility of this definition vis-à-vis established definitions of the metabolic syndrome. According to a recent study on south Indians, the prevalence of the metabolic syndrome (%) was estimated to be 23.2, 18.3 and 25.8 according to the WHO, ATP III and IDF definitions respectively<sup>25</sup>.

One could put a similar argument for serum triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C); other components of the metabolic syndrome. The NCEP, ATP III criterion which is most likely to identify insulin resistance in individuals is the TG/HDL-C ratio<sup>26</sup>. Further, these lipid variables have been shown to capture much of the CHD risk associated with the metabolic syndrome in some but not all ethnic groups<sup>27</sup>. Interestingly, different ethnic groups exhibit different prevalence and severity levels of dyslipidaemia, yet no large scale clinical trials have been conducted to determine the relative risk of an adverse TG/HDL ratio and its relations with the metabolic syndrome in different ethnic groups.

Investigators have used percentile-based cut-off points, and other modifications of NCEP, ATP III criteria for defining the metabolic syndrome in children<sup>28,29</sup>. It is important to note that percentiles from the US data are not applicable to South Asian ethnic groups. According to our recent data in Asian Indian adolescents, the NCEP, ATP III definition with appropriate percentile-based cut-off points fared

poorly and was able to identify only six (0.8%) out of 793 subjects as having the metabolic syndrome<sup>20</sup>. Prevalence of the metabolic syndrome increased to 4.3 per cent on inclusion of BMI, 4.2 per cent on inclusion of fasting hyperinsulinaemia and to 10.2 per cent with inclusion of both BMI and fasting hyperinsulinaemia as non-mandatory variables with other components of NCEP, ATP III definition. The data indicate that insulin resistance and hyperinsulinaemia are early metabolic manifestations and should be included to define insulin resistance and the metabolic syndrome more correctly in children<sup>20</sup>.

### **Insulin resistance and adiposity**

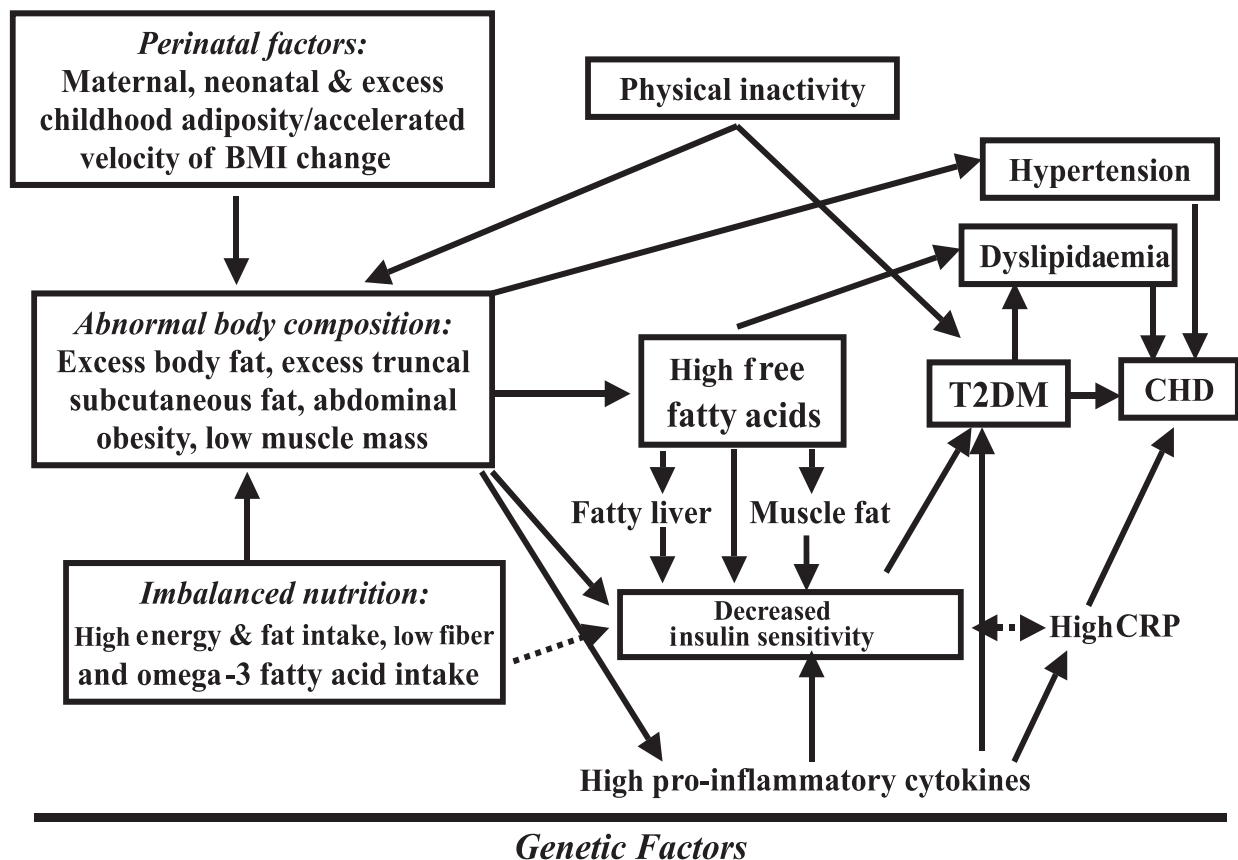
Adiposity is the most important correlate of insulin resistance and the metabolic syndrome. The severity of insulin resistance increases with increasing adiposity. Body composition of South Asians is conducive to development of the metabolic syndrome; South Asians have high percentage of body fat<sup>17,30-33</sup>, abdominal obesity<sup>17,32</sup>, insulin resistance<sup>34</sup>, hyperinsulinaemia<sup>35</sup> and low muscle mass<sup>36</sup>. In particular, abdominal obesity is common in South Asians, and evident even in non-obese people. Further, thick subcutaneous adipose tissue in Asian Indians may be a key correlate of insulin resistance<sup>13,37</sup>. In our recent investigation, we correlated cross-sectional subcutaneous and intra-abdominal fat area at lumbar vertebra 3-4 (measured with magnetic resonance imaging) with insulin resistance (assessed by fasting insulin, HOMA-IR, and short insulin tolerance test) and showed that measures of insulin resistance correlated significantly to subcutaneous fat and not to intra-abdominal fat (Misra A, unpublished observations). Interestingly, thicker subscapular subcutaneous fat in Asian Indians has been recorded at birth, and associated with higher insulin levels when compared to British neonates<sup>38</sup>.

