Metabolic Syndrome in Andean Populations

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ABSTRACT

The metabolic syndrome, a cluster of metabolic abnormalities, has been linked to both cardiovascular disease and type 2 diabetes mellitus risk. Several studies have shown that ethnicity is an important determinant for risk of developing the metabolic syndrome; therefore, further understanding of the prevalence and presentation of the metabolic syndrome in various ethnic groups is needed. Latin American communities, and particularly Andean countries, are largely understudied in relation to the metabolic syndrome and until recently, the prevalence of this metabolic disturbance in Andean Hispanics was unknown. Nonetheless, recent (and ongoing) population studies are providing important data regarding the prevalence and patterns of the metabolic syndrome in various Andean countries. This review aims to summarize and interpret the information provided by these studies in an effort to better characterize the metabolic syndrome in Andean Hispanics.

Cardiovascular disease is an emergent cause of death in many Latin American and Andean countries, and it is expected that its burden will increase in the near future unless appropriate control prevention strategies are implemented [1—6]. To design adequate prevention strategies, it is necessary to estimate the prevalence, characteristics, and distribution of various cardiovascular risk factors in these populations. Similarly, validated operational definitions will be needed to characterize conditions associated with increased cardiovascular risk, such as abdominal obesity and the metabolic syndrome (MetS). The MetS is a cluster of metabolic abnormalities associated with elevated risk of cardiovascular morbidity and mortality [7—11]. A recently published joint interim statement issued by several organizations has established an updated MetS definition, recognizing central adiposity, abnormal glucose regulation, elevated triglycerides, lowered high-density lipoprotein cholesterol (HDL-C), and elevated blood pressure as its central components [12]. Prospective data suggest that death from coronary heart disease is 3× higher among middle-age men with MetS after adjustment for conventional cardiovascular risk factors [13]. MetS is also an independent predictor for the development of type 2 diabetes mellitus [11,14]. In a large prospective study, the risk for diabetes after 7 years of follow-up was more than 3-fold higher in subjects with MetS, even after the adjustment for other risk factors for diabetes including impaired glucose tolerance and impaired fasting insulin [14].

Several studies have shown that ethnicity and sex are important determinants for the risk of having MetS [15—23]. In the United States, NHANES III (Third National Health and Nutrition Examination Survey) differences in the prevalence of MetS between ethnic groups were clearly observed. African American women and Mexican American women had higher prevalence rates of MetS than African American men and Mexican American men did, respectively, whereas the risk in Caucasians was similar between sexes [15]. Although several lines of evidence indicated that ethnicity is an important determinant of the MetS phenotype, until recently, the prevalence of MetS in Andean communities was largely unknown. Andean countries share indigenous population groups and historic patterns of colonization that have resulted in comparable genetic admixtures and cultural traditions that make them very similar. Recently published (and ongoing) population studies are providing important data regarding the prevalence and patterns of MetS in different Andean countries (Table 1). Among the largest of these are the study of coronary risk factors in the state of Zulia in Venezuela [15], the PREVENCION (Peruvian Study of Cardiovascular Disease Prevalence) study in the city of Arequipa in Peru [23—28], the National Survey of Health in Chile [29], and the CINDI/CARMEN (Countrywide Integrated Noncommunicable Disease Intervention Programme) study in the Colombian city of Bucaramanga [30]. Although the latter study did not specifically assess the prevalence of MetS [30], it provided important data regarding the prevalence of obesity and other cardiovascular risk factors in these populations. This paper aims to summarize and interpret the information provided by these studies to better characterize the MetS in Andean countries.

