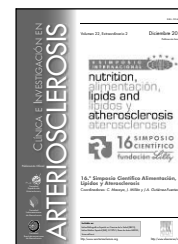




## CLÍNICA E INVESTIGACIÓN EN ARTERIOSCLEROSIS

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### 16.º SIMPOSIO CIENTÍFICO ALIMENTACIÓN, LÍPIDOS Y ATHEROSCLEROSIS

## Fetal programming and cardiometabolic diseases: the role of angiotensin II and inflammation

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### Introduction

Low birth weight remains an important public health problem in underdeveloped countries. In other hand, cardiometabolic diseases (CMD) as diabetes mellitus type 2 (DM2), metabolic syndrome (MS), myocardial infarction and stroke, are the firsts cause of morbidity and mortality in all the world and has characteristics of epidemic in undeveloped countries. Poor early nutrition has varying effects on subsequent CMD rates. The relative roles played by genetic and environmental factors and the interaction between the two remain the subject of much current debate. However, growing bodies of evidences suggest that epigenetic changes are a prime possibility.

### Fetal and neonatal development of systems involved in CMD

Some years ago it was demonstrated that men with a low birth weigh were six times more likely to have diabetes than men with a high birth weigh. This also showed that the relationship with birth weigh was continuous across the normal birth weigh range. In rats, detrimental effects on growth during fetal and early postnatal life can negatively affect both number and secretor function of the pancreatic beta cells. A series of studies have demonstrated a relationship between birth weight and child under nutrition and the presence of cardiovascular risk factors later on life.

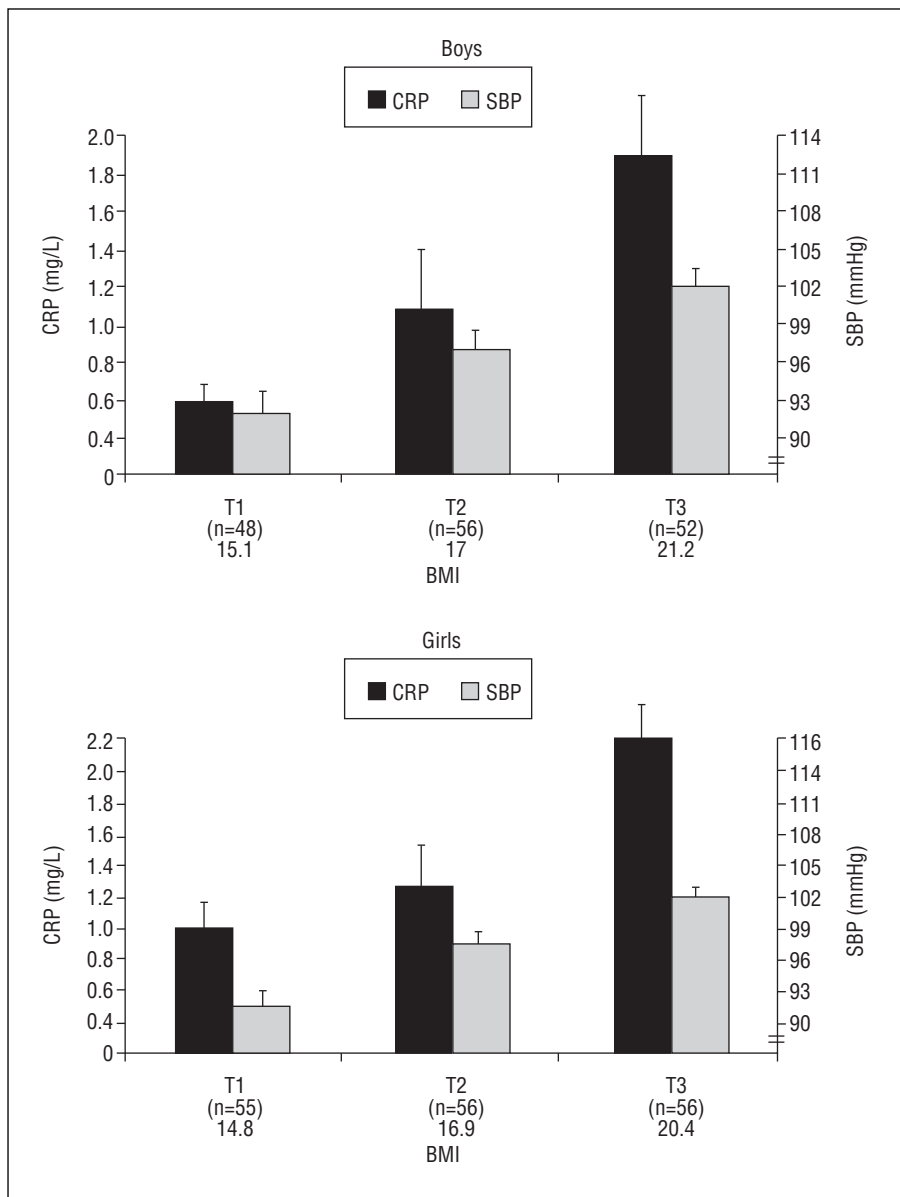
It is also known that low birth weight individuals show reduced growth of the kidneys and a reduced number of nephrons, that results in a reduction in filtration area, sodium retention, increased extracellular fluid volume and increased arterial blood pressure. Moreover, it has been reported that intrauterine growth restriction result in a decreased number of cardiomyocytes. Thus, it is interesting to speculate that the increased rates of hypertension, MS, DM2, renal failure and heart failure observed in undeveloped countries is the result of the discrepancy between the nutritional environmental cues during the fetal and early life that can lead to adaptive and integrated changes that relate to the anticipated adult environment, but may also give rise to disease if the environment changes or if the prediction is inaccurate, which causes a mismatch between the subject and its circumstances created by the imposition of new life styles.

