Original Paper

The Metabolic Syndrome: A Modern Plague Spread by Modern Technology

Aaron Spalding, MD, PhD;[1] Joseph Kernan, BA, MS;[2] Warren Lockette, MD[2,3,4]

Malnutrition and infectious disease represent the most common health threats facing the developing world. However, increasing technological developments and the expansion of western culture have contributed to the increasing prevalence of the metabolic syndrome. The epidemiologic significance and potential costs to governmental health care systems of an increasing incidence of metabolic syndrome could become high. The role of environmental influences that lead to the development of the metabolic syndrome needs to be explored. Because the metabolic syndrome becomes more common as nations develop, investigations into the ramifications of this disease often come too late. J Clin Hypertens (Greenwich). *2009;11:755–760.* ©*2009 Wiley Periodicals, Inc.*

Everyone loves a good mystery. No one knows with certainty the population of the pre-Columbian New World, nor the extent of population changes since the 1500s. Estimates have ranged from a conservative low of 8 million, to a high of 145 million; the most common consensus is that approximately 54 million indigenous Indians populated the Americas during the initial Spanish conquest. During the 16th century, there were 3 distinct major population collapses in Mexico at that time. Approximately 8 million deaths occurred in 1520, 12 to 15 million more deaths followed in 1545, and, subsequently, evidence shows that there were an additional 2 million deaths in 1576. These numbers are significant no matter what size one considers to have been the pre-Columbus population of Central and South America.[1] What caused the deaths of so many?

There has been long-standing consensus that most of these losses were due to communicable diseases, and, until recently, most fingers pointed to diseases *imported* to the New World—either from smallpox, typhus, or measles—despite lacking proof of "who done it." However, could indigenous microbes have been responsible? Recent evidence suggests that a nascent disease, whose spread was facilitated by the actions of the Spanish, was indeed responsible for these later epidemics. Most likely, these latter depopulations, sufficiently severe at that time to warrant a new name, *cocoliztli* in the native Nahuatl/Aztec vernacular, is now felt to be the result of indigenous viral hemorrhagic fevers whose spread was eased by rodent hosts during extreme drought conditions.[2,3] This conclusion was finally made possible by the astute observations of some infectious disease specialists who noted that patterns of drought affected the outbreak of lethal infections caused by the *Sin Nombre* virus in the Four Corners region of the United States in 1993. The cultural, social, and political transformation of

From the Department of Radiation Oncology, Norton Cancer Institute, Louisville, KY;[1] the US Naval Forces Southern Command, Fourth Fleet, Jacksonville, FL;[2] the International House and Department of Internal Medicine/Geriatrics, University of California, San Diego, CA;[3] and the Department of Physiology, University of Michigan, Ann Arbor, MI[4]
Address for correspondence:
Warren Lockette, MD, International House and Department of Internal Medicine/Geriatrics, University of California, 200 West Arbor Drive, MC8415, San Diego, CA
E-mail: wlockette@ucsd.edu
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Mesoamerica brought about by the Spanish, coupled with the effect of a changing climate in the region, created conditions favorable for these epidemics in 16th century Mexico. Two medical historians recently noted:

> [The] concentration of previously dispersed rural populations into new towns centered around churches, the centralization of food supplies, changes in crop production in concert with ecological events (deforestation, droughts, dust storms) may have fostered selective disease spread among the indigenous peoples.... Large-scale depopulation led to a destruction of local agrarian infrastructures which fostered and sustained these epidemics, and disease foci receded and then disappeared....[2]

As the end of this mystery unfolds, another one begins in the 21st century. Although problems brought about by infectious diseases remain prevalent in many regions of Central and South America, recent cultural, social, and political transformations have brought about the rise of a new epidemic, the metabolic syndrome. The lesson learned from the infectious disease specialists, *vide supra*, is helpful in framing how we view this new epidemic and as we try to separate its causes into imported or indigenous sources.

THE METABOLIC SYNDROME: A MODERN PLAGUE

The metabolic syndrome is a group of traits that occur together and promote the development of diabetes mellitus and cardiovascular disease. Specifically, patients with the metabolic syndrome have a 5-fold increased risk of type II diabetes mellitus and a 2-fold increased risk of cardiovascular disease. The recent geometric growth of the metabolic syndrome (Table) in developing countries has been attributed, for the most part, to the import of technology and cultural adaptations that have promoted industrialization. Indeed, those countries that are the most industrialized have the greatest prevalence of the metabolic syndrome. However, our mystery has taught us that we must look at both indigenous and imported contributions to understand the development of this latest epidemic.

