NUTRITION REVIEWS

Special Article

Overweight and obesity: a review of their relationship to metabolic syndrome, cardiovascular disease, and cancer in South America

Laura R Aballay, Aldo R Eynard, María del Pilar Díaz, Alicia Navarro, and Sonia E Muñoz

Socioeconomic and demographic transformations are occurring very rapidly in some areas of the world, especially in South America, and are accompanied by changes in lifestyle, dietary patterns, and the epidemiological profile of prevalent diseases. This review examines whether obesity and overweight are related to metabolic syndrome, cardiovascular disease, and cancer in South America. Research carried out in more than 6,000 cases and controls was evaluated, along with most of the available publications related to South America. In South America, obesity and risk factors for cardiovascular disease are related mainly to aging, ethnicity effects, and preventable risky lifestyle conditions. Most of the studies that found an association between cancer and obesity are from the Southern Cone, the geographic area most affected by this pathology. Overall, the prevalence of metabolic syndrome was highest in Chile, followed in decreasing order by Colombia, Peru, Argentina, and Ecuador, with differences noted between urban and rural areas or between urban and periurban areas. Obesity and cancer may be preventable, at least in part, by healthy behavior; hence, exercise, weight control, and healthy dietary habits are important to reduce the risk of these major chronic diseases.

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INTRODUCTION

Obesity is a major public health concern worldwide, contributing to increased morbidity and mortality. It has emerged as a significant cause of diabetes, cardiovascular disease (CVD), and renal insufficiency. The accelerated worldwide increase of obesity prevalence has been named "globesity," with considerable variations observed between and within countries. Coincidentally, epidemiological patterns, food habits, and lifestyles are changing very fast.[1,2] Obesity affects both sexes and all ages, and, in Latin America, it increases with age and is always more prevalent in women, especially those from lower social strata.[3,4]

In recent decades, there has been an increase in chronic nontransmissible diseases (NTDs) in South America, associated with increased longevity and a decrease in infectious diseases.[5,6] Although the South American countries have different health profiles, CVD has become the leading cause of mortality in all of them, and metabolic syndrome (MetS) and cancer are also among the main causes of mortality.[5]

Studies about obesity in relation to other NTDs warrant special attention for several reasons. First, those affected by obesity and NTDs often share some unseen common causal factors, such as inappropriate eating habits and sedentarism. In addition, when obese people are identified, a high proportion of them are also found to

Affiliations: *LR Aballay, MP Díaz*, and *A Navarro are* with the Escuela de Nutrición, Facultad de Ciencias Médicas, Universidad Nacional de Córdoba, Córdoba, Argentina. *AR Eynard* and *SE Muñoz* are with the Instituto Biología Celular, Facultad de Ciencias Médicas, Universidad Nacional de Córdoba, Córdoba, Argentina, and Consejo Nacional de Investigaciones Científicas y Técnicas (INICSA-CONICET), Argentina.

Correspondence: *SE Muñoz*, Instituto de Biología Celular, Enrique Barros esq. Enfermera Gordillo, Ciudad Universitaria, Córdoba C.P. 5000, Argentina. E-mail: smunoz@cmefcm.uncor.edu. Phone: +54-351-4629530/+54-351-4334021. Cell: +54-9-351-5211100. Fax: +54-351-4334021.

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be at risk of other NTDs. Thus, by preventing obesity, most NTDs are prevented as well. Finally, when obesity is treated, the risks of complications diminish, thus reducing the effect of obesity on other risk factors.[7,8]

Similar to what has occurred in more developed societies, obesity is increasing in South America. However, the marked cultural, economic, and racial heterogeneity in the South American population generates conditions in which obesity, poverty, and malnutrition often coexist.[3,6]

LITERATURE SEARCH METHODS

A systematic literature search was conducted for the major sources of national and international surveys relating to obesity and overweight, MetS, CVD, and cancer. The search was restricted to articles published up to July 2011 for each South American country and to the adult population, although some consideration was given to obesity in childhood and adolescence.

GENERAL CONSIDERATIONS OF OBESITY

Obesity is a multifactorial disease caused mainly by the interaction of genetic and environmental factors.[9] The increase in body fat deposits generally coincides with an increase in body weight, leading to a greater risk of comorbidities and affecting both quality of life and life expectancy.[10] Adipose tissue plays a critical role in energy homeostasis in higher organisms. It serves as the main site for energy storage in the form of triglycerides (TGs), and it also contributes to systemic glucose and lipid metabolism via its function as an endocrine organ.[11]

The adipocyte, a highly differentiated cell from adipose tissue, synthesizes and releases a variety of substances that include tumor necrosis factor α (TNF-α), protein C, intercellular adhesion molecule, angiotensinogen, plasminogen activator inhibitor, adiponectin, and resistin, among others,[12] all of which fulfill different roles and are involved in the pathogenesis of chronic diseases. The discovery of leptin, melanocortin-4, and leptin receptors and the knowledge of hormonal mediator functions that participate in keeping correct body weight have enabled further understanding of the pathogenic processes and causes of obesity.[13]