### Low degree inflammation and abdominal obesity

The Framingham cohort demonstrated that obesity is an independent predictor of CMD in both sexes. The INTERHEART study demonstrated that abdominal obesity (AO) is the most important factor in this relationship, especially in Latin American countries. The International Diabetes Federation (IDF) established the presence of AO as an obligatory criterion for the diagnosis of MS, which is strongly related to the development of CMD. Moreover, the IDF proposed a different threshold for waist circumference depending on regions and ethnic groups. In the Andean population with no previous CMD history, we reported that

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**Figure 1** Plasma C-reactive protein (CRP) and systolic blood pressure (SBP) in Colombian scholar children by body mass index (BMI) tertiles (T).

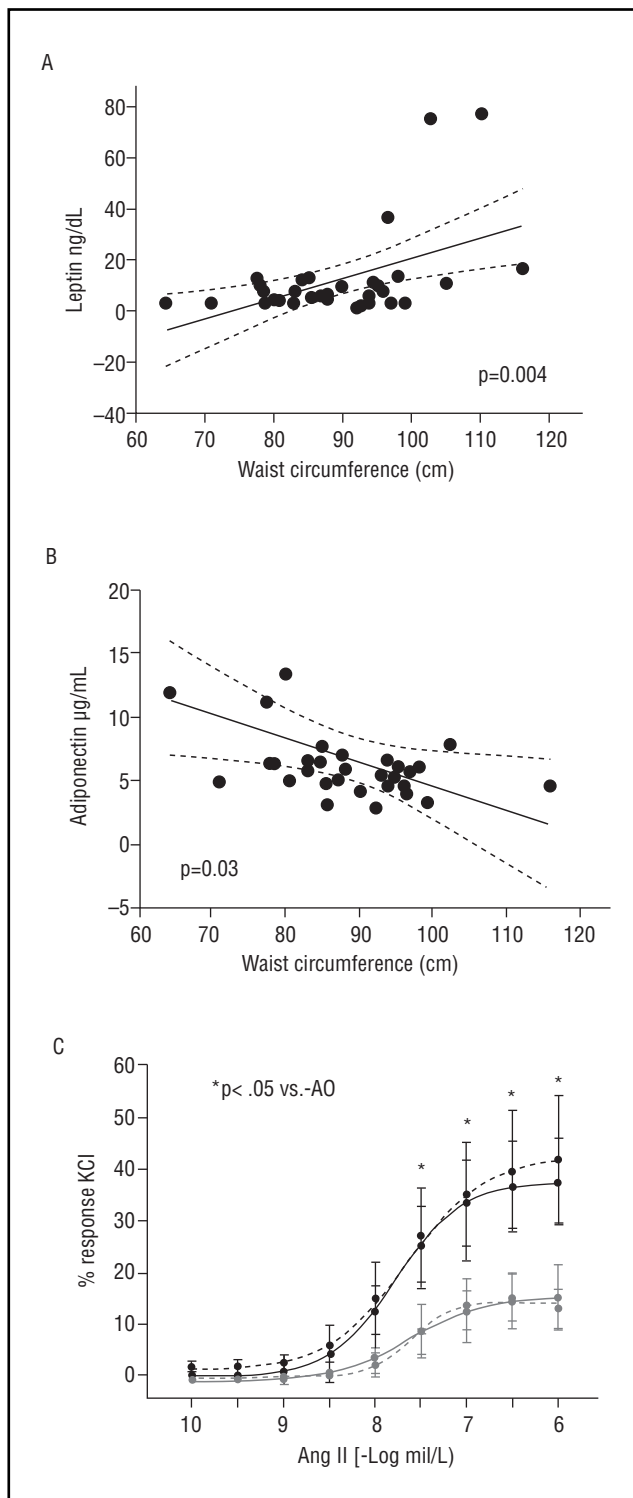
the criteria for MS proposed by the IDF are more useful to identify subjects with MS. In addition, several studies carried out in developing countries have reported lower waist circumference cutoff points associated with cardiovascular risk than those reported in developed countries. Waist circumference has been demonstrated to be an easier parameter to evaluate the content of visceral fat, which is the main source of pro-inflammatory cytokines. These cytokines are elevated in AO and it has been proposed that the systemic inflammation produced by the adipose tissue participates in all stages of the development of CMD. C-reactive protein (CRP), produced by the liver in response to the stimulus of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin 6 (IL-6), is increased in subjects with multiple acute coronary events and is a strong independent predictor of new acute coronary events. We have demonstrated that CRP is an independent risk factor for essential hypertension

