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Hypertension and the cardiometabolic syndrome in Chile: a review of concepts and consequences for the developing world

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***Abstract*:** We review some recent developments regarding the concept of cardiometabolic syndrome and its relation with hypertension and overall cardiovascular disease risk. We emphasize how this new clinical entity has helped to understand multimorbidity in chronic diseases. This concept has important consequences for individual patient treatment as well as public health policy. The challenge derived from cardiovascular disease and other chronic conditions is increasing worldwide, but the highest burden is located in the developing world. Thus, new and cost-effective approaches are needed for diseases that are mainly occurring in the poorest and less educated populations. We illustrate this situation analyzing hypertension and cardiometabolic syndrome data derived from a recent national health survey in Chile.

***Keywords*:** hypertension, metabolic syndrome, cardiometabolic syndrome, cardiovascular disease, cardiovascular risk, epidemiology.

The purpose of this review is to summarize and discuss some recent developments regarding the concept of cardiometabolic syndrome and its relation with hypertension and overall cardiovascular risk. By describing the findings of the recent first Chilean National Health Survey (MINSAL: 2003), we wish to emphasize the challenges posed by these conditions to developing countries.

Hypertension and cardiometabolic syndrome: the case of Chile

ENS was conducted and aimed at measuring the simultaneous population burden and distribution of 21 chronic conditions. ENS 2003 was a cross-sectional household survey using a stratified multistage probability sample of non-institutionalized adults over 17 years of age. Three thousand six hundred and nineteen subjects were enrolled; the response rate was 63.5% and the refusal rate was 7.5%. A detailed report, including study protocols and manuals, is available on its website [MINSAL, 2003].

Prevalence rates were based on internationally accepted cut-offs, weighted for complex sample design and adjusted to represent the Chilean 2003 population. Hypertension screening was measured for public health surveillance purposes. Hypertension was defined as an average of 2 morning measures of blood pressure (BP) $\geq$140/90 mmHg measured in the same day using the OMROM 713-C automated device, or by the reported use of antihypertensive medications. Awareness, treatment and control were conservative estimates using hypertension screening prevalence with no different cut-offs for the diabetic population. Cardiovascular risk and metabolic syndrome was recalculated using the updated ATPIII criteria [Grundy *et al.* 2004]. Medications were classified using the ATC-WHO criteria [WHO, 2007].

The burden of hypertension and cardiometabolic syndrome

Demographic characteristics, BP, body mass index (BMI) and diabetes prevalence in the Chilean population are depicted in Table 1. Mean age of the population was 41.1 years old. Mean systolic and diastolic blood pressure in Chile was 127.8 and 79.8 mmHg respectively. Mean BMI of the study population was 26.8 kg/m^2.

The hypertension prevalence by age and gender is illustrated in Figure 1. Positive screening

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Table 1. Characteristics of the study population, ENS, Chile, 2003.

Characteristic	Percent Adjusted*
Men	48.9%
Age (years)	
Under 40	51,9%
40 to 59	32,4%
60 and above	15,7%
Urban areas	86.4%
Schooling	
None	3.0%
1–7 years	22.3%
8–12 years	55.6%
more than 12 years	19.1%
Married/cohabiting	56.9%
Labor active	46.4%
BMI ≥ 30	23.2
Diabetes[1]	6.3%

*complex design weighted prevalences.
[1]glucose ≥ 126 mg/dl or self report of medical diagnosis.

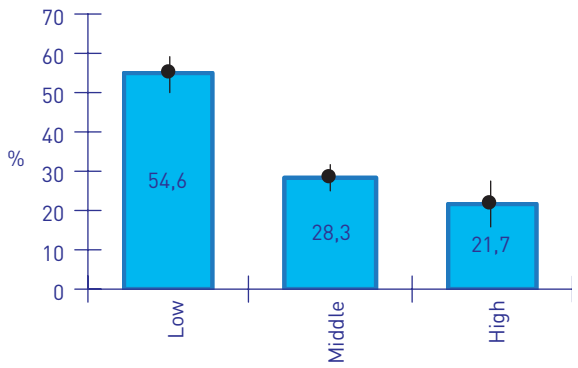

Figure 2. Hypertension prevalence and educational level, Chile ENS 2003. "Low": under 8 years; "middle": 8–12 years; "high": over 12 years of education. Adjusted Odds (95% confidence interval) = 1.7 (1.1–2.6) for Low vs High education, controlling by age, gender and zone.