This exercise is important. Identification of patients with the metabolic syndrome may help determine which individuals should receive interventions when resources in a developing country are scant. The constellation of findings in patients with the metabolic syndrome—high levels of plasma insulin, impaired glucose tolerance, hyperlipidemia (ie, increased triglycerides [very low-density lipoprotein] with low levels of high-density lipoprotein cholesterol [HDL-C]), and high blood pressure—was originally called *syndrome X*, and it has also been called the *insulin resistance syndrome*. Other criteria may be added to the definition of the metabolic syndrome, such as central obesity (ie, increased waist circumference for men of >40 in and for women >35 in), microalbuminuria, or a procoagulant state that could be reflected by a number of factors such as increased plasma fibrinogen concentrations.[4] Also, in addition to diabetes mellitus and cardiovascular disease, other abnormalities have been associated with the metabolic syndrome such as nonalcoholic fatty liver disease. The mechanisms by which this syndrome and its consequences develop are unknown.

POTENTIAL INHERITABLE RISK FACTORS

A genetic predisposition to the metabolic syndrome can explain some, but not all, of the increasing prevalence of this disorder in the developing world. For example, one cross-sectional survey of a random representative sample from each health district in Zulia State, Venezuela, showed a high overall prevalence of the metabolic syndrome (31%). The occurrence of the metabolic syndrome revealed a distinct ethnic predisposition; Amerindian men had a prevalence of only 17%, whereas men of mixed Hispanic descent had more than twice the rate (37.4%).[5] With industrialization, it will be of interest to know whether the indigenous populations are more or less susceptible to the development of the metabolic syndrome.

Others have described sex-specific risks towards developing the metabolic syndrome. Premenopausal women seem to resist the development of the metabolic syndrome, but this protection disappears after menopause.[6] Hormonal manipulation of experimental animals points to a link between estrogen, testosterone, and development of metabolic syndrome markers. Rats overfed with a sucrose diet develop metabolic syndrome manifested by increased blood pressure, proteinuria, and lipid peroxidation. The severity of the metabolic syndrome correlated with decreased expression of enzymes that reduce free radicals. Most interestingly, oophorectomy decreased the protection against oxidative stress in females; the opposite occurred in castrated males.[7] These laboratory and clinical studies suggest that testosterone increases susceptibility to the metabolic syndrome, whereas estrogen may be protective.

Table. Worldwide Estimates of the Metabolic Syndrome Among Countries With Recent Industrialization

Country	Ages, y	Incidence, Male, %	Incidence, Female, %	Reference
Korea	40–60	17	10	Sung et al.[37]
Brazil	60–79	64	44	Dalacorte et al.[38]
Brazil	6–10		9[a]	Strufaldi et al.[39]
Bolivia	5–18	40	32	Caceres et al.[40]
Chile	30–60	39	34	Mujica et al.[41]
Colombia	41 (average)		33[a]	Pinzón et al.[42]
Mexico	35–65	41[b]		Ramírez-Vargas et al.[43]
Mexico	20–40	49	43	Echavarría-Pinto et al.[44]
Mexico	35–64	40	60	Lorenzo et al.[45]

[a]The sex of participants was not reported in this study. [b]Female patients were not included in this study.

Epidemiologic studies have shown an inverse correlation between birth weight and cardiovascular disease. Perhaps early life stressors, such as poor maternal nutrition, maternal obesity, and rapid postnatal weight gain program metabolic adaptations for subsequent survival in a nutrient-poor environment such as would occur during a drought. However, when calories are later plentiful, this same programming results in the metabolic syndrome in adolescents and adults. Accordingly, increasing food consumption and calories could contribute to the appearance of the metabolic syndrome in individuals so predisposed because they were stressed during intrauterine life.[8–11] As industrialization has led to higher per capita income, food availability has increased, consistent with this hypothesis. Furthermore, the primary focus in preventing the metabolic syndrome should be to ensure adequate maternal nutrition.

However, as practitioners in the developing world, we have learned the lesson taught by our study of the epidemiology of infectious diseases: we must not forget to look at *all* ways the environment shapes the presentation of disease. We postulate that poorly regulated environmental factors in some developing regions, primarily environmental pollutants, can also contribute to the growing problem of the metabolic syndrome in the developing world.