Among the factors that contribute to the etiology of obesity, the genetic background inevitably overlaps with environmental factors as a necessary condition for the establishment of the disease. While the former probably sets the stage for obesity, the latter seems to determine the magnitude of the problem.[10,14,15] Even though differential characteristics can be observed in all South American countries, there are common aspects that include a dietary pattern with a higher caloric intake and a concomitant reduced nutrient density.[16] This implies an increase in the consumption of animal fat, added sugar, and refined foods, along with a decrease in the total intake of complex carbohydrates, fiber, fruits, and vegetables.[17–19] This leads to increased per capita caloric availability, coupled with a social environment in which little physical activity is likely. Hence, these are not single dietary changes but interrelated multifactorial processes, often involving modifications in sociocultural and economic conditions, individual behavior, and lifestyle.[20]

Some consideration should be given to obesity in childhood and adolescence as a predictor of this pathology in adults, and there are studies related to adolescents and adults in some South American countries. The Pan American Health Organization reports that, in Argentina, Colombia, Peru, Paraguay, and Uruguay, more than 15% of the entire population is obese. In Bolivia, Chile, Ecuador, and Peru, obesity in adolescent populations ranges between 11% and 15%, affecting a greater proportion of those in urban areas and of low socioeconomic status.[21–26]

National comparative studies found that the prevalence of obesity in the adult population is over 20% in 17 of 20 Latin American countries.[27] A summary of the data on the prevalence of overweight and obesity in South America (Table 1) shows that, in all South American countries except Brazil, Argentina, Colombia, and Bolivia, more than 50% of the population is overweight.[28–38] The countries with the highest prevalence of obesity are Chile, Trinidad and Tobago, and Paraguay, with the prevalence reaching 31% in Paraguay.[5] Other studies have been conducted in Uruguay and Argentina. In Uruguay, the Second National Survey of Overweight and Obesity in Adults showed overweight and obesity increasing linearly with age, with a sharp rise beginning at age 35 and reaching the highest levels after age 45.[39]

A recent population-based prevalence study (Córdoba Obesity and Diet Study) investigating the association of social and other factors with overweight and obesity in Argentina was conducted in a small- to medium-sized population with a sample size of 4,567 subjects in the years 2005–2006. The findings showed 52% of the subjects to be overweight and 17% to be obese.[6] The National Survey on Nutrition and Health, conducted in women in 2007, reported the prevalence of overweight to be 44.3% and that of obesity 19.4%.[28] Other available data derive from the general population of the cities of Venado Tuerto (Santa Fé province) and Dean Funes (Córdoba province), where the prevalence of overweight and obesity was found to be 59.3% and 62.6%, respectively.[40,41] In Argentina, one case-control study on dietary consumption and colon cancer showed that more than 40.0% of cases and 14.0% of controls were overweight and obese.[42]

Table 1 **Prevalence of obesity and overweight according to different South American national studies.**

Country	Overweight (%)	Preobesity (%)	Obesity (%)	Sex	Year	Reference
Argentina	44.3	24.9	19.4	Female	2004–2005	Ministerio de Salud, Presidencia de la Nación (2007)[28]
Brazil	40.60	29.5	11.1	Male and female	2003	Ministerio Saúde (2008)[29]
Bolivia	49.7	32.3	17.4	Female	2008	Ministerio de Salud y Deportes, Programa Reforma de Salud, and Instituto Nacional de Estadística (2009)[30]
Colombia	46.02	32.31	13.71	Male and female	2007	Rodriquez et al. (2009)[31]
Chile	59.7	37.8	21.9	Male and female	2003	Pérez et al. (1999)[32]
Ecuador	55	40.4	14.6	Female	2004	Centro de Estudios de Población y Desarrollo Social (2005)[33]
Peru	55.4	39.1	16.3	Male and female	2000	Instituto Cuánto (2000)[34]
Uruguay	52.4	35.4	17	Male and female	1998	Pisabarro et al. (2000)[35]
Guyana	51.4	29	22.4	Male and female	2003	Howard et al. (2003)[36]
Paraguay	69.5	37.9	31.6	Male and female	1991–1992	Figueredo (2001)[37]
Trinidad and Tobago	60	34	26	Male and female	2001	Ennis et al. (2003)[38]

No national studies were found for French Guyana, Venezuela, or Surinam.

The main comorbidities associated with obesity include MetS, CVD, and cancer, the magnitude and prevalence of which are increasing.[4] The next section reviews the main mechanisms involved in these diseases, along with the major epidemiological publications available in South America.