PREVALENCE OF THE MetS AND ITS COMPONENTS IN ANDEAN POPULATIONS

One of the first large studies assessing the prevalence of the MetS and its individual components in an Andean population was the Zulia study of coronary risk factors [15]. It included >3,000 subjects from a representative sample

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TABLE 1. Epidemiological studies examining the MetS among Andean Hispanics

Ref. #	Study	Geographic area	Years of observation	Sample, n (% females)	Age range, yrs	Diagnosis criteria
15	Zulia Coronary Heart Disease Risk Factor Study	Zulia, Venezuela	1999–2001	3,108 (69.6)	≥20	NCEP ATP III
24	PREVENCION study	Arequipa, Peru	2003–2007	1,878 (53.8)	20–80	NCEP ATP III; AHA/NHLBI
29	National Health Survey in Chile	Chile	2003	1,818 (54.2)	≥17	NCEP ATP III; IDF
30	CINDI/CARMEN study	Bucaramanga, Colombia	2001	2,989 (NA)	15–64	NA

AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; CINDI/CARMEN, Countrywide Integrated Noncommunicable Disease Intervention Programme; IDF, International Diabetes Federation; MetS, metabolic syndrome; NA, not available; NCEP ATP III, Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment Panel; PREVENCION, Prevalence and Patterns of Hypertension in Peruvian Andean Hispanics.

from each health district in the Venezuelan state of Zulia. This study showed that more than 60% of adults had low levels of HDL-C (defined as a serum level <50 mg/dl in women and <40 mg/dl in men), and that there were high age-adjusted prevalences of abdominal obesity (42.9%), hypertriglyceridemia (32.3%), and high blood pressure (38.1%) in this population. In contrast, the investigators reported a relatively low prevalence of abnormal fasting glucose (10.9%) [15]. Overall, the age-adjusted prevalence of MetS was 35% among men and 29.8% in women. Measurement procedures across studies are described in Appendix 1 (available online).

Another important study that provided national estimates of the prevalence of MetS among Andean Hispanics was the National Survey in Chile [29]. A total of 1,833 randomly selected adults aged 17 years were included in the study. Overall, the age-adjusted prevalence of the MetS, according to the NCEP ATP III (Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults) definition, was 31.6%, with similar prevalence estimates across sex (32.7% and 30.8% for men and women, respectively). In concordance to findings from Zulia, this study showed that low HDL-C (defined as a serum level <50 mg/dl in women and <40 mg/dl in men) was the most prevalent component of the MetS among Chilean adults with a prevalence of 52.3%, followed by hypertension, hypertriglyceridemia, and abdominal obesity with prevalence rates of 46.0%, 30.3%, and 29.7%, respectively (95% confidence intervals are shown in Table 2). In this population, however, the investigators reported a low prevalence of abnormal fasting glucose (22%).

The PREVENCION study subsequently reported data from a population-based sample of 1,878 adults in Arequipa, Peru [24–26]. Comparable to the findings from Venezuela and Chile, this study reported very high age-standardized prevalences of low HDL-cholesterol (32.3% of men and 60% of women) and significant prevalences of abdominal obesity (15.2% of men and 39.7% of women) as defined by the NCEP ATP III. The age-standardized prevalences of hypertriglyceridemia, high blood pressure, and high fasting glucose were 54.2%, 28.2%, and 6.3% in men, and 38.2%, 25.2%, and 5.9% in women, respectively [26]. In this population, the prevalence of MetS was 23.2% in women and 14.3% in men [24]. These data clearly showed that in Arequipa abdominal obesity and low HDL-C were significantly more frequent among women, whereas hypertriglyceridemia was more frequent in men. Similar sex differences in the prevalences of low HDL-C and hypertriglyceridemia were also reported in the Zulia study. It is worth noting that sex-specific HDL-C cutoffs are used to determine the presence of this MetS component (<50 mg/dl in women and <40 mg/dl in men). Therefore, although mean levels of HDL-C were comparable between sexes in Andean Hispanics (i.e., 48.4 and 46.0 mg/dl in Peruvian men and women, respectively), prevalence of low HDL-C was strikingly higher in Andean women when compared with women of other ethnicities. For example, prevalence estimates of low HDL-C were 68% and 60% for women in the Zulia [15] and PREVENCION study [24], respectively; whereas the latest estimates in the United States indicate only 32% of women present this component [31]. Similar comparisons have been presented in a recently published paper by the Latin American Consortium of Studies in Obesity [32].