ENVIRONMENTAL EXPOSURE TO ORGANIC TOXINS AS INSULIN DISRUPTORS

In most cases, the exact environmental pollutants associated with the development of the metabolic syndrome are not known. For example, individuals working in petrochemical plants in Brazil and Venezuela have been shown to have a high incidence of the metabolic syndrome.[12,13] In these cases, exposure to various industrial chemicals such as benzene, xylene, ethylene, and vinyl chloride was noted. Working in these types of plants is often not necessary for one to be at increased risk for the metabolic syndrome; just living in residential areas surrounding industrial areas increases the risk of the metabolic syndrome.[14] Benzene derivatives induce hyperinsulinemia in a dose-dependent manner in animal experiments. This could potentially contribute to the insulin resistance found in the metabolic syndrome.[15]

Although association does not prove causation, recent findings suggest a cause and effect relationship between environmental pollutants and susceptibility to the metabolic syndrome. For example, bisphenol A is one of the highest volume chemicals produced in the world. It is an essential ingredient in the production of plastic polymers and is used in the manufacturing of food and beverage containers. It is found in significant concentration in the urine of 95% of people living in the United States and it has been shown that exposure of laboratory animals to doses about 1000-fold *less* than what is allowed by the US Environmental Protection Agency alters glucose tolerance and induces insulin resistance.[16,17] Bisphenol A affects the expression of the glut4 cell membrane glucose transporter in cultured adipocytes, increasing glucose uptake and adipogenesis.[18] So concerned with the public health implication of this finding, Canada has even taken steps to ban baby bottles manufactured with this chemical.[19]

Similarly, dioxins are lipophilic organochlorine compounds that accumulate virtually irreversibly in fat tissue. Humans are ubiquitously exposed to dioxins through a number of sources. For example, these compounds are used in the processing of timber or manufacturing of paper, the production of herbicides, or through improper disposal of products made from plastics. Because dioxins are stored in fat tissue, almost *all* humans examined have

detectable burdens of dioxins. Experimental evidence has linked dioxin exposure to impaired glucose transport, and it is likely that long-term low level exposure to dioxin is a risk factor for glucose intolerance and insulin resistance.[20] The strongest data in support of this link come from a government study of US Air Force veterans who participated in "Operation Ranch Hand." These personnel had contact with a dioxin contaminant in an herbicide, Agent Orange. Compared with a control population, these veterans had a 3-fold increase in dioxin levels, 12 parts per trillion, compared with the control group of patients, 4 parts per trillion. Despite the trace amount of dioxin present, the exposed group had greatly increased rates of glucose intolerance, type II diabetes mellitus, the development of diabetes at an earlier age, and abnormalities in plasma insulin concentrations.[21] In vitro experiments clearly demonstrate dioxin selectively targets the pancreatic β cells, to disrupt insulin secretion, and at high levels cause islet cell death.[22] At levels found in serum of exposed humans, dioxin decreases expression of glut4 in pancreatic islet cells, *disrupting the negative feedback loop for insulin secretion*, potentially leading to hyperinsulinemia.[23]

The problem of environmental contamination is not limited to North America. There is widespread contamination by these compounds in the marine environment throughout the coastal waters of South America,[24] and levels have been so high in some South American products that their exports were halted.[25] Because the metabolic syndrome can represent a prediabetic state, it is worrisome that these compounds could facilitate the development of the metabolic syndrome and diabetes mellitus.

HEAVY METAL EXPOSURE

It is not only organic chemicals that may predispose an individual to the metabolic syndrome. It has been known for some time that environmental exposure to lead and cadmium is associated with higher blood pressure, especially in the Hispanic population, and the heavy metals also potentiate the development of renal insufficiency (eg, saturnine nephropathy). Accordingly, lead may contribute to the higher blood pressures found in patients with the metabolic syndrome.[26–28] Similarly, organic mercurials are widely found as environmental pollutants. Although there is no evidence that organic mercurials contribute to the direct evolution of glucose intolerance to the metabolic syndrome, mercury exposure could increase the untoward sequelae of full-blown diabetes, such as peripheral neuropathy, that may occur in these patients.