OBESITY AND COMORBIDITIES

Obesity and metabolic syndrome

Physiopathogeny. Obesity, especially abdomino-visceral, is associated with certain pathogenic factors that contribute to normal glucose homeostasis: high plasma levels of free fatty acids, increased hepatic glycogenesis, and peripheral insulin resistance.[43] In obesity, there is a chronic inflammatory state mediated by cytokines released by adipose tissue and by immune cells such as TNF-α, interleukin-6 (IL-6), plasminogen activator inhibitor, C-reactive protein, and resistin. This inflammatory background is not merely an undesirable by-product but a homeostatic mechanism to prevent the accumulation of excess fat. Lipid storage and weight increase require anabolic processes, while inflammation stimulates catabolism, including lipolysis. Homeostatic mechanisms, such as catabolism activation, via inflammation and resistance to anabolic signals, such as insulin, can be a way for the body to limit weight gain.[44–46]

As a consequence of chronic lipolysis, there is a continuous liberation of free fatty acids (fFAs) that are transferred directly, via the portal vein, to the liver. Increased plasma fFAs, together with inflammatory cytokines and lipoxins, trigger a decrease in insulin sensitivity in tissues that depend on insulin, which is caused by the inhibition of receptor signaling. This situation, known as insulin resistance (IR), leads to increased insulin synthesis and secretion by β pancreatic cells and, thus, to a compensatory hyperinsulinemia. Initially, the response may be able to maintain normal glucose homeostasis. Simultaneously, fFAs are oxidized in the liver, triggering neoglycogenesis and thus increasing glycemia. Concomitantly, there is an increase in the synthesis of very-low-density lipoproteins (VLDLs) that, once in the bloodstream, generate small, dense, and atherogenic low-density lipoproteins.[10,47–50]

Currently available data indicate that IR occurs mainly at the muscular postreceptor level, where 80% of circulating glucose is captured.[51] After a number of years, hyperinsulinemia can no longer compensate for this resistance. Consequently, the diminished muscular capacity for glucose uptake, added to a chronic, massive uptake of fFAs by the liver, results in an increase of hepatic gluconeogenesis to provide energy to the muscle and to avoid hepatic steatosis.

The process described is a landmark in the evolution of diabetes and is termed "prediabetes" or "glucose intolerance." The characteristics of prediabetes are part of the manifestations of Reaven's Syndrome X, now known as MetS, which, besides type 2 diabetes mellitus, or IR, or glycol intolerance, includes two of the following criteria: arterial hypertension, dyslipidemia, and abdominal obesity.[44,46,47,52] As a useful preventive measure, weight loss

diminishes insulin secretion by reducing IR, thereby reducing glucose intolerance.[53]

Glucose intolerance, when maintained longer than one or two decades, overloads the pancreas, resulting in a decline in insulin secretion due to the exhaustion of β cells.[54] These and other coexisting factors, such as genetic defects, insulin secretion interference, or increase of proinsulin, can lead to symptomatic diabetes mellitus. Finally, the main linking factor between chronic metabolic conditions (e.g., MetS) is IR, which is almost always associated with obesity, particularly abdominal-visceral obesity.[55]

Epidemiology of the metabolic syndrome in South America

MetS is a set of interrelated risk factors, including obesity, atherogenic dyslipidemia, arterial hypertension, and IR, which exponentially increase the risk of developing CVD and type 2 diabetes mellitus. There is little information published about the prevalence of chronic metabolic diseases in many Latin American countries. A cross-sectional, population-based, observational study (CARMELA) was conducted in Barquisimeto (Venezuela), Bogota (Colombia), Buenos Aires (Argentina), Lima (Peru), Mexico City (Mexico), Quito (Ecuador), and Santiago (Chile). The aim of the research was to study the prevalence of MetS in Latin America and its association with atherosclerosis.[56] Among the overall study population, the prevalence of diagnosed MetS was highest in Barquisimeto (26%), followed by Santiago (21%), Bogota (20%), Lima (18%), Buenos Aires (17%), and Quito (14%). When only nondiabetic participants were considered, prevalence followed a comparable ranking. Moreover, studies in Ecuador and Argentina showed that prevalence differed between urban and rural areas or between urban and periurban areas.[57,58]

Genetic load could be influencing the proneness to MetS onset. Indeed, a study comparing the risk factors for MetS among Afro-Hispanics and mixed Hispanics conducted in Zulia State (Venezuela) found higher blood pressure (BP), higher fasting blood glucose, more abdominal obesity, and lower HDL cholesterol among Afro-Hispanics.[59] Some early lifestyle factors may also influence MetS onset, leading to different patterns of CVD in the elderly and in rural areas.[60]

MetS also contributes heavily to the prevalence of CVD in Peru, where two studies found a higher prevalence of abdominal obesity coupled with MetS in women.[61] Abdominal obesity was also positively associated with MetS in a Chilean prevalence study, as were BP and plasma TGs.[62] Obesity was also related to MetS in Argentina,[63] Brazil,[64] and Trinidad and Tobago.[65] Finally, obesity and menopause are also associated with MetS, perhaps linked to secondary hypoestrogenemia at the end of ovarian cycling.[66,67]