As shown in Table 2, another similarity between the Zulia and the PREVENCION study populations was the higher prevalence of abdominal obesity among women versus men. In contrast, a significantly greater prevalence of elevated blood pressure was noted in Zulia's men and accounted for the high overall prevalence of the MetS among men in this population. In Arequipa, the prevalence of high blood pressure was similar across sexes (see Table 2). It appears that the risk of MetS and abdominal obesity in Andean populations increases steeply with age, particularly in women. Before age 50 years, no significant sex differences in the prevalence of the MetS were found in the PREVENCION study (13.5% vs. 10% in women and men, respectively; $p = NS$); whereas at or after age 50 years, the prevalence was nearly twice as high among women than men (52.8% vs. 27.8%; $p < 0.0001$). The prevalence of abdominal obesity in Arequipa was

TABLE 2. Age-adjusted prevalence rates of the metabolic syndrome and its components by sex

	Venezuela [15]	Peru [24]	Chile [29]	Colombia [30]
Abdominal obesity*				
Overall	42.9 (41.2–44.6)	NA	29.7 (26.6–33.0)	13.2 (12.0–14.6)
Men	31.4 (28.4–34.4)	15.2 (12.8–18.11)	NA	6.1 (4.7–7.8)
Women	47.9 (45.8–50.0)	39.7 (36.3–43.2)	NA	17.0 (15.3–18.8)
Low HDL-C†				
Overall	65.3 (63.6–67.0)	NA	52.6 (48.7–55.6)	27.7 (25.9–29.6)
Men	59.9 (56.8–63.0)	32.3 (28.7–36.1)	NA	37.6 (34.5–40.9)
Women	67.5 (65.5–69.4)	60.0 (56.2–63.6)	NA	22.2 (20.2–24.4)
Hypertriglyceridemia‡				
Overall	32.3 (30.7–34.0)	NA	30.0 (27.0–33.2)	NA
Men	43.1 (39.9–46.3)	54.2 (50.3–58.1)	NA	NA
Women	27.8 (25.9–29.7)	38.2 (35.0–41.5)	NA	NA
Hypertension§				
Overall	37.1 (36.4–39.9)	NA	46.0 (42.5–49.6)	9.5 (9.4–9.6)
Men	53.3 (50.1–56.5)	28.2 (25.2–31.6)	NA	8.8 (8.6–9.0)
Women	31.5 (29.6–33.5)	25.2 (22.6–28.0)	NA	9.9 (9.8–10.0)
Elevated fasting blood glucose‖				
Overall	10.9 (9.8–12.0)	NA	22.0 (19.0–25.4)	5.8 (4.7–7.2)
Men	13.1 (11.1–15.4)	6.3 (4.9–8.0)	NA	7.0 (5.2–9.5)
Women	10.0 (8.8–11.3)	5.9 (4.6–7.4)	NA	5.1 (4.0–6.6)
Metabolic syndrome¶				
Overall	31.2 (29.6–32.9)	18.1 (16.1–20.2)	31.6 (28.6–35.1)	NA
Men	35.0 (32.0–38.1)	14.3 (11.9–17.1)	32.7 (28.3–37.5)	NA
Women	29.8 (27.9–31.8)	23.2 (20.4–26.2)	30.8 (26.7–35.2)	NA

Values are percentages (95% confidence intervals). HDL-C, high-density lipoprotein cholesterol; NA, not available.

*Waist circumference over 102 cm in men and over 88 cm in women.

†HDL-C <40 mg/dl in men and <50 mg/dl in women.

‡Serum triglycerides ≥150 mg/dl.

§Blood pressure of ≥130/85 mm Hg.