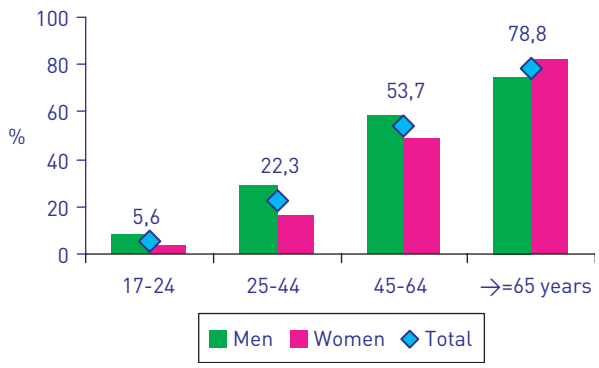

Figure 1. Hypertension screening prevalence by age and Gender, Chile ENS 2003. Hypertension screening prevalence: ≥140/90 mmHg or normotensive under medication.

prevalence was 33.7% (36.7 and 30.8% for total population men and women, respectively). This prevalence goes down to 26–27% when recalculated applying the confirmation rates by age obtained in another Chilean population visited in a subsequent day [Fasce *et al.* 1992]. Figure 2 shows rates by educational level. Age-sex-adjusted odds are significant, showing higher hypertension prevalence in the population with less than eight years of education. The highest inequalities were observed in women under 60 years old with a prevalence odds ratio of 5.5 [95% confidence interval (CI) 2.7–11.5].

The overall prevalence of metabolic syndrome (MS) was 31.6% reaching 61.6% in the hypertensive population. When defined by the cut-off values for the MS, hypertension (BP ≥ 130/85) was present in 46%, and central obesity in 29.7% of the study population. The overall prevalence of "high" plus "very high" cardiovascular risk was 14% in the general population and reached 29.5% among hypertensives. Hypertensive population had higher prevalence of co-morbid chronic conditions like: diabetes (12.5%), obesity (37.9%), symptomatic cardiovascular disease (16.2%) and dyslipidemia (78% using high total cholesterol or low HDL-C criteria). In 11.8% of adults in the general population dyslipidemia (total cholesterol >200 mg/dl or HDL-C under 40 mg/dl), hypertension and obesity (BMI ≥ 30) coexisted. Isolated hypertension was a rare condition.

Figure 3 shows hypertension awareness, treatment and control; overall 60% of the hypertensive subjects are aware of their condition, 36% are under treatment and 12% are controlled (33% among the treated are at BP goals). Women and the elderly have higher estimates. Hypertensives with less than 8 years of education have higher awareness, treatment and control rates, but these differences are not significant when controlling by age, gender and zone (Table 2). Less than 2% of hypertensives were only on lifestyle modifications, 26% only on drugs and 10.3% received both. The most used antihypertensive drugs in Chile in decreasing prevalence order were: ACE inhibitors, diuretics, beta blockers, and calcium antagonists.

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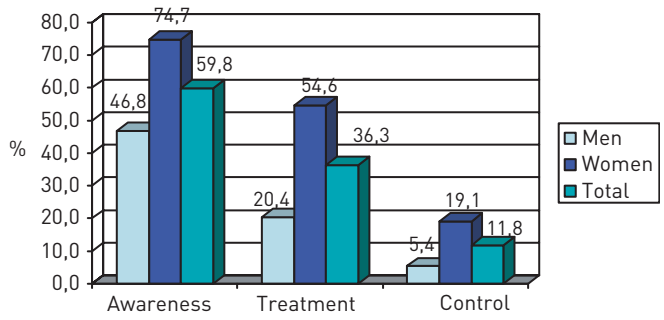

Figure 3. Awareness, treatment and control of hypertension in Chile, ENS 2003. Aware: a doctor or nurse had told him he had high blood pressure (at least once); Treated: uses antihypertensive medication; Control (among all hypertensives): pharmacological treatment associated with blood pressure <140 and <90 mmHg.