Of all of the heavy metals that contaminate the environment, both from natural sources such as groundwater and that which is a byproduct of mining operations, arsenic exposure most strongly predisposes one toward the metabolic syndrome, *at levels below which are considered toxic*. Arsenic contamination of drinking water has been linked in several areas to insulin resistance. A study of 660 random people from central Taiwan showed that after adjustment for age, sex, occupation, and lifestyle factors including cigarette smoking (a principal cause of heavy metal exposure), arsenic levels correlated with the prevalence of the metabolic syndrome. Furthermore, arsenic concentrations had a linear relationship with increasing levels of plasma glucose, plasma lipids, and blood pressure. A study performed in the United States investigated the association of very mild arsenic exposure, as measured with urinary arsenic excretion, with the prevalence of type II diabetes mellitus. This cross-sectional study of 788 adults found that the median urine level of total arsenic was 7.1 μg/L, with a prevalence of type II diabetes mellitus of 7.7%. After adjustment for diabetes risk factors and markers of seafood intake, patients with type II diabetes had a 26% higher level of total arsenic than participants who were euglycemic. After similar adjustments, the odds ratio for type II diabetes comparing participants at the 80th vs the 20th percentiles of arsenic load was 3.58 for the level of total arsenic. That study concluded that the low levels of exposure to inorganic arsenic in otherwise "safe" drinking water may play a role in the incidence of diabetes. Arsenic has similarly been linked to the progression of the metabolic syndrome and diabetes in other countries. A case-control study in an arsenic-endemic region from Coahuila, a northern state in Mexico with a high incidence of diabetes, was conducted that included 200 cases and 200 controls. Patients with higher urinary arsenic concentrations had a 2- to 3-fold higher risk of having type II diabetes mellitus, as indicated by fasting glucose values >126 mg/dL, or the use of insulin or oral hypoglycemic agents.[29–33]

Laboratory data suggest that arsenic, similar to dioxin, specifically alters glucose homeostasis through targeting pancreatic β cells. Downstream signaling of the insulin receptor relies on kinase activity. Arsenic inhibits phosphorylation of Akt at both threonine 308 and serine 473 after insulin exposure, *desensitizing cells to insulin*.[34] Rats exposed to arsenic in their drinking water to mimic industrial exposure develop

hyperglycemia and decreased insulin secretion, with increased islet cell apoptosis.[35] In islet cells, cell death and decreased insulin secretion could produce hyperglycemia. Coupled with target cell insulin desensitivity, arsenic exposure can lead to the metabolic syndrome.

CONCLUSIONS

Molecular genetics has shown us that traits such as glucose intolerance, insulin resistance, and blood pressure are complex quantitative traits. That is, there are several genes that contribute to our heritable predisposition for each of these phenotypes, and there are obvious environmental contributions to the metabolic syndrome, such as the intake of excess calories or low levels of exertion and exercise. However, the role of environmental pollutants, both naturally occurring and man-made, should be further investigated.

It is recognized in many developing areas where the metabolic syndrome is becoming endemic that there is no infrastructure in place or resources to support such inquiry. Fortunately, it has been shown that laboratory-based tests, ie, blood sampling, are not needed to determine an *individual's* cardiovascular disease risk. A careful survey can be equally reliable.[36] As individuals who provide humanitarian assistance to the health care infrastructure of the developing world, we must be reminded that our evaluation and counseling of patients predisposed to diabetes and the metabolic syndrome in resource-poor environments should have a broad perspective. Despite the lack of internal resources, it would be helpful if those who perform humanitarian medical assistance to developing regions of the globe also help to assess and document the growing risk for the metabolic syndrome. Specifically, we urge those agencies that support such programs to help facilitate environmental assessments during those missions for the risk factors we have described above. Data generated in such a manner can be used to help host nations plan their interventions at diminishing the untoward effects of diabetes mellitus and cardiovascular disease. When we examine patients, we must remember to examine the environment in which they live. We can learn much by lessons taught to us by our colleagues who specialize in infectious disease.