‖Fasting blood glucose of ≥110 mg/dl (Zulia) or ≥100 mg/dl (Arequipa).

¶Three or more of the abovementioned abnormalities.

particularly high among women ≥50 years of age (61.9%) [24]. Similar findings have been reported in other Andean populations, where sex differences in the prevalence of abdominal obesity occurred predominantly in older groups, particularly among older women. For example, the CINDI/CARMEN study, a study on cardiovascular risk factors among Colombian adults aged 15 to 64 years showed the prevalence of abdominal obesity among women between the ages of 60 and 64 was 41.7%, in sharp contrast with the low prevalence rates of abdominal obesity reported in all male groups, including men older than 60 years. The prevalence of abdominal obesity defined by the NCEP ATP III criteria was 13.6% in men between the ages of 60 and 64 years [30]. Prevalence estimates of other MetS components in the CINDI/CARMEN study in Bucaramanga, Colombia, including hypertension, low HDL-C, and abnormal fasting glucose, are presented in Table 2.

Available data suggest that older Andean women not only have a higher prevalence of abdominal obesity, but they also tend to have more components of the MetS. In the PREVENCION study, independent analyses by sex showed that the odds ratio for the risk of MetS associated with a 10-year increase in age was 2.03 among women versus 1.61 among men ($p < 0.003$) (Table 3). When analyzing the odds ratio associated with a 10-year increase in age for the individual MetS components, the greatest difference between men and women was found in the prevalence of hypertension, followed by hypertriglyceridemia and abdominal obesity (Table 3).

Another interesting finding from the PREVENCION study was that the risk of having low HDL-C did not increase with age, in contrast with the other components of the MetS (Table 3) [24]. The reason for this epidemiologic dissociation is unclear but could be explained by several factors. First, it is possible that a survival bias is present, so that subjects with low HDL-C have a premature mortality, leading to a lower prevalence of this dyslipidemia pattern in older-age subjects. However, high cardiovascular mortality in younger-age groups has been found to occur in later stages of the epidemiologic transition, when the shift from infectious and deficiency diseases to the preponderance of noncommunicable, chronic illnesses occurs.

TABLE 3. Odds ratio associated with a 10-year increase in age for the risk of MetS and its components according to AHA/NHLBI criteria in men and women

	Men*		Women*		
	OR (95% CI)	p value	OR (95% CI)	p value	p value for age by sex interaction†
Metabolic syndrome	1.61 (1.44–1.79)	<0.0001	2.03 (1.82–2.28)	<0.0001	0.003
Abdominal obesity	1.45 (1.31–1.60)	<0.0001	1.62 (1.48–1.79)	<0.0001	0.09
High triglycerides	1.38 (1.26–1.52)	<0.0001	1.66 (1.51–1.83)	<0.0001	0.008
Elevated fasting glucose	1.90 (1.62–2.22)	<0.0001	2.12 (1.81–2.47)	<0.0001	0.33
Low HDL-C	0.99 (0.91–1.09)	NS	0.90 (0.83–0.98)	0.02	0.13
High blood pressure	1.96 (1.74–2.20)	<0.0001	2.80 (2.43–3.23)	<0.0001	<0.0001

CI, confidence interval; NS, not significant; OR, odds ratio; other abbreviations as in Tables 1 and 2.

*Odds ratios associated with increased risk of MetS and its components among men and women for every 10-year increase in age.

†The p value for age-sex interaction as a predictor of risk of MetS and its components.

Peru is undergoing relatively early stages of this epidemiologic transition, making it unlikely that an important survival bias occurred in younger-adult age groups. Another possible explanation could be the presence of genetic polymorphisms associated with lower HDL-C levels, which could explain the high prevalence of low HDL-C in these populations, including the younger groups. Dietary and other cultural patterns may also play a role. To clarify these findings, carefully designed genetic epidemiologic studies, as well as prospective studies looking at changes on the levels of HDL-C with aging and the effects of different dyslipidemia patterns on cardiovascular and total mortality are required.

