The importance of local criteria in the diagnosis of metabolic syndrome in Saudi Arabia

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Abstract: The clustering of risk factors predisposing an individual to cardiovascular morbidity and mortality are usually referred to as the ‘metabolic syndrome’ (MS). Several definitions exist, causing confusion to practicing clinicians. A consensus definition was reached by several major organizations stating that the presence of any three of five risk factors (abdominal obesity, elevated triglyceride, reduced high-density lipoprotein cholesterol, elevated blood pressure, and elevated fasting glucose) constitutes a diagnosis. Cutoff points for each of the risk factors were defined, taking into account ethnicity in case of abdominal obesity. The prevalence of MS has been reported to be on the rise globally, and was mainly attributed to changes in diet and lifestyle, in addition to genetic factors and metabolic susceptibility. The risk of cardiovascular disease (CVD) has almost doubled and the risk of developing type 2 diabetes mellitus (T2DM) has increased fivefold in individuals diagnosed with MS. The prevalence T2DM in Saudi Arabia is increasing, making it an epidemic health hazard. Intervention programs to decrease the risk of progression from MS to full T2DM, and later CVD have been successful in many countries. Therefore, diagnosing MS is important to address risk factors and to prevent progression to the more serious chronic conditions.

The prevalence of MS in Saudi adults varies from 16% to 40% depending on the definition used and the study location. Use of the consensus definition might decrease the number of missed cases. However, in the absence of local cutoff points for various risk factors for MS, the use of ratios such as waist/hip ratio and low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio, and family history of diabetes and CVD might aid diagnosis. Priority should be given to establishing national normal ranges, screening programs for hyperglycemia and hypertension, and community-directed programs to combat obesity and inactivity.

Keywords: criteria, definition, metabolic syndrome, prevalence, Saudis

Introduction

The clustering of risk factors predisposing an individual to cardiovascular morbidity and mortality are usually referred to as ‘metabolic syndrome’ (MS) [Alberti *et al.* 2005; Scott, 2003]. A considerable disagreement between different expert groups over the terminology and the clinical criteria for its diagnosis is noted, leading to some confusion on the part of clinicians regarding how to identify patients with the syndrome. More recently, several major organizations agreed to unify criteria and came up with a consensus definition stating that abdominal obesity should not be a prerequisite for diagnosis, so that the presence of any three

of five risk factors [abdominal obesity, elevated triglyceride, reduced high-density lipoprotein cholesterol (HDL-C), elevated blood pressure, and elevated fasting glucose] constitutes a diagnosis of MS [Alberti *et al.* 2009]. Cutoff points for each of these risk factors were also defined, taking into account ethnic variations in the thresholds for abdominal obesity. Nevertheless, the prevalence of MS, using different definitions, has been reported to be on the rise globally, and this was mainly attributed to changes in diet and lifestyle [Park *et al.* 2003]. However, genetic factors and metabolic susceptibility were also reported to play an important role [Grundy, 2007]

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The importance of early diagnosis of metabolic syndrome

The risk of cardiovascular disease (CVD) has almost doubled in individuals diagnosed with MS [Despres and Lemieux, 2006; Gami *et al.* 2007; Grundy *et al.* 2006; Grundy, 2007]. Furthermore, the risk of developing type 2 diabetes mellitus (T2DM) is increased fivefold in the presence of the syndrome [Ford, 2005b]. Diabetes mellitus is considered to be one of the most costly medical disorders globally due to its chronic complications that can exhaust the health resources of any given country. Studies show that the medical costs for people with diabetes are 2.4 times those for people without the condition. Chronic cardiovascular complications are the most costly, contributing to 19.2% of the total direct and indirect costs of the disease [Scholze *et al.* 2010].

An epidemiological study published in 2004 has shown that the prevalence of T2DM in Saudi Arabia is approximately 23.7% in adults older than 30 years of age [Al-Nozha *et al.* 2004], indicating a substantial increase of around 10% on a report published in 1997 [Al-Nuaim, 1997]. A later review on diabetes in Saudi Arabia concluded that all published epidemiological studies point to an exponential rise in diabetes prevalence coupled with a parallel rise in obesity rates, so that T2DM is now considered to be an epidemic health hazard [Elhadd *et al.* 2007].

The direct and indirect costs of diabetes in Saudi Arabia are currently 23% of the health-care expenditure and 17% of direct medical service costs, totaling over US\$1.3 billion/year [Al Rubeaan, 2010].