Obesity and cardiovascular disease

Physiopathogeny. The global epidemic of obesity is especially significant because obesity has been identified as the primary risk factor associated with the increased prevalence of CVD, diabetes, and hypertension.[9] The rates of CVD are known to be higher in overweight people. Although the mechanism of this association is not clear, there is considerable evidence relating it to an increase in cardiovascular risk factors.[10,45,68]

One of the metabolic alterations in obesity is the perturbation of lipoprotein metabolism and, in turn, the production of coronary atherosclerosis. Subjects with visceral obesity tend to have hypertriglyceridemia accompanied by low concentrations of high-density lipoprotein (HDL), which is the main factor responsible for poor scoring in total cholesterol/HDL cholesterol, a well-known powerful predictive risk parameter for coronary heart disease.[69–71]

Increased intra-abdominal fat is risky because adipocytes located in this area are metabolically very active and have intense lipogenesis and lipolysis.[72] In visceral adipose tissue, beta adrenergic-3 receptors predominate, and these are highly sensitive to the action of catecholamines. Catecholamines stimulate hormone-sensitive lipase, producing unbalanced lipolysis and hence the output of large amounts of fFAs into the portal circulation, with consequent liver overload.[73] Once fFAs are in the liver, the resynthesis of TGs, together with the overproduction of apolipoprotein B, results in the formation of increased amounts of VLDL, which is rich in TGs.[74] VLDL is degraded slowly, due to the decreased activity of lipoprotein lipase as a result of IR/hyperinsulinemia, which is very often present in individuals with visceral obesity.[74]

The alteration in the metabolism of VLDL causes reduced availability of substrates for the formation of HDL, which leads to the formation of highly atherogenic low-density lipoprotein, which then easily crosses the arterial endothelium, thereby starting the atherosclerotic process.[73] Therefore, the abnormalities produced during the metabolism of lipoproteins in subjects with visceral obesity determine the presence of the "atherogenic triad" (increased TG-rich VLDL, low amounts of HDL, and high levels of low-density lipoprotein).[67] Eventually, these abnormalities lead to atherosclerosis of the coronary arteries and the onset of coronary heart disease.[75–78]

Arterial hypertension is a cardiovascular condition that merits special attention, and thus it is discussed further in the following paragraphs.

Arterial hypertension. Weight gain can induce a significant increase in BP, and some studies have shown higher BP values in obese or preobese populations.[79,80] In normotensive and hypertensive subjects, there is a positive correlation between body mass index and BP.[81] However, not all overweight or obese people are hypertensive, which may be explained by a genetic difference in BP response to weight gain.[47,51,81]

In obese people, inflammation, the common response of the body to tissue injury, becomes chronic. Inflammatory messengers are released by stressed adipocytes and, over the course of time, inflammatory cells cause vascular damage, leading to atherosclerotic phenomena. Eventually, these perturbations lead to severe problems such as ischemic heart disease, renal insufficiency, and blindness.[82]

Approximately 50% of obese people develop arterial hypertension at some point.[83] The mechanisms involved are multiple. One is hyperinsulinemia, which results in increased reabsorption of sodium (Na^+) and water. In addition, in the obese, the activity of the sympathetic nervous system (SNS) increases with meals, often resulting in hyperinsulinemia and hyperleptinemia. Moreover, this increased activity counteracts arteriolar vasodilatation, causes the release of angiotensinogen, and disturbs nitric oxide (NO) bioactivity. The presence of arterial hypertension in obese subjects often coincides with the presence of lipid abnormalities, adding the risk of vascular alterations.[84,85]

There is a worldwide agreement that an increase in physical activity prevents obesity and that regular exercise provides many health benefits. A sedentary lifestyle is the primary cause of obesity, one of the main risk factors for MetS, CVD, and cancer. Recent studies from Argentina, Chile, and Brazil show that this seems also the case for South America.[6,86,87] The Argentinean study showed that overweight was strongly dependent on gender, age, social status, and physical activity. Moderate and intense physical activity (>1,500 standard metabolic equivalent units [METs]) reduces the risk of obesity by around 40–65%.[6,87] As suggested by Das,[88] exercise attenuates the development of risk factors for arterial hypertension and CVD by increasing the number of NO-positive neurons, as shown in spontaneously hypertensive rats, and by exerting an anti-inflammatory effect.