Table 2. Hypertension awareness, treatment and control by educational level. ENS, Chile, 2003.

Education	Awareness*	Treatment*	Control*
>12 years	50.1	23.2	10.7
8–12 years	55.9	23.2	12.1
<8 years	67.1	46.6	11.8

Aware: a doctor or nurse had told him he had high blood pressure (at least once).
Treated: uses antihypertensive medication.
Control: pharmacological treatment associated with blood pressure <140 and <90 mmHg.
*Differences are not significant when controlling by age, gender, and zone.

Smoking, obesity and physical inactivity, considered today as the main population health determinants and part of the natural history of hypertension and cardiometabolic syndrome, coexisted in 10% of adults between 25 and 44 years in Chile.

The high prevalence of the MS and hypertension in Chile, a developing country, makes it urgent that we better understand their association, their pathophysiology and therapeutic alternatives.

Hypertension and metabolic syndrome: review of concepts

The (cardio) metabolic syndrome is currently characterized by the cluster of physical and biochemical abnormalities in an individual patient, leading to an increased long-term risk of developing ischemic cardiovascular disease and/or type II diabetes. Though this condition poses a low to moderate short term risk based on current clinical algorithms used to define the predisposition to coronary heart disease, in the long term it seems to confer additional cardiovascular risk than more traditional risk factors, such as family history, age, gender, smoking, hypertension, and hypercholesterolemia.

Development of the metabolic syndrome concept and definition

For almost a century, the clustering of a variety of metabolic risk factors in patients with higher risk for cardiovascular disease has been periodically described. Indeed, the term 'metabolic syndrome' was first used by Haller and colleagues to define the association of obesity, high blood pressure, dyslipidemia, and abnormal glucose metabolism with increased risk for cardiovascular disease [Meisinger *et al.* 2006; Sarafidis and Nilsson, 2006]. However, this contribution and additional early studies [Leslie, 2005] did not consistently and fully address the underlying abnormality that led to this metabolic clustering, as well as the increased risk for cardiovascular disease.

The origin of the current concept of metabolic syndrome and of its most likely underlying pathophysiology is attributed to Reaven, who first presented it in the Bantig Lecture to the American Diabetes Association in 1988 [Reaven, 1988]. Reaven used the term 'syndrome X' to name the association of hyperinsulinemia, glucose intolerance, hypertension, increased VLDL cholesterol and reduced HDL cholesterol with a particularly high risk for developing atherosclerotic heart disease. Reaven proposed that insulin resistance was the key pathogenic process leading the coexistence of these biochemical abnormalities based on extensive clinical work accumulated over several years

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[Reaven, 1988]. Indeed, Reaven's definition of syndrome X was essentially a pathophysiological construct, which has been used as a platform for further refinements leading to simpler and more clinically-oriented definitions of the syndrome to facilitate its diagnosis in routine medical practice. For instance, abdominal obesity was added to the Reaven's definition as another contributing factor that must be considered as critical component of the metabolic syndrome [Kaplan, 1989].

Since the first descriptions of this clustering of metabolic risk factors, different organizations and researchers have proposed additional names and criteria (reviewed in [Sarafidis and Nilsson, 2006; Leslie, 2005]) to diagnose this condition. The World Health Organization (WHO) suggested in 1998 the first diagnostic definition of the metabolic syndrome as a clinical entity, using specific cut-off points for a set of physical and biochemical components [Alberti and Zimmet, 1998]. More recently, the European Group for Study of Insulin Resistance (EGIR) [Balkau and Charles, 1999], the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, ATPIII) of the US National Cholesterol Education Program [National Cholesterol Education Program, 2001], and the American Association of Clinical Endocrinologists (AACE) [Einhorn *et al.* 2003], have also proposed their own criteria for clinical diagnosis of the metabolic syndrome. Most of these definitions require performing laborious and not well and widely standardized laboratory measures to demonstrate insulin resistance, or include less specific tests as glucose tolerance or microalbuminuria.