In the absence of effective interventions for the prevention of diabetes, the frequency will escalate worldwide, with the main impact being seen in developing nations such as Saudi Arabia and the disadvantaged minorities in developed nations [Amos *et al.* 1997; King *et al.* 1998]. Thus, the prevention of diabetes and its micro- and macrovascular complications should be an essential component of future public health strategies for all nations, and especially in Saudi Arabia, or diabetes is likely to remain a huge threat to public health in the years to come.

The results from studies of disease etiology have been successfully used in different countries to develop intervention programs to decrease the

risk of progression from MS, impaired glucose tolerance or prediabetes to full T2DM [Eriksson and Lindgarde, 1991; Knowler *et al.* 2002; Pan *et al.* 1997; Tuomilehto *et al.* 2001] or to prevent noncommunicable diseases, especially CVD [Papadakis and Moroz, 2008]. Therefore, it is of utmost importance to identify individuals with MS so that their multiple risk factors can be addressed and reduced in the hope of preventing progression to the more serious chronic conditions that cannot be reversed once established, namely CVD and T2DM. Present controversies, as well as the importance of establishing clear criteria to define MS, are discussed in a review by Kassi and colleagues [Kassi *et al.* 2011].

Metabolic syndrome in Saudi Arabia

Several attempts to study the prevalence and characteristics of MS based on different definitions were carried out in Saudi Arabia and are summarized in Table 1 [Akbar, 2002; Al zahrani *et al.* 2012; Al-Daghri *et al.* 2010; Al-Nozha *et al.* 2005; Al-Qahtani *et al.* 2006; Al-Qahtani and Intiaz, 2005; Barrimah *et al.* 2009].

The first of these studies, published in 2002, used World Health Organization criteria and included patients with diabetes treated at King Abdulaziz University Hospital in Jeddah. The study reported the prevalence of MS to be 56% in men and 57% in women, with hypertension being the most common component [Akbar, 2002]. Based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition [Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001] (Table 2), the largest study, conducted over a 5-year period between 1995 and 2000 and covering different regions of Saudi Arabia, reported the overall MS prevalence in adults aged 30–70 years to be about 40%, with the most common factor being low HDL-C [Al-Nozha *et al.* 2005]. Using the same definition, two other smaller studies conducted in the central region of Saudi Arabia reported the prevalence to be 31.4% in men [Barrimah *et al.* 2009] and 35.3% in the whole population [Al-Daghri *et al.* 2010]. Another study, conducted recently in the city of Jeddah in the western region, included healthy National Guard employees and their dependants and used the same definition. The study reported the MS

Table 1. Prevalence studies of metabolic syndrome performed on adults in Saudi Arabia.

Sample characteristics	Study location	Used definition	MS prevalence	Authors [year]
Patients with T2DM Mean age $\pm$ SD: 60 $\pm$ 13 years (N = 428)	King Abdulaziz University Hospital, Jeddah	WHO	56% in men 57% in women	Akbar [2002]
Male soldiers Aged 20–60 years Mean age $\pm$ SD: 36.15 $\pm$ 7.2 years (N = 1079)	Military base at Hafr Albatin	NCEP ATP III	Overall 18.6% Age adjusted 20.8%	Al-Qahtani and Imtiaz [2005]
Saudi adults Aged 30–70 years (N = 17,293)	Different regions of Saudi Arabia	NCEP ATP III	39.3% overall 37.2% in men 42% in women	Al-Nozha <i>et al.</i> [2005]
Saudi women Aged 18–59 years (N = 1922)	Military base at Hafr Albatin	IDF and NCEP ATP III	Age-adjusted 16.1% (IDF) and 13.6% (NCEP ATP III)	Al-Qahtani <i>et al.</i> [2006]
Adult men (Saudis and others) Aged <30 to 50+ (N = 560)	Qassim University	NCEP ATP III	Overall 31.4%, increasing with age and BMI Higher prevalence in Saudis	Barrimah <i>et al.</i> [2009]
Saudi adults Aged 18–55 years (N = 2850)	The city of Riyadh	NCEP ATP III	Overall 35.3% Age adjusted $\approx$ 37.0% No significant difference between men and women	Al-Daghri <i>et al.</i> [2010]
Healthy Saudi adults Aged 20–50 years (N = 600, 311 men, 289 women)	National Guard Hospital, Jeddah	NCEP ATP III	Overall prevalence 21% increasing with age, higher among men	Al zahrani <i>et al.</i> [2012]
Healthy Saudi adults Aged 18–55 years Mean age $\pm$ SD: 31.0 $\pm$ 9.4 years (N = 233, 94 men, 139 women)	Cross-sectional study in the city of Jeddah	NCEP ATP III and IDF	Overall prevalence 16.7% (NCEP ATP III) and 18.9% (IDF)	Bahijri <i>et al.</i> [2013]
ATP III, Adult Treatment Panel III; BMI, body mass index; IDF, International Diabetes Federation; MS, metabolic syndrome; NCEP, National Cholesterol Education Program; SD, standard deviation; T2DM, type 2 diabetes mellitus; WHO, World Health Organization.				