Hausberg et al.[89] proposed an explanation of the association between overweight, obesity, and hypertension from a physiological point of view. With higher caloric intake or reduced thermogenesis, subjects tend to progress towards overweight or obesity. As a response, the body tries to burn calories, thereby stimulating thermogenesis, which requires activation of the SNS. These processes cause vascular constriction, elevated heart rate, and increased cardiac output. The increase in cardiac output coupled with the rise in peripheral resistance leads to a hypertensive effect. In addition, insulin stimulates the activity of the SNS, worsening the situation. Hyperinsulinemia, which results from the strength of the effects of insulin on glucose uptake, increases sympathetic activity, which facilitates the increase in BP. SNS activity and the increase in circulating insulin may increase sodium reabsorption in the kidney, thus increasing BP. This is called salt sensitivity. Weight loss improves renal sodium handling by decreasing sympathetic activity, potentially allowing hyperinsulinemia, salt sensitivity, and hypertension to be reversed.[78,81]

Adipose tissue is an essential, complex, metabolically active tissue with central endocrine functions. Fat cells actively regulate the pathways responsible for energy balance through a complex network of hormonal and neural signals and chemical messengers such as TNF-α, angiotensinogen, and leptin complex.[90,91] TNF-α stimulates production of angiotensinogen and angiotensin II, among others. Chronic exposure of tissues to elevated insulin levels leads to activation of the renin-angiotensin system through TNF-α, favoring increased BP.[44,81]

All components of the renin-angiotensin system are present in different tissues, including adipose tissue, and may be linked to obesity and arterial hypertension.[83] Adipose tissue produces several proteins of the renin-angiotensin system in increased amounts, including angiotensin II.[10] Abdominal fat cells release angiotensin with greater intensity than subcutaneous fat tissues. Hence leptin, an adipocytokine with receptors in the hypothalamus, has been proposed as a link between obesity and elevated SNS activity and can be considered one of the major factors in the development of obesity-associated arterial hypertension.[91]

Epidemiology of cardiovascular disease

Even though CVD is a major cause of death in South America and obesity is the prevalent risk factor for CVD, published research on CVD and obesity is still scarce.[92] The rates of CVD range from 9% in Ecuador to more than 34% in the countries of the Southern Cone.[93] A recent study describing CVD mortality trends in the Americas during 1970–2000 found a decrease in coronary heart disease mortality for Argentina, Brazil, and Chile. Mortality rates among men were highest in Venezuela and lowest in Argentina. In women, rates were highest in Cuba and lowest in Argentina.[94]

The Andean region. Several published works analyze the association of obesity and/or anthropometric parameters as indicators of ischemic coronary disease in Andean South America. The main findings show a positive association between high anthropometric indicators for

waist-to-hip index and body mass index in men, with obesity being an important risk factor for ischemic coronary disease.[95] The five most prevalent cardiometabolic factors were low HDL, overweight/obesity, abdominal obesity, hypercholesterolemia, and IR. MetS was most prevalent among women.[96]

Some authors point out the importance of interethnic differences, especially for men.[97,98] Indeed, the sociocultural context alters the risk for obesity and CVD associated with individual-level variables and accounts for gender and cross-national differences in the migration-illness association.[99] Not only international cross-border migrations but also intranational migrations of different ethnic groups change the risk of obesity and associated disorders as well.[100]

Tropical and subtropical regions. CVD causes approximately 30% of all deaths in Brazil. Of these, approximately 50% occur in adults aged 30–69 years. Central obesity, physical inactivity, and unhealthy diet were all inversely associated with income and schooling and were found at higher levels in subjects aged 50–59 years, without significant differences between sexes.[101] A follow-up study showed that the BP of young individuals was significantly associated with cardiovascular risk variables such as glucose levels, TGs, total cholesterol and its fractions, waist-to-hip ratio, and the occurrence of MetS at the young adult stage.[102] Obesity and overweight and other lifestyle conditions are strong risk factors for CVD in Brazil, even when the distinct characteristics within the country's great geographical size, the urban and rural heterogeneities, and the ethnic differences in the population are taken into account.[103,104]

In contrast, in Trinidad and Tobago, differences in morbidity and mortality are attributable to ethnicity. Individuals from these two Caribbean islands have different genetic backgrounds and lifestyles. While Tobago is a peaceful tourist center, Trinidad has a comparatively bustling lifestyle. Generalized (31.7% versus 38.8%) and central (78.5% versus 83.7%) obesity are similar in both islands, but islanders from Trinidad have a greater risk of CVD.[65] Another study conducted in both islands found that body mass index, abdominal obesity, and diabetes were all associated with increased systolic BP.[105]

The temperate countries of the Southern Cone. The prevalence of CVD is highest in the Southern Cone, where it is approximately 34% among the entire population. In a well-controlled survey carried out in the adult general population of Uruguay, obesity was significantly associated with hypertension, and both conditions were independent risk factors for CVD.[106]

Stroke and CVD are also major causes of death in Paraguay.[81] In a cross-sectional study conducted in an urban white-Hispanic population, the prevalence of obesity was 31.6% and was greater in women. Subjects with impaired glucose tolerance had cardiovascular risk factors significantly more often than the normal population.[107,108]