In 2001, the Adult Treatment Panel III of the US National Cholesterol Education Program adopted the term 'metabolic syndrome' provided by previous definitions, and proposed the first that did not require complex laboratory tests (e.g. insulin resistance measurements). Thus, metabolic syndrome can be diagnosed in an individual patient more easily by determining waist circumference and blood pressure and performing simple laboratory determinations, as blood glucose, triglyceride and HDL cholesterol levels. Based on this definition, the diagnosis of metabolic syndrome is established by the presence of 3 of any of the 5 following criteria: 1) abdominal obesity, 2) high blood pressure, 3) hyperglycemia, 4) increased triglycerides, and 5) reduced HDL cholesterol.

Subsequently, the International Diabetes Federation (IDF) supported this definition of the metabolic syndrome because of its straightforwardness and easy application in clinical practice; even though it proposed that the increased waist circumference criterion is required for the diagnosis. It also suggested that different cut-off points for this parameter must be applied in different populations [International Diabetes Federation, 2005], based in evidence that suggests significant ethnicity-dependent variations in the association between central adiposity and other metabolic risk factors. Despite significant criticisms to the clinical definition and its usefulness [Kahn *et al.* 2005; Reaven, 2005, 2006], the ATPIII criteria for diagnosing the MS has prevailed, and it is the most well known and commonly used tool for identification of patients suffering this chronic and high risk condition.

Pathophysiology of metabolic syndrome

Knowing if the MS components are intermediate variables or independent conditions with synergic effects in a cardiovascular and metabolic disease causal model is an important challenge in the field of cardiovascular research and has clinical consequences regarding patient management. Independent effects would pose diverse therapeutic strategies, while an intermediate variable model, may lead to focus therapeutic interventions on the most distal factors from cardiovascular disease, e.g. obesity. Thus, the understanding of the pathways that compose and interact to induce the MS is mandatory.

The underlying pathophysiology of the metabolic syndrome is probably multifactorial, thus it has been difficult to define a single unifying pathogenic process that leads to this condition. However, the two most commonly accepted etiopathogenic factors for developing of metabolic syndrome are central obesity and insulin resistance [Grundy *et al.* 2004; Eckel *et al.* 2005].

Obesity and metabolic syndrome

Up to now, the best understood and most powerful causal association between components of the MS is that between obesity and hypertension [Hall *et al.* 1992; Thomas *et al.* 2000; Wofford *et al.* 2004]. Obesity, seen as a distal factor, exercises an independent pressor effect through multiple mechanisms. Adipose tissue

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represents an endocrine organ that synthesizes components of the renin-angiotensin-system and proinflammatory cytokines and exports them to the systemic circulation [Kershaw and Flier, 2004]. In addition, obese subjects present hypervolemia, with an increased cardiac output, an inappropiately normal or slightly elevated peripheral resistance, a rigid vasculature, and a renal compression by adipose tissue that might also interfere with volume expansion. Obesity causes increased hyperadrenergic activity, which in part could be due to the intermittent hypoxemia of sleep apnea [Kunze *et al.* 2007]. Furthermore, dyslipidemia, another obesity linked metabolic derangement, reduces endothelial function, and could also increase blood pressure [Simons *et al.* 1998; Ferrario, 2002]. Moreover, hyperleptinemia is capable of stimulating the pro-opiod-melanocorticoid axis in the hypothalamus.

Abdominal obesity is considered a key pathogenic factor predisposing to MS [Grundy *et al.* 2004; Eckel *et al.* 2005; Despres, 2006; Despres and Lemieux, 2006; Bergman *et al.* 2007]. As central adiposity is highly associated with insulin resistance, and hyperglycemia, dyslipidemia, and hypertension, it is an appealing unifying pathophysiological abnormality. Visceral adipose tissue exhibits distinctive metabolic, hyperlipolytic activity, and proinflammatory properties that are relevant for the clustering of MS components. Altered biochemical (e.g. increased release of free fatty acids) and endocrine (e.g. reduced adiponectin secretion) functions of the abdominal fat are likely mechanisms leading to the development of this high risk condition [Despres, 2006; Despres and Lemieux, 2006; Bergman *et al.* 2007].