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REFERENCES

1 Acuna-Soto R, Stahle DW, Cleaveland MK, et al. Megadrought and megadeath in 16th century Mexico. *Emerg Infect Dis.* 2002;8:360–362.
2 Marr JS, Kiracofe JB. Was the *Huey Cocoliztli* a hemorrhagic fever? *Med Hist.* 2000;44:341–362.
3 Hjelle B, Glass GE. Outbreak of Hantavirus infection in the four corners region of the United States in the wake of the 1997–1998 El Nino-Southern Oscillation. *J Infect Dis.* 2000;181:1569–1573.
4 Lusis AJ, Attie AD, Reue K. Metabolic syndrome: from epidemiology to systems biology. *Nat Rev Genet.* 2008;9:819–830.
5 Florez H, Silva E, Fernandez V, et al. Prevalence and risk factors associated with the metabolic syndrome and dyslipidemia in White, Black, Amerindian, and mixed Hispanics in Zulia State, Venezuela. *Diabetes Res Clin Pract.* 2005;69:63–77.
6 Ren J, Kelley RO. Cardiac health in women with metabolic syndrome: clinical aspects and pathophysiology. *Obesity (Silver Spring).* 2009;17:1114–1123.
7 Perez-Torres I, Roque P, El Hafidi M, et al. Association of renal damage and oxidative stress in a rat model of metabolic syndrome. Influence of gender. *Free Radic Res.* 2009;43(8):761–771.
8 Painter RC, Roseboom TJ, van Montfrans GA, et al. Microalbuminuria in adults after prenatal exposure to the Dutch famine. *J Am Soc Nephrol.* 2005;6:189–194.
9 Painter RC, de Rooij SR, Bossuyt PM, et al. Blood pressure response to psychological stressors in adults after prenatal exposure to the Dutch famine. *J Hypertens.* 2006;24:1771–1778.
10 Eriksson JG, Osmond C, Kajantie E, et al. Patterns of growth among children who later develop type II diabetes or its risk factors. *Diabetologia.* 2006;49:2853–2858.
11 Mohan-Kumar SMJ, King A, Shin AC, et al. Developmental programming of cardiovascular disorders: focus on hypertension. *Rev Endocr Metab Disord.* 2007;8:115–125.
12 Cotrim HP, Carvalho F, Siquiera AC, et al. Nonalcoholic fatty liver and insulin resistance among petrochemical workers. *JAMA.* 2005;294:1618–1619.
13 Sirit Y, Acero C, Bellorin M, et al. Metabolic syndrome and other cardiovascular risk factors in workers of a plant of vinyl polychloride. *Rev Saude Publica.* 2008;10:239–249.
14 Mohan V, Deepa M, Farooq S, et al. Surveillance for risk factors of cardiovascular disease among an industrial population in southern India. *Natl Med J India.* 2008;21:8–13.
15 Mineo H, Ohdate T, Fukumura K, et al. Effects of benzoic acid and its analogues on insulin and glucagon secretion in sheep. *Eur J Pharmacol.* 1995;280:149–154.
16 Alonso-Magdalena P, Morimoto S, Ripoli C, et al. Estrogenic effect of bisphenol A disrupts pancreatic β-cell function in vivo and induces insulin resistance. *Environ Health Perspect.* 2006;114:106–112.
17 Lang IA, Galloway TS, Scarlett A, et al. Association of urinary bisphenol. A concentration with medical disorders and laboratory abnormalities in adults. *JAMA.* 2008; 300:1303–1310.
18 Sakurai K, Kawazuma M, Adachi T, et al. Bisphenol A affects glucose transport in mouse 3T3-F442A adipocytes. *Br J Pharmacol.* 2004;141(2):209–214, [Epub 2004 Jan 5].

19 http://www.nytimes.com/2008/04/19/business/worldbusiness/19plastic.html. Accessed April 19 2008.

20 Remmard RBJ, Bunce NJ. Linking dioxins to diabetes: epidemiology and biologic plausibility. *Environ Health Perspect*. 2002;110:853–858.

21 Henridsen GL, Ketchum NS, Michalek JE, et al. Serum dioxin and diabetes mellitus in veterans of Operation Ranch Hand. *Epidemiology*. 1997;8:252–258.

22 Piaggi S, Novelli M, Martino L, et al. Cell death and impairment of glucose-stimulated insulin secretion induced by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in the beta-cell line INS-1E. *Toxicol Appl Pharmacol*. 2007;220:333–340.

23 Novelli M, Piaggi S, De Tata V. 2,3,7,8-Tetrachlorodibenzo-p-dioxin-induced impairment of glucose-stimulated insulin secretion in isolated rat pancreatic islets. *Toxicol Lett*. 2005;156:307–314.

24 Daisuke U, Watanable M, Subramanian A, et al. Global pollution monitoring of polychlorinated dibenzo-p-dioxins (PCCDs) furans (PCDFs) and coplanar polychlorinated biphenyls (coplanar PCBs) using skipjacka tuna as bioindicator. *Environ Pollut*. 2005;136:303–313.

25 Carvalhaes GK, Brooks P, Marques CG, et al. Lime as the source of PCDD/F contamination in citrus pulp pellets from Brazil and status of monitoring program. *Chemosphere*. 2002;46:1413–1416.