Based on the abovementioned data, it appears that the phenotypic pattern of the MetS in Andean adults is characterized by: 1) a high prevalence of abdominal obesity when the NCEP ATP III and American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) abdominal obesity criteria are used, particularly in older women; 2) a high prevalence of dyslipidemia, with low HDL-C levels being particularly prevalent in women and hypertriglyceridemia being particularly prevalent in men; and 3) an increase in the prevalence of MetS with aging that is sharper in women than in men and that is explained by a greater age-related increase in the prevalence of abdominal obesity, hypertriglyceridemia, and high blood pressure in women.

OPTIMAL DEFINITIONS OF ABDOMINAL OBESITY AND MetS IN ANDEAN POPULATIONS

The seemingly high rates of abdominal obesity among Andean adults raise the question of what is actually the correct definition of abdominal obesity for these populations. The most commonly used definitions in the studies described in this review are those from the AHA/NHLBI [33] and the NCEP ATP III [34]. A definition from the International Diabetes Federation (IDF) had also been proposed [35]. According to the NCEP ATP III, the MetS is defined by the presence of ≥3 of the following components: 1) abdominal obesity, defined as a waist circumference >102 cm in men and >88 cm in women; 2) elevated triglycerides (>150 mg/dl); 3) low HDL-cholesterol (<40 mg/dl in men or <50 mg/dl in women); 4) high fasting glucose (≥110 mg/dl); 5) high blood pressure (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg, or use of pharmacologic treatment for hypertension). The subsequent AHA/NHLBI criteria decreased the cutoff to define abnormal fasting glucose to >100 mg/dl (instead of 110 mg/dl) and identified the use of fibrates or niacin as markers of high triglyceride levels or low HDL-cholesterol. The main difference between the IDF criteria and the criteria proposed by the NCEP ATP III and AHA/NHLBI lies in the definition of abdominal obesity. The IDF criteria included different cutoff values to identify abdominal obesity according to ethnicity and required the presence of abdominal obesity for the diagnosis of MetS. In an effort to harmonize the definition of MetS, a joint interim statement of various international organizations, including the IDF, NHLBI, AHA, World Heart Federation, International Atherosclerosis Society, and the International Association for the Study of Obesity, was published in 2009 [12]. The updated definition resembled that of the AHA/NHLBI, however, it included population- and country-specific definitions of abdominal obesity. It recommended that the IDF cut points be used for non-European populations, such as Andean Hispanics. Due to the lack of studies in South American and Central American populations, the IDF recommended the use of the cutoff values proposed for South Asian populations, which defined abdominal obesity as waist circumference of ≥90 cm in men and ≥80 cm in women, until more specific data are available [35].

Clearly, the use of different operating definitions can lead to important differences in the prevalence estimates of MetS in Andean and other Latin American or Hispanic populations. A study that compared the prevalences of MetS in San Antonio, Texas, USA; Mexico City; Spain; and Peru found that the IDF definition generated higher