Despite the importance of this form of obesity in the pathogenic model, patients with normal weight and adipose tissue distribution can also be insulin-resistant and be diagnosed with metabolic syndrome. For this reason, the ATPIII definition of this condition does not require the presence of abdominal obesity to establish its diagnosis in a patient [Grundy *et al.* 2004; National Cholesterol Education Program, 2001].

Insulin resistance metabolic syndrome

Despite general agreement that an elevated proportion of obese subjects present insulin resistance, it is possible to postulate that this condition itself represents an underlying pathophysiological factor both for metabolic syndrome and hypertension, and both factors probably act synergistically on blood pressure. Insulin facilitates sodium retention [DeFronzo *et al.* 1975], increases adrenergic activity, and stimulates vascular smooth muscle proliferation, thus contributing to increased peripheral resistance/vascular compliance through vascular hypertrophy [Stout, 1991, 1992]. Insulin resistance also decreases endothelial-mediated vasodilatation though the uncoupling of endothelial nitric oxide synthase, and by oxidating nitric oxide [Arcaro *et al.* 2002]. It is interesting that in a recent study of individuals of Mexican descent, sensitivity to insulin was associated with genetic markers of arterial hypertension (M235T mutations of angiotensinogen, and mutations of A(-992)G, E298, and ADD1 G460W in the gene encoding the nitric oxide synthase), being obesity a modifier of some of the genetic conditions [Guo, 2005].

Regardless of the presence of obesity, insulin resistance/hyperinsulinemia is an important abnormality that appears to play a significant causal role in the development of the MS [National Chlesterol Education Program, 2001; Reaven, 1988, 1993, 1995]. Indeed, insulin resistance *per se* can lead to the majority of the components of the syndrome as abnormal plasma glucose levels due to impaired tissue disposal and increased hepatic gluconeogenesis, atherogenic dyslipidemia (high triglycerides with low HDL cholesterol) secondary to raised hepatic production as well as reduced peripheral catabolism of VLDL.

In addition to insulin resistance and central adiposity, a series of additional factors of genetic and environmental origin (e.g. psychosocial factors, sedentary lifestyle, smoking, and diet habits) can modulate the expression of the various definition components of MS [National Cholesterol Education Program, 2001; Raikkonen *et al.* 2007]. Furthermore, a proinflammatory state is increasingly recognized as a contributing factor to insulin resistance, MS, and atherosclerotic cardiovascular disease [National Cholesterol Education Program, 2001; Roberts and Evans, 2004; Lee and Pratley, 2005; Kempf *et al.* 2006].

In Figure 4 we propose a multifactorial causal model and pathophysiologic pathways leading to MS and the links between its components.

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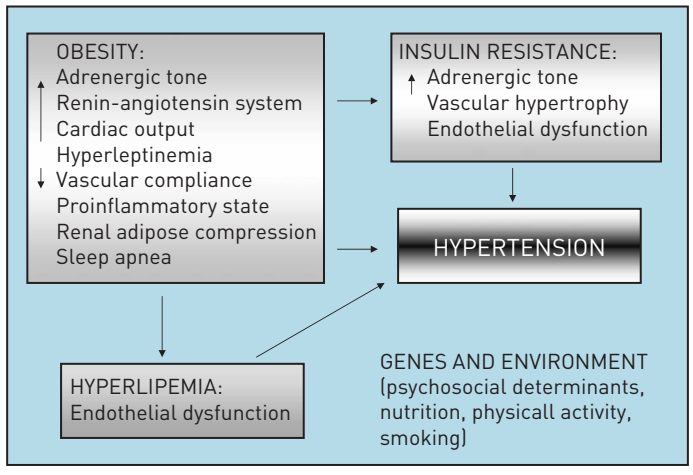

Figure 4. Metabolic syndrome and hypertension: pathophysiological pathways.