26 Navas-Acien A, Guallar E, Silbergeld EK, et al. Lead exposure and cardiovascular disease – a systematic review. *Environ Health Perspect*. 2007;115:472–482.

27 Muntner P, Menke A, DeSalvo KB, et al. Continued decline in blood lead levels among adults in the United States. The National Health and Nutrition Examination Surveys. *Arch Intern Med*. 2005;165:2155–2161.

28 Prozialeck WC, Edwards JR, Nebert DW, et al. The vascular system as a target of metal toxicity. *Toxicol Sci*. 2008;102:207–218.

29 Wang SL, Chiou JM, Chen CJ, et al. Prevalence of non-insulin dependent diabetes mellitus and related vascular diseases in southwestern arseniasis-endemic and non-endemic areas in Taiwan. *Environ Health Perspect*. 2003;111:155–159.

30 Rahman M, Tondel M, Ahmad SA, et al. Diabetes mellitus associated with arsenic exposure in Bangladesh. *Am J Epidemiol*. 1998;148:198–203.

31 Afridi HI, Kazi TG, Kazi N, et al. Evaluation of status of toxic metals in biological samples of diabetes mellitus patients. *Diabetes Res Clin Pract*. 2008;80:280–288.

32 Coronado-Gonzalez JA, Del Razo LM, Garcia-Vargas G, et al. Inorganic arsenic exposure and type II diabetes mellitus in Mexico. *Environ Res*. 2007;104:383–389.

33 Navas-Acien A, Silbergeld EK, Pastor-Barriuso R, et al. Arsenic exposure and prevalence of type II diabetes in US adults. *JAMA*. 2008;300:814–822.

34 Paul DS, Harmon AW, Devesa V, et al. Molecular mechanisms of the diabetogenic effects of arsenic: inhibition of insulin signaling by arsenite and methylarsonous acid. *Environ Health Perspect*. 2007;115(5):734–742, [Epub 2007 Jan 29].

35 Yen CC, Lu FJ, Huang CF, et al. The diabetogenic effects of the combination of humic acid and arsenic: in vitro and in vivo studies. *Toxicol Lett*. 2007;172(3):91–105, [Epub 2007 May 24].

36 Gaziano TA, Young CR, Fitzmaurice G, et al. Laboratory-based versus non-laboratory based method for assessment of cardiovascular disease risk: the NHANES I follow up study cohort. *Lancet*. 2008;371:923–931.

37 Sung KC, Kim BJ, Kim BS, et al. A comparison of the prevalence of the MS and its complications using three proposed definitions in Korean subjects. *Am J Cardiol*. 2009;103:1732–1735.

38 Dalacorte RR, Reichert CL, Vieira JL. Metabolic syndrome and physical activity in southern Brazilian community-dwelling elders: a population-based, cross-sectional study. *BMC Public Health*. 2009;9:25.

39 Strufaldi MW, Silva EM, Puccini RF. Metabolic syndrome among prepubertal Brazilian schoolchildren. *Diab Vasc Dis Res*. 2008;5:291–297.

40 Caceres M, Teran CG, Rodriguez S, et al. Prevalence of insulin resistance and its association with metabolic syndrome criteria among Bolivian children and adolescents with obesity. *BMC Pediatr*. 2008;12:8.

41 Mujica V, Leiva E, Icaza G, et al. Evaluation of metabolic syndrome in adults of Talca city, Chile. *Nutr J*. 2008; 15:7–14.

42 Pinzón JB, Serrano NC, Díaz LA, et al. Impact of the new definitions in the prevalence of the metabolic syndrome in an adult population at Bucaramanga, Colombia. *Biomedica*. 2007;27:172–179.

43 Ramírez-Vargas E, Arnaud-Viñas Mdel R, Delisle H. Prevalence of the metabolic syndrome and associated lifestyles in adult males from Oaxaca, Mexico. *Salud Publica Mex*. 2007;49:94–102.

44 Echavarría-Pinto M, Hernández-Lomelí A, Alcocer-Gamba MA, et al. Metabolic syndrome in adults from 20 to 40 years old in a rural Mexican community. *Rev Med Inst Mex Seguro Soc*. 2006;44:329–335.

45 Lorenzo C, Williams K, Gonzalez-Villalpando C, et al. The prevalence of the metabolic syndrome did not increase in Mexico City between 1990–1992 and 1997–1999 despite more central obesity. *Diabetes Care*. 2005; 28:2480–2485.