### Ectopic fat deposition and insulin resistance

**Muscle:** Investigations in white Caucasians have shown the lipid accumulation in skeletal muscle (intramyocellular lipids, IMCL), which is non-invasively assessed with proton nuclear magnetic resonance spectroscopy over the soleus muscle, could be a marker for insulin resistance<sup>39,40</sup>. Few investigations have been done on IMCL in South Asians, but the findings differ as compared to those reported for white Caucasians<sup>41,42</sup>. Absence of any relationship between IMCL and insulin sensitivity has been reported in South Asians in UK and Asian Indians living in India<sup>41,43</sup>, but IMCL was related to excess body fat and abdominal obesity<sup>41</sup>. Finally,

our recent data show no relationship of C-reactive protein (CRP), another possible correlate of insulin resistance, with IMCL<sup>44</sup>. Overall, significance of IMCL in pathogenesis of insulin resistance, particularly in South Asians remains to be determined.

**Liver:** Data regarding the prevalence of non-alcoholic fatty liver disease (NAFLD) in South Asians are limited. It is important to note that all the associations of NAFLD; obesity, abdominal obesity, diabetes, hypertriglyceridaemia, and insulin resistance are highly prevalent in urban Asian Indians, and may be important for pathogenesis of NAFLD (Fig.). For example, we recently reported obesity in about



**Fig.** Complex interactions of genetic, perinatal, nutritional and other acquired factors in development of insulin resistance, type 2 diabetes and coronary heart disease in South Asians. T2DM, type 2 diabetes mellitus; CRP, C-reactive protein; CHD, coronary heart disease; dotted lines represent weak relationships. *Source:* Ref. 67.

14 per cent, abdominal obesity in about 46 per cent and hypertriglyceridaemia in 25 per cent of subjects from north India<sup>10,45</sup>. In a hospital-based study from north India, non-alcoholic steatohepatitis (NASH) was present in 25 subjects (including 24 men) out of 52 patients with persistently elevated serum aminotransferases<sup>46</sup>. Anecdotal reports, mostly in the form of abstracts, indicate that nearly 25 per cent of the urban population in India has NAFLD, however, fibrosis appears to be rare. Recently we have observed that obese or non-obese adults with NAFLD have significantly higher insulin resistance than those without NAFLD (Misra A, unpublished observations). Further, a proton magnetic resonance spectroscopy study of enzymes involved on gluconeogenesis pathway indicates increased gluconeogenesis in non-diabetic, non-obese Indian patients with NAFLD, indicating increased future risk for development of T2DM (Misra A, unpublished observations).