In 2005, the Argentine National Health Ministry conducted a survey of risk factors for NTDs in adults ≥18 years of age to determine the prevalence of risk factors for chronic disease. The sample represented 96% of adults living in urban areas. Low income and poor education were associated with increased risk of hypertension and diabetes in all subjects, and with obesity in women. The habit of eating fruits and vegetables 5 days per week was positively associated with higher income.[109] The burden of CVD was associated with modifiable and, therefore, preventable lifestyle risk factors.[110] This cross-sectional study of a major urban area provides some insight into the global transition toward concentrations of risk factors in poorer populations.[109]

An observational prospective cohort study to identify CVD risk factors is being conducted in the Southern Cone region to develop public health strategies.[111] All of these findings, however, confirm that obesity and other risk factors for CVD in South America are mainly related to aging, ethnicity effects, and preventable risky lifestyle conditions.

Obesity and cancer

Many studies have shown that obesity is a risk factor for diabetes, but a link between obesity and cancer is generally less widely reported. Some works, however, have confirmed that obesity may be associated with mortality from a number of malignancies, including cancers of the colon, pancreas, kidney, prostate, breast, and endometrium.[112] Evidence suggests that the link between obesity and cancer may involve metabolic perturbations similar to those shown to exist between obesity and diabetes.[113]

Pathogenesis. Like obesity, cancer is a multifactorial disease of aging in which race and inheritance are recognized as genetic determinants of risk, which varies according to different localizations. On the other hand, diet, toxic habits, lifestyle, and environment, including infections, are factors that act on the cell genome as initiators or promoters of malignant cell transformation and progression.[114–117]

The association between viral, bacterial, or chemical inflammation and different cancers strongly suggests that chronic inflammation may be involved in the development of tumors.[118–120] Clinical and epidemiological studies have suggested a strong association between chronic infection, inflammation, and cancer.[120–124] As stated by Das in 2007,[125] inflammation is a protective response in order to eliminate the injury-inducing agent,

prevent tissue damage, and initiate the repair process. Among the inflammation mediators are histamine, serotonin, lysosomal enzymes, prostaglandins, leukotrienes, lipoxins, platelet-activating factors, reactive oxygen species, NO, hypochlorite, and various cytokines, along with the kinin, the coagulation-fibrinolysis, and the complement systems. Once released or activated, most of these mediators decay quickly or are inactivated, suggesting that, under normal physiological conditions, there are both positive and negative checks and balances. When a continuous imbalance occurs, a pathological event, such as cancer, may appear.[126]

Chronic inflammation is considered a common feature of MetS and age-associated neuroendocrine disorders (MetS/AAND).[125,126] Oxenkrug[127] suggests that one of the mechanisms by which chronic inflammation might trigger and/or maintain the development of MetS/AAND is transcriptional induction via certain cytokines. Cytokines are low-molecular-weight peptides, essential for cell communication, which are produced mainly by cells that belong to the immune system. Cytokines control several key cell functions, such as differentiation, inflammation, local or systemic immune response, tissue repair, hematopoiesis, apoptosis, and regulation of energy intake and expenditure.[128] They can also play a role in the control of tumor cells (transforming growth factor β). Cytokines are apparently redundant and pleiotropic; as a result, they can share functions and act on many cell types, since a cell can have receptors for more than one cytokine. Alternatively, they may act as paired agonist/antagonist ligands in several cell functions[129,130]

Since proinflammatory cytokines influence tumor microenvironment, promote cell growth and survival, and angiogenesis, tumor cell is facilitated.[131] It has been suggested that one of the mechanisms is transcriptional induction of indoleamine 2,3-dioxygenase, a rate-limiting enzyme of the tryptophan-kynurenine pathway.[132] This process is mediated by proinflammatory cytokines whose induction may activate tryptophan metabolism for kynurenine formation.[133–135] Kynurenines are immune mediators that may contribute to MetS/AAND via their apoptotic, neurotoxic, and pro-oxidative effects and their upregulation of inducible NO synthase, phospholipase A2, arachidonic acid, prostaglandin, 5-lipoxygenase, leukotriene, and other eicosanoid cascades. All of these molecules play key roles in neoplasia.[130,132]

According to Karin and Greten,[133,134] one of the links between inflammation and tumorigenesis is provided by inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) kinase signaling pathway. NF-κB, a transcription factor that mediates the transcription of a vast array of proteins involved in cell survival and proliferation, is itself activated by many proinflammatory cytokines. Indeed, it has recently been shown that proinflammatory cytokines (TNF-α, also called cachexin or cachectin, and interleukin 1) can activate a novel transcriptional mechanism by which estrogen receptors and NF-κB cooperate to upregulate the expression of ATP-binding cassette transporter G2. This molecule is a transmembrane transporter that plays a key role in the response to therapeutic drugs in breast cancer cells.[135,136]