Table 2. Criteria for clinical diagnosis of the metabolic syndrome by different definitions.

Component	Definition		
	NCEP ATP III	IDF	Consensus
Elevated waist circumference	>102 M, >88 F	>94 M, >80 F	>94 M, >80 F
Elevated triglycerides (mmol/liter)	≥ 1.7	≥ 1.7 or Rx	≥ 1.7 or Rx
Reduced HDL-C (mmol/liter)	<1.04 M, <1.29 F	<1.03 M, <1.29 F or Rx	<1.00 M, <1.30 F or Rx
Elevated blood pressure	$\geq 130/85$	$\geq 130/85$ or Rx	$\geq 130/85$ or Rx
Elevated fasting glucose (mmol/liter)	≥ 6.1	≥ 5.6 or Rx	≥ 5.5 or Rx
Number of components for diagnosis	≥ 3 of components above	Central obesity (elevated waist circumference) plus 2 other components Waist circumference is ethnicity dependant	≥ 3 of components above Waist circumference is ethnicity dependant
ATP III, Adult Treatment Panel III; F, female; HDL-C, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; M, male; NCEP, National Cholesterol Education Program; Rx, taking treatment.			

prevalence to be 21% [Al zahrani *et al.* 2012]. All of these studies reported low HDL-C as the most common component.

In contrast, using the same definition and the International Diabetes Federation (IDF) definition [IDF, 2006], abdominal obesity was reported

as the most common component in two other studies conducted in other regions of Saudi Arabia on military staff and their families [Al-Qahtani *et al.* 2006; Al-Qahtani and Imtiaz, 2005].

In a cross-sectional study conducted by our group in the city of Jeddah [Bahijri *et al.* 2013], both the NCEP ATP III and the IDF definitions were used to diagnose MS to compare the degree by which the two definitions agree in classifying subjects. The sample was chosen from apparently healthy subjects (self-reporting), randomly selected from people visiting health centers as companions of sick relatives. They were examined to ensure absence of hypertension (taking antihypertensive medications, or having systolic blood pressure > 140 mmHg, or diastolic blood pressure > 90 mmHg) and hyperglycemia (random blood glucose ≥ 126 mg/dl or 7.0 mmol/liter). MS prevalence was found to be 16.7% with low HDL-C the most common component when the NCEP ATP III definition was used, and 18.9% with abdominal obesity as the most common component when the IDF definition was used (Table 1). The two definitions use different cutoff points for abdominal obesity, with the IDF definition using lower values and also having abdominal obesity as mandatory for diagnosis, not just one of the risk factors (Table 2). This explains the finding of abdominal obesity being the most common component, and the higher prevalence when this definition was employed. However, it was worrying to note that the two definitions did not always identify the same subjects. Less than 60% of subjects diagnosed with MS using the IDF definition were also identified to have MS using the NCEP ATP III definition, and 66.7% of those diagnosed using the NCEP ATP III definition were also identified using the IDF definition. It was also noted that subjects identified only using the IDF definition were all obese [body mass index (BMI) ≥ 30], while those identified only using the NCEP ATP III definition were not but had hypertriglyceridemia. Therefore, it was suggested that using the IDF definition in the Saudi population might lead to people with unfavorable metabolic profiles being classified as normal with no need for special medical attention, thus increasing their future risk of T2DM and CVD.

A different approach to improve diagnosis

The use of the recommended cutoff point for abdominal obesity might not be appropriate for the Saudi population since it has not been

defined for many ethnic groups, including Arabs. Furthermore, serum lipid and apolipoprotein levels are reported to be dependent on genetic background, ethnicity, and dietary pattern of a particular population as well as advancing age, sex, lifestyle, and environmental factors [Bhopal *et al.* 1999; Frohlich *et al.* 1998; Misra *et al.* 2004; Tilly *et al.* 2003]. Therefore, specified cutoff points for HDL-C and triglycerides, which are components in all known definitions of MS, might not be suitable for the Saudi population, especially in view of the reports of a high prevalence of low HDL-C among Saudi subjects from different regions and of all age groups [Al-Daghri *et al.* 2010; Al-Kadi and Alissa, 2011; Al-Nozha *et al.* 2005; Barrimah *et al.* 2009].