Treatment of hypertensive patients with metabolic syndrome

The management of hypertension associated to other components of MS constitutes a mandatory indication for non-pharmacological interventions. Weight reduction, physical activity, and reduction of excess alcohol intake should be strictly enforced. Each of these indications interrupts several of the mechanisms involved in the pathogenesis and maintenance of MS. When antihypertensive medication needs to be added because of the magnitude of hypertension, or due to target organ damage (which is amplified in hypertensive individuals with MS), drugs that do not alter glycemic or lipid control should be used. It is important to consider that MS accentuates target organ damage [Cuspidi *et al.* 2007], a logical complication as this syndrome enhances the renin-angiotensin and the adrenergic systems, and is frequently associated with higher insulin levels. Calcium antagonists, α-blockers and especially blockade of the renin-angiotensin system should be used. The use of the latter has been associated with improvement of the abnormal metabolic profile [Kintschner *et al.* 2007], and with decreased appearance of diabetes [Kjeldsen *et al.* 2006], thus this drug class should be used whenever clinical (e.g. acanthosis nigricans) or laboratory indexes suggest or demonstrate insulin resistance. On the other hand, glitazones have also been shown to decrease blood pressure [Negro *et al.* 2004, 2005].

Consequences for the developing World

The case of Chile represents an example of what may occur in other developing countries. Chile has reached a very low infant and maternal mortality, its population is ageing, fertility rates have decreased to the level of developed countries and infections and undernourishment, which been the focus of the health system are now relegated to relatively small pockets of poverty. In spite of these positive health indicators the country has experienced an accelerated epidemiological transition towards chronic disease conditions. As shown by ENS [MINSAL, 2003], hypertension estimates are now similar to, and MS prevalence is higher than that of high income nations, as has also been described in other Latin communities [Ong *et al.* 2007; Aguilar-Salinas *et al.* 2004].

The size of this burden exceeds the resources available for individual medical care approach. Population intervention strategies to lower obesity, promote physical activity and reduce smoking are urgently needed. However, political support will tend to be low in developing countries because of the delay in the expression of the risk factors on the final cardiovascular outcomes. Besides, developing countries have other coexisting competing health problems that also require urgent solutions.

A cardiovascular epidemiological paradox, characterized by high prevalence of cardiovascular risk factors and low cardiovascular morbidity and mortality, is present in Chile and its causes are still not clear. Most developing countries are expected to show this paradox in future years and causes may be different from country to country, depending on their accumulated exposure time, and their competing causes of death.

As chronic disease therapy has low coverage and low population effectiveness, simultaneous small changes in the population distribution of multiple risk factors could bring better long-term benefits than a clinical individual approach. At the individual patient level, we should prefer low cost lowering of cardiovascular risks (tobacco control, hypertension treatment) versus high cost lowering of these risks (lipid lowering drugs, pharmacological or surgical treatment of obesity).

The lack of differences in the attainment of normotension observed at the different

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educational levels in ENS indicates that this goal may not be as responsive to economic resources in low income countries as in higher income societies [Ong *et al.* 2007]. The absence of this association could also be explained by the existence of an integrated approach in the National Cardiovascular Disease Health Program provided by the public health system in Chile, at the primary care level. If this were so, it is especially relevant for poorer countries, which may never reach the high level of health investment of developed nations.

In conclusion, we believe that the multicausal model associated to MS and hypertension is characterized by two main synergic pathophysiologic pathways. The first is composed by several intermediate variables, of which central obesity is the most distal factor. The second pathway is related to IR and both, central obesity and insulin resistance have genetic and environmental determinants. In scenarios with low health literacy and scarce economic resources, there is urgent need to create novel public health policies. These policies should include population and individual level strategies. The first should focus on the population determinants of physical activity, nutrition and smoking. The second should consider health psychology, and other compliance issues related to chronic disease.

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Conflict of interest

None declared.

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