### **Obstructive sleep apnoea and insulin resistance**

Obstructive sleep apnoea (OSA) is associated with metabolic (insulin resistance), cardiovascular (hypertension and cardiac arrhythmias) and neuropsychological disorders. It affects 4-11 per cent of the white Caucasian population. Obesity appears to increase risk of OSA nearly 10–14-folds, with the most marked effects observed in middle-aged subjects<sup>47</sup>. Obesity may increase susceptibility to OSA through fat deposition in upper airway tissues, reducing nasopharyngeal caliber and/or from hypoventilation occurring in association with reduced chest wall compliance. The co-occurrence of OSA, central obesity, hypertension, and hyperglycaemia suggests that OSA is a part of the metabolic syndrome<sup>47,48</sup>. Despite some evidence, relationship of OSA with insulin resistance independent of obesity remains to be established<sup>49</sup>. In our ongoing investigation on metabolic and genetic factors of OSA, nearly 2/3<sup>rd</sup> patients with the metabolic

syndrome have OSA (Misra A, unpublished observations). Clearly, more investigations on the relationship between the metabolic syndrome and OSA are needed in South Asians.

### **Genetics of insulin resistance and the metabolic syndrome**

Genetic propensity to develop dyslipidaemia, obesity and diabetes<sup>50-55</sup> has been shown in South Asians but insulin resistance and the metabolic syndrome have been poorly researched. A recent study has shown correlation of polymorphism of *hepatic glucokinase promoter* gene to hepatic insulin resistance in Asian Indians<sup>56</sup>. The Ala54Thr polymorphism in the *fatty acid binding protein-2* (FABP2) gene as well as T-455C and C-482T polymorphism in *apolipoprotein C-III* \*APOC3) gene promoter polymorphism were associated with the metabolic syndrome in South Indians<sup>57</sup>. The promoter polymorphisms -482T and -455C of *APOC3* gene is recently shown to be associated with the metabolic syndrome in both Asian Indians and North Americans in a comparative study<sup>58</sup>.

A complex interplay of genetic, metabolic and environmental risk factors resulting in insulin resistance, the metabolic syndrome, T2DM and CHD are shown in the Fig.

### **Prevention and control of the metabolic syndrome in South Asians**

1. Intensive efforts should be made to make South Asians aware that they are at high risk for development of T2DM and CHD. The health education programmes should be directed towards all socio-economic strata of society.
2. The preventive measures should be particularly vigorous for those with the family history of T2DM and/or premature CHD.

3. The therapeutic lifestyle changes should be encouraged from the childhood. The school curriculum should be suitably modified to include messages related to healthy nutrition and physical exercise. Regular physical activity should be strongly advised and television and internet usage should be restricted.

4. Body weight and anthropometric indices should be maintained within normal limits as given below. The physicians should be made aware that these provisional limits for defining normal BMI and waist circumference might be revised in the future.

5. Based on the recent data<sup>57-60</sup>, and provisional recommendations of WHO<sup>61</sup>, BMI should be maintained between 19-23 kg/m<sup>2</sup>.

6. The waist circumference should be maintained below 90 cm for men and 80 cm for women<sup>20,62,63-65</sup>.

7. Overweight individuals and those with abdominal obesity should be actively managed to lose weight by lifestyle measures.

8. Detection of one component of the metabolic syndrome should lead to search for the other components and appropriate management.

9. Currently, no drug (*e.g.*, metformin) is recommended for management of insulin resistance and the metabolic syndrome. However, these guidelines may change in future, particularly for those who have impaired glucose tolerance (IGT), in particularly in view of recent evidence from a prevention trial from India<sup>66</sup>.

10. Adequate nutrition during the intrauterine period should be given to prevent early-life adverse

events, which may promote insulin resistance in adulthood.

11. Finally, the national control programmes for diabetes and cardiovascular diseases should be adequately strengthened and modified in view of the recent knowledge and guidelines in the respective South Asian countries.

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