Apart from the risk factors appearing in the IDF definition [IDF, 2006], the IDF has highlighted a number of other parameters that appear to be related to MS which should be included in research studies to help determine the predictive power of these extra criteria for CVD and diabetes. They speculated that the use of these additional factors in research will also allow further modification of the definition if necessary and the validation of the new clinical definition in different ethnic groups. Keeping this in mind, in an attempt to refine any definition used to better serve its purpose based on local criteria, it was decided to use subject data collected by our group in the survey mentioned above [Bahijri *et al.* 2013] to investigate the importance of demographic characteristics and other measures of obesity, dysglycemia, and dyslipidemia as added tools for the diagnosis of MS in Saudi subjects. Furthermore, and since none of the studies in Saudi Arabia used the latest consensus definition [Alberti *et al.* 2009], it was decided to calculate the MS prevalence and determine the characteristics of subjects identified by this definition to have MS. In addition, the extent of agreement in diagnosis between this definition and the two older definitions was investigated.

Using the consensus definition changed the picture further. It was noted that 15.9% of the subjects had none of the risk factors for MS, while 33.5% had one and 28.8% had two risk factors. The MS prevalence and the different components according to the consensus definition are presented in Figure 1.

The overall MS prevalence (21.9%) was higher than when the other two definitions were used,

Figure 1. Prevalence of metabolic syndrome and its individual components according to the consensus definition. DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.

Table 3. Demographic characteristics of normal and metabolic syndrome groups using the consensus definition.

	+MS (N = 51)	–MS (N = 182)	p Value
Age (years), mean $\pm$ SD	35.1 $\pm$ 9.36	29.6 $\pm$ 8.30	<0.0001
BMI (kg/m ²), mean $\pm$ SD	30.2 $\pm$ 5.2	25.6 $\pm$ 5.6	<0.0001
Smoking (%)	15.7	25.3	0.152
Exercise (%)	54.9	41.2	0.082
Family history of DM (%)	41.2	49.4	0.251
Family history of CVD (%)	33.3	15.2	0.017

+MS, diagnosed to have MS; –MS, not diagnosed to have MS.
 BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; MS, metabolic syndrome; SD, standard deviation.

reflecting the fact that abdominal obesity was no longer mandatory, and the lower cutoff value compared with the NCEP ATP III definition (Table 2). Similar to findings when the IDF definition was used, abdominal obesity was found to be the most common component, followed closely by increased fasting glucose, while low HDL-C came third.

There was a low level of agreement between the used definition and the two older definitions. Only 43.1% of subjects identified to have MS using the consensus definition were also identified to have MS with the ATP III definition, reflecting a very low value for κ (-0.071). A similar result was obtained when the IDF definition was used; only 49.0% of those diagnosed with MS using the consensus definition were also identified with the IDF definition, reflecting a κ value of -0.08 .

The percentage of women with MS was significantly higher than for men using the ATP III definition (22.3% of women, 8.5% of men) and the consensus definition (27.3% of women compared with 13.8% of men), with $p = 0.006$ and 0.014 respectively. This was not found when the IDF definition was used (22.3% of women and 13.8% of men, with $p = 0.105$).

The demographic characteristics of normal and MS groups using the consensus definition are presented in Table 3.

The mean age, BMI, and family history of CVD were all significantly higher in the MS group. The biochemical profiles of normal and MS groups using the consensus definition are presented in Table 4.

A statistically significant difference between the means or medians of groups diagnosed with MS

Table 4. Biochemical profile of normal and metabolic syndrome groups using the consensus definition.

	+MS (N = 51)	–MS (N = 182)	p Value
Triacylglycerols [§] (mmol/liter)	1.96 [1.27]	1.03 [59]	<0.0001*
Total cholesterol [‡] (mmol/liter)	5.20 ± 1.17	5.10 ± 1.0	0.505
LDL-C [‡] (mmol/liter)	3.21 ± 0.84	3.06 ± 0.76	0.214
HDL-C [‡] (mmol/liter)	1.26 ± 0.33	1.49 ± 0.39	<0.0001
LDL-C/HDL-C ratio [‡]	2.64 ± 0.77	2.21 ± 0.78	<0.0001
Plasma atherogenic index [‡]	0.93 ± 0.31	0.73 ± 0.37	0.001
Free fatty acids [§] (mg/dl)	9.17 [6.37]	8.49 [4.8]	0.081*
Fasting glucose [‡] (mmol/liter)	5.54 ± 0.90	5.50 ± 0.81	0.756
Insulin [§] (mU/liter)	9.32 [8.13]	7.82 [5.29]	0.006*

+MS, diagnosed to have MS; –MS, not diagnosed to have MS.
 *p Value was calculated using Mann–Whitney U; unpaired t test was used for all others.
 §Median (interquartile range).
 ‡Mean ± standard deviation.
 HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MS, metabolic syndrome.

and normal groups were found for some but not all parameters used for diagnosis, namely triglycerides and HDL-C. In addition, significant differences between the means or medians of the MS and normal groups were also found for other measures of dyslipidemia and insulin resistance introduced in this study, namely low-density lipoprotein cholesterol (LDL-C)/HDL-C ratio, plasma atherogenic index, and insulin.