In short, the whole outcome of a persistent inflammatory microenvironment is enhanced tumor promotion, accelerated tumor progression, invasion of the surrounding tissues, angiogenesis, and, often, collaboration toward a suitable tumor bed for metastasis.[122,124,133,135]

Obesity is a low-inflammation state in which cytokine production from visceral adipose tissue (adipocytokines) increases, which causes endothelial dysfunction and IR.[128] This low-grade inflammatory process is defined as a two- to-four-fold rise in circulating levels of 1) proinflammatory and anti-inflammatory cytokines, 2) naturally occurring cytokine antagonists, and 3) acute-phase inflammatory proteins, as well as minor increases in counts of neutrophils and natural killer cells.[124,137,138] High levels of two inflammation markers, butyrylcholinesterase and acetylcholinesterase, may be included in this scenario.[125]

Adipocytokines are the cytokines produced by adipose tissue. They include leptin, adiponectin, resistin, visfatin, retinol binding protein (RBP) 4, angiotensinogen, TNF-α, plasminogen activator inhibitor 1, interleukin (IL) 1, IL-6. IL-8, adipsin, several polyunsaturated fatty acids and derivatives, sex steroids, different growth factors, serum amyloid, and lipocalcin, among others. Adipocytokines act synergistically or competitively with insulin, which explains their modulatory role in IR. Inflammatory cytokines from adipose tissue could affect blood vessel endothelial function even without increases in plasma concentrations.[139]

Leptin participates in many diverse physiological processes, such as reproduction, immunity, and angiogenesis. Angiogenesis is one of the conditions necessary for tumoral progression.[140] On the other hand, adiponectin improves insulin sensitivity and inhibits vascular inflammation. One of its functions is autocrine inhibition of endoplasmic synthesis of proinflammatory adipokines.[141]

TNF-α is one of the most powerful inflammatory adipokines. It stimulates the acute phase reaction of inflammation. The primary role of TNF is the regulation of immune cells. TNF is also able to induce apoptotic cell death, suppress appetite (thus the reason it is also called cachectin), and inhibit tumorigenesis and viral replication. Dysregulation of TNF production has been implicated in a variety of human diseases such as cancer, IR, and adiposity.[136,142]

IL-6, an adipokine, is a multifunctional cytokine that was originally characterized as a regulator of specific immune and inflammatory responses. IL-6 inhibits insulin 2 receptor, lipogenesis, and adipokine synthesis. Elevated expression of IL-6 has been detected in breast and lung tumors.[138,143,144] It has also been related to cancers of the liver,[145] cervix,[146] prostate,[147–150] and breast.[151]

Other authors suggest that the link between obesity and cancer is mainly due to IR. The link between IR and cancer may be related to high compensatory levels of insulin. This hormone may increase cell proliferation either directly[152,153] or by increasing the levels of other more potent growth factors, such as insulin-like growth factor, which is one of the growth factors responsible for the initial steps of cancer development. However, evidence that IR is the major cause of increased risk of cancer, other than colon cancer, is still inconsistent.

In diet-induced obesity, hypothalamic inflammation is triggered as an outcome of prolonged exposure to diets high in fat and/or sugar.[154] Saturated fatty acids can induce endoplasmic reticulum stress in the hypothalamus tissue. On the other hand, there is evidence that polyunsaturated fatty acids, such as gamma-linolenic acid, may inhibit tumor growth due to the production of lipid peroxides, apoptosis, and lipoxygenase-derived eicosanoids.[155] Hence, obesity may promote carcinogenesis because it shares some metabolic pathways of inflammation with carcinogenesis.

Epidemiology of cancer in South America. Epidemiological studies indicate that overweight and obesity, along with diet and lifestyle, contribute to the risk for some cancers. In countries where people have adopted so-called "Western diets," the incidence of tumors, particularly those of diet-related cancers, is increasing. This trend in developing countries is associated with increased consumption of fatty and/or sugary foods and decreased physical activity, resulting in obesity.[156]

In South America, the five most incident cancers in men are prostate, lung, stomach, colorectal, and bladder, while in women these are breast, uterine cervical, colorectal, stomach, and lung.[157] Cancer is the second-leading cause of mortality after CVD in half of the South American countries, i.e., Uruguay, Argentina,[158–164] Chile, Peru, Trinidad and Tobago, Bolivia, and Venezuela.[157] However, only a few works assessing the relationship between obesity/overweight and cancer have been published in this subcontinent.