prevalence estimates than the NCEP ATP III definition did [22]. Prevalence differences were more significant in men of Mexican and Peruvian Mestizo ethnic origin than in Europid subjects. The kappa coefficient of agreement between the ATP III and IDF definitions was only 0.54 in Peruvian men. Even more importantly, it should be noted that the available MetS and abdominal obesity prevalences from these studies were estimated using cut points recommended for Caucasian (ATP III and AHA/NHLBI) and South Asian populations (IDF). Whether these cut points were adequate for Andean adults was unknown at the time of these reports. At least 2 previous studies in men from Colombia and Ecuador suggested that the cutoffs to define abdominal obesity in Andean adults should be different from those for Caucasians [36,37]. A recently published study from the PREVENCION investigators [25] aimed to assess the optimal definitions for abdominal obesity in Andean adults by establishing the relationship of different waist circumference cut points with the presence of clinically apparent cardiovascular disease as well as with the presence of subclinical atherosclerosis assessed by carotid intima-media thickness, a validated independent surrogate marker for the risk of future cardiovascular events in the general population [38,39]. After identifying the normal values of intimal thickness in a highly selected healthy reference sample free of cardiovascular risk factors, receiver-operating characteristic curves were constructed on the basis of the detection of abnormally high carotid intimal thickness with different cut points of waist circumference in men and women. Similar analyses were performed using the presence of clinically established cardiovascular disease as an endpoint. Results consistently indicated that optimal cut points associated with subclinical atherosclerosis and clinically evident cardiovascular diseases were lower than the ones recommended for Caucasians by the NCEP ATP III in both men and women. The optimal cut points for waist circumference were found to be >97 cm in men and >87 cm in women [25]. Using these optimal cutoffs, a modified updated ethnic-specific MetS definition generated slightly higher prevalence estimates than the AHA/NHLBI definition did, particularly among men. The original AHA/NHLBI and updated definitions differed in classifying 4.4% of men (kappa = 0.85) and 1.3% of women (kappa = 0.99). Also, using these optimal cut points, individuals who met the ethnic-specific updated MetS criteria (and not the original AHA/NHLBI criteria) demonstrated higher carotid intima-media thickness than subjects who did not have MetS by either criteria, indicating that the more sensitive updated classification is not spurious but rather associated with early vascular disease. These findings are important because they provide preliminary definitions of abdominal obesity for the purpose of atherosclerotic risk assessment and identify a useful ethnic-specific MetS definition in Andean adults until more definitive prospective data become available.

CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

Given the association of the MetS with an increased risk of cardiovascular disease and type 2 diabetes mellitus, the high prevalence of MetS in Andean populations has high clinical and epidemiologic relevance. Data have emerged from Andean populations describing distinct patterns of the MetS (with high prevalence of abdominal obesity and dyslipidemia, including low HDL levels and hypertriglyceridemia). An operative definition for abdominal obesity in this population is now available and should be implemented in detection programs. This definition also provides clinicians with adequate cut points for waist circumference to use in the diagnosis of MetS among Andean Hispanics.

Available prevalence data of these and other cardiovascular risk factors could be used to target prevention strategies and to estimate the cost-benefit ratio for various potential interventions in the region. However, there are still important challenges for the future, including the design of longitudinal studies aimed to establish the absolute risk of cardiovascular events and to validate surrogate markers of cardiovascular outcomes in Andean populations.

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APPENDIX

APPENDIX 1. Measurement procedures across studies

	Zulia Coronary Heart Disease Risk Factor Study	PREVENCION study	National Health Survey in Chile	CINDI/CARMEN study
Waist circumference	Measured at umbilical level while subjects were standing with weight equally distributed on both feet	Measured at umbilical level while subjects were standing with weight equally distributed on both feet	Measured at umbilical level while subjects were standing with weight equally distributed on both feet	Measured at umbilical level while subjects were standing with weight equally distributed on both feet
Blood pressure	Measured twice after participant was seated for 5 min	Measured between 7 and 10 AM according to recommendations from the Seventh Report of the Joint National Committee for the Diagnosis, Evaluation, and Treatment of High Blood Pressure	Measured twice after participant was seated for 5 min during the morning hours	Blood pressure was measured independently by 2 observers in each participant, following standard recommendations
Lipids	Sample of venous blood was drawn after 12—14 h of overnight fasting and was centrifuged within 30—45 min of collection	Samples of venous blood were obtained after ≥8 h of fasting and serum was used for biochemical measurements	Samples of venous blood were obtained after ≥9 h of fasting and serum was used for biochemical measurements	Fasting blood samples were drawn from each participant and processed and stored at −70°C

CINDI/CARMEN, Countrywide Integrated Noncommunicable Disease Intervention Programme; PREVENCION, Prevalence and Patterns of Hypertension in Peruvian Andean Hispanics.