and preeclampsia. Moreover, the concentration of CRP is increased in subjects with MS and in overweight children. The concentration of pro-inflammatory cytokines is higher in our population than that reported in the population of developed countries, suggesting a higher sensibility of this population to develop systemic low degree inflammation as response to AO. It has been observed a higher CRP concentration in children of Mexican-American origin in comparison with Caucasian-American children of same age and similar weight. In Colombia, we found a significant positive correlation between body mass index (BMI) and CRP, and higher levels of CRP and blood pressure among boys and girls in the upper tertile of BMI (Fig. 1). The concentrations of CRP that we encountered in the second tertile of BMI were as high as those registered in Caucasian-American children and European children of a similar age who were overweight or obese. Despite the possible differences in

methodology for quantification of CRP in the different studies, this result suggest that Latin American populations have a greater predisposition to generate an inflammatory response at lower body fat levels than those reported for Caucasian populations. The question then is why the populations of developing countries should be more sensitive to this process. We suggest that this is a result of the lower exposure time of developing countries to the new lifestyles associated with bad adaptation to the modernization. The shorter the exposure time, the less adapted the population and the greater the risk of insulin resistance and inflammatory response at lower levels of abdominal obesity. It is well known that the Hispanic population in the United States and that the Hindu population in the United Kingdom is at greater risk for low-grade chronic inflammation, DM2, and cardiovascular mortality than the Caucasian populations of those countries. However, it is currently not clear whether these differences are due to genetic or socioeconomic factors, as these groups migrated relatively recently to developed countries and have therefore only had a short exposure to risk factors and are anyway usually in lower socioeconomic categories. Moreover, in Latino American countries, the bad habits and defects of the two worlds have collided: Lack of potable water, defective waste and sewage removal, high rates of intestinal parasitism, non-preventable infections, and tropical diseases are all still present, but are now coupled with diets which are high in saturated fats and refined flours, more smoking, higher rates of physical inactivity, and AO.

The visceral adiposities of people suffering the rapid changes described above are over expressing Ang II. This hormone has 3 important effects in humans that were crucial to permits to survive when the human been was nomad, collector of fruits, hunter and fisherman, and support long periods of starving:

- It blocks the insulin intracellular signaling routes, producing insulin resistance, as a mechanism to keep energy.
- It stimulates the production of aldosterone, for to keep sodium and water.
- It stimulates the production of pro-inflammatory cytokines, to maintain an alert state to fight with the infectious. However, nowadays the production of Ang II in the visceral adiposities appears to be deleterious since we have change to an excess of food and swift drinks. In this case the insulin resistance and the water retention produced by Ang II are associated to hypertension and CMD. It appears that the adaptation to this situation in obese people of developed countries is an over expression of adiponectin, substance that contrary to Ang II improve the insulin sensibility and have anti-inflammatory effects. In segments of internal mammary arteries of Colombian individuals with severe coronary artery disease (CAD) who underwent coronary artery bypass graft, independently of the presence of classical risk factors, AO was related to diminish endothelium-dependent and endothelium-independent relaxations, and with an increased contractile response to Ang II. Also was observed an imbalance in the plasma relationship of leptin/adiponectine (Fig. 2). Moreover, patients with a clinically



**Figure 2** Plasma levels of leptin and adiponectin in subjects with coronary artery disease (CAD) related with waist circumference. There is an increase of leptin (A) and a decrease in adiponectin (B) associated with higher values of waist circumference. The response ex vivo of segments of internal mammary artery to the stimulus of angiotensin II (C) is increased in the individuals with abdominal obesity controlled by others cardiovascular risk factors. Adapted of Rueda-Clausen et al. *Int J Cardiol.* 2010;139:32-41.

documented history of CAD have higher concentrations of CRP and IL-6, when compared to patients without CAD. The elevation in inflammatory markers was not associated with any further impairment of endothelial function but was associated with a higher carotid IMT, suggesting an association between inflammation and a more severe stage of CAD.

## Conclusion

We propose that the increased production of Ang II and the decreased of adiponectin in the visceral fat, is a natural human biological response to the rapid imposition of lifestyles for which the human been in developing countries, are not particularly well adapted and give as result an increased sensibility to develop inflammation, insulin resistance and CMD.

## Conflict of interest

The authors declare they have not any conflict of interest.

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