The increase in cancer and obesity in the temperate region that includes Argentina, Chile, Uruguay, and Southern Brazil probably reflects the adoption of Western behaviors and lifestyles in parallel with the alluvial European immigration of the last half of the 19th century and the beginning of the 20th century.[165] Moreover, the temperate regions have lately experienced a rapid agricultural evolution, and rural areas have undergone a significant economic transition.[166] In these areas, people have a high-fat diet, a low average fertility rate, and a higher socioeconomic status, and the influence of European immigration on the genetic background of the population is more pronounced.[167] Argentina and Uruguay are also characterized by their traditional high consumption of beef, which corresponds to a high intake of total and saturated fats.[28,167–172] In Chile, the progressive improvement of social conditions has generated an important economic and epidemiological transition, and morbimortality patterns are changing in terms of chronic NTDs. Since the 1980s, CVD and tumors are the main causes of mortality in Chile.[173] Brazil traditionally consumes large quantities of poultry, legumes, and fruits. However, with their technological and economic improvement, there has been an increased production and consumption of red meats. As a consequence, the studies relating to cancer and obesity come mainly from Argentina, Brazil, Chile, and Uruguay, the members of the so-called Southern Cone.

A number of studies in South America have investigated different type of cancers and their association with obesity, including breast, prostate, colon, and urinary tract tumors and endometrial cancers. Breast cancer is the most common cancer in women worldwide. Several studies have been conducted in Chile, Uruguay, and Argentina. A case-control study performed in Chile to analyze the association between food patterns, obesity, and breast cancer revealed that obesity was a risk factor, independently of the differences in food patterns.[174] A case-control study carried out in Uruguay showed that an endomorphic body type was significantly associated with breast cancer, regardless of menopausal status or BMI level.[175] The authors found that fat fraction and fat-to-muscle ratio were both positively associated with breast cancer.[175,176] No association between overweight and breast cancer was found in Argentina, although a significantly higher caloric intake was found among cases.[177] A comparative study of breast cancer in countries with different incidence rates suggests that reproductive events and body fat may exert similar effects on all women, due to similarities of parameter estimates across the region, regardless of breast cancer rates in their country of residence.[178]

Prostate cancer is the second most common cancer in men worldwide, and it also ranks second in men in South America.[179] Obesity, central adiposity, and several dietary factors have been suggested as risk factors. Although obesity has been positively associated with prostate cancer, López Fontana et al.[180] suggest that obesity may promote the progression of established prostate cancer rather than being a risk factor. In work carried

out in Puerto Rico in which Hispanics were compared with white people, overweight was a less sensitive marker for prostate cancer in Hispanics, but the prevalence of metastasis was higher in individuals with a higher body mass index.[181]

Globally, colorectal cancer is the third-leading cause of cancer in males and the fourth-leading cause of cancer in females. The frequency of colorectal cancer varies around the world. It is common in the Western world and is rare in Asia and Africa. In countries where people have adopted Western diets, the incidence of colorectal cancer is increasing. Argentina, in the central temperate region of South America, has important ethnic and geographical variations and was a suitable setting for case-control studies into the risk of cancer in relation to diet and other lifestyle factors.[182,183] Several studies produced original data on colorectal cancer[42,167–171] and urinary tract tumors.[184,185] In these studies, most patients were overweight to some extent, although there were no significant differences between cases and controls. Interestingly, the Western dietary pattern of high energy intake, sweet foods and beverages, fatty meats, potatoes, alcohol, and low fiber intake was associated with cases.

Obesity has also been related to endometrial cancer. In a Chilean study of the effect of obesity on endometrial cell proliferation, the authors showed a correlation between obesity and overweight and increased endometrial cell proliferation as a possible factor related to the higher risk of developing type I endometrial cancer in overweight and obese women.[186]

Three of the nine most common cancers – breast, prostate, and colon – have already been associated with obesity in South America. Obesity and cancer predominate in the temperate region of South America. This pattern coincides with a period of greater industrialization, and therefore a possible exposure to other contaminants may exist, suggesting that, unfortunately, in a few years other countries such as Bolivia and Paraguay may also appear in this worrying scenario.

CONCLUSION

Those countries in South America whose ethnicity changed due to waves of immigrants in the middle of the 19th and beginning of the 20th centuries, like Argentina, Brazil, Trinidad and Tobago, Uruguay, and, to a lesser extent, Chile, show a pattern of dietary habits and lifestyle that is progressively closer to that of the so-called "Western lifestyle." Diseases closely related to environment and lifestyle, such as diabetes, obesity, cancer, and CVD, have been rapidly increasing in these countries over the last five decades. In contrast, in other South American countries where ancient, healthy, nutritional habits and dietary behaviors are still maintained, the prevalence of such chronic and partly avoidable diseases is lower. Some risks, such as high waist-to-hip index, low income, and poor education, are common. Many Hispanic immigrants in the United States and Western Europe originate from South America. Although the incidence and frequency of these diseases may change over one or two generations, a starting point to prevent these illnesses in other parts of the world would be to conduct epidemiological studies in the countries of origin of Latin-American populations, including studies on the role of ethnicity. Taken together, the data presented in this overview indicate that measures to prevent diet- and lifestyle-related diseases are imperative in South America and should include education in nutrition, health, and lifestyle habits.

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