To investigate which of the added biochemical measures of dyslipidemia and insulin resistance, and which demographic and anthropometric measures were the strongest predictors of MS when different definitions were used, multiple logistic regression was performed with MS as the independent variable. The strongest predictors of MS were found to be age, sex, and LDL-C/HDL-C ratio when the NCEP ATP III definition was used, and sex, waist/hip ratio, total cholesterol, and LDL-C/HDL-C ratio when the IDF definition was used. When the consensus definition was used only age, sex, and LDL-C/HDL-C ratio remained in common with either or both previous definitions as predictors of MS. In addition, new predictors became apparent, namely insulin level, plasma-free fatty acids level, and family history of diabetes or CVD.

Therefore, it is apparent that the prevalence of MS in our studied population of apparently healthy subjects is quite high, and appeared to be dependent on definition as reported previously [Cheung *et al.* 2006; DECODA Study Group, 2007; Santos and Barros, 2007]. Moreover, prevalence was age

and sex dependent, being higher in women and increasing with age, as noted previously [Al-Nozha *et al.* 2005; Cheung *et al.* 2006; DECODA Study Group, 2007; Ford, 2005a; Santos and Barros, 2007]. Age continued to be an important predictor following regression analysis when the consensus definition and NCEP ATP III definition were used. Aging is usually associated with decreased physical activity, leading to loss of muscle mass and increased adiposity. Obesity is reported to increase insulin resistance [Kahn *et al.* 2006; Xu *et al.* 2003], a key feature of MS [Alberti *et al.* 2005; Deurenberg *et al.* 1998; Reaven, 1997; Zimmet *et al.* 2005]. However, some individuals diagnosed with MS were neither overweight nor obese according to the BMI cutoff points used for Europeans. These cutoff points might not be suitable for the Saudi population because the relationship between percentage body fat and BMI is different among different ethnic groups [Deurenberg *et al.* 1998]. However, central rather than general obesity is believed to be the major cause of MS [Eckel *et al.* 2010]. Therefore, BMI need not be increased as long as there is visceral adiposity. However, not all people diagnosed with MS using the NCEP ATP III definition or the consensus definition had abdominal obesity according to IDF cutoff points. To clarify this, further studies are needed in the Saudi region to define appropriate cutoff points for general and central obesity, and overweight. Meanwhile, it might be useful to use waist to hip ratio, which was found to be a strong predictor of MS when the IDF definition was used.

Insulin resistance is expected to increase in MS, explaining the higher median insulin level in MS groups using the three definitions. Following regression analysis, insulin level remained a strong predictor of MS when the consensus definition was used. Furthermore, when this definition was used for diagnosis, a significant increase in the median serum free fatty acids of the MS group was noted, a sign of impaired regulation of lipolysis and another indication of increased insulin resistance [Stumvoll *et al.* 2002]. The difference remained following regression analysis, making it another strong predictor of MS. The difference in cutoff points used for diagnosing MS between definitions might be the reason for not noting the increase when the two other definitions were used. The same explanation could apply to the lack of difference in mean glucose level between the MS and the normal groups when the consensus definition was used.

Finally, and in view of not having national cutoff values for dyslipidemia, it might be advisable to use LDL-C/HDL-C ratio to aid diagnosis in the Saudi population since, following regression analysis, it was found to be a strong predictor of MS when all three definitions were used. Family history of diabetes or CVD might be another useful indicator because when the consensus definition was used it was found to be a strong predictor following regression analysis.

Conclusion

For all definitions used, the calculated prevalence of MS was found to be high in the Saudi population of healthy subjects, raising alarm about the overall prevalence in the general population. Using the latest consensus definition might help to decrease the number of cases that are missed using the other definitions. In the absence of local cutoff points for risk factors of MS, it might be appropriate to use the waist/hip ratio or LDL-C/HDL-C ratio to aid diagnosis. A family history of diabetes or CVD might also be indicative. Priority should be given to establishing national normal ranges, screening programs for hyperglycemia and hypertension, and community-directed programs to combat obesity and inactivity.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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