



## Revisión

# Adhesion molecules and chemokines: relation to anthropometric, body composition, biochemical and dietary variables

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## Abstract

**Introduction:** Among the inflammatory mediators involved in the pathogenesis of obesity, the cell adhesion molecules P-selectin, E-selectin, VCAM-1, ICAM-1 and the chemokine MCP-1 stand out. They play a crucial role in adherence of cells to endothelial surfaces, in the integrity of the vascular wall and can be modulated by body composition and dietary pattern.

**Objectives:** To describe and discuss the relation of these cell adhesion molecules and chemokines to anthropometric, body composition, dietary and biochemical markers.

**Methods:** Papers were located using scientific databases by topic searches with no restriction on year of publication.

**Results:** All molecules were associated positively with anthropometric markers, but controversial results were found for ICAM-1 and VCAM-1. Not only obesity, but visceral fat is more strongly correlated with E-selectin and MCP-1 levels. Weight loss influences the reduction in the levels of these molecules, except VCAM-1. The distribution of macronutrients, excessive consumption of saturated and trans fat and a Western dietary pattern are associated with increased levels. The opposite could be observed with supplementation of w-3 fatty acid, healthy dietary pattern, high calcium diet and high dairy intake. Regarding the biochemical parameters, they have inverse relation to HDL-C and positive relation to total cholesterol, triglycerides, blood glucose, fasting insulin and insulin resistance.

**Conclusion:** Normal anthropometric indicators, body composition, biochemical parameters and eating pattern positively modulate the subclinical inflammation that results from obesity by reducing the cell adhesion molecules and chemokines.

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Key words: Cell adhesion molecules. Inflammation. Body composition. Anthropometry. Dietary habits.

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## MOLÉCULAS DE ADHESIÓN Y QUIMIOCINAS; RELACIÓN CON VARIABLES ANTROPOMÉTRICAS, DE COMPOSICIÓN CORPORAL, BIOQUÍMICAS Y DIETÉTICAS

### Resumen

**Introducción:** Entre los mediadores inflamatorios involucrados en la fisiopatología de la obesidad, se destacan las moléculas de adhesión P-selectina, E-selectina, VCAM-1, ICAM-1 y la quimiocina MCP-1. Estas desempeñan un papel crucial en la adherencia de células en las superficies endoteliales y en la integridad de la pared vascular y pueden ser moduladas por la composición corporal y patrón alimentario.

**Objetivos:** Describir y discutir la relación de esas moléculas de adhesión y quimiocina con marcadores antropométricos, composición corporal, bioquímicas y dietéticas.

**Métodos:** Se utilizaron bases científicas electrónicas para selección de artículos, sin límite de año de publicación.

**Resultados:** Todas las moléculas se asociaron de forma positiva con marcadores antropométricos; sin embargo, se encontraron resultados controvertidos para ICAM-1 y VCAM-1. No solamente la obesidad per se, sino también la grasa visceral está más fuertemente relacionadas con las concentraciones de E-selectina y MCP-1. La pérdida de peso influencia en la reducción de las concentraciones de esas moléculas, con excepción de la VCAM-1. La distribución de macronutrientes, el consumo excesivo de grasa saturada y trans y un patrón alimentario occidental están asociados con aumento de sus concentraciones. El inverso se pudo observar con la suplementación de ácido graso w-3 en la dieta, el patrón alimentario sano y dieta rica en calcio y productos lácteos. Ya en cuanto a los parámetros bioquímicos, las mismas poseen relación inversa con HDL-c y positiva con colesterol total, triacilglicérols, glicemia e insulinemia de ayuno y resistencia a insulina.

**Conclusión:** Marcadores antropométricos, composición corporal, parámetros bioquímicos y patrón alimentario adecuados modulan positivamente la inflamación subclínica derivada de la obesidad por medio de la reducción de las moléculas de adhesión y quimiocinas.

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Palabras clave: Moléculas de adhesión celular. Inflamación. Composición corporal. Antropometría. Hábitos Alimenticios.

## Abbreviations

BMI: Body mass index.  
CAMs: Cell adhesion molecules.  
CCL2: Chemokine ligand 2.  
CVD: Cardiovascular disease.  
HDL-c: High-density lipoprotein.  
HOMA-IR: Homeostatic model assessment insulin resistance.  
ICAM-1: Intercellular adhesion molecule-1.  
IFN- $\gamma$ : Interferon  $\gamma$ .  
IL4: Interleukin 4.  
IL6: Interleukin 6.  
IL8: Interleukin 8.  
IL1: Interleukin 1.  
IR: Insulin Resistance.  
LDL-c: Low-density lipoprotein.  
MCP-1: Monocyte chemoattractant protein-1.  
MS: Metabolic syndrome.  
ROS: Reactive oxygen species.  
T2DM: Type 2 Diabetes Melitus.  
TNF- $\alpha$ : Tumor necrosis factor-alpha.  
VCAM-1: Vascular adhesion molecule-1.  
WC: Waist circumference.  
WHR: Waist-hip ratio.

## Introduction

Obesity is a complex disease of multifactorial causes that is growing exponentially worldwide,<sup>1</sup> defined as excessive accumulation of body fat to such an extent that is detrimental to health.<sup>2</sup>

Studies show the relation between obesity and subclinical inflammation.<sup>3,4</sup> This process is related to expansion of adipocytes and infiltration of macrophages into adipose tissue, where there is an increased secretion of pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-8, tumor necrosis factor (TNF- $\alpha$ ), complement C3 and monocyte chemoattractant protein-1 (MCP-1).<sup>5-8</sup> These pro-inflammatory cytokines can also substantially affect insulin sensitivity and endothelial dysfunction, as well as stimulate a proliferative response in the vascular wall, which clearly promotes an increased risk for type 2 diabetes (T2DM) and cardiovascular diseases (CVD).<sup>9,10</sup>

When endothelial dysfunction occurs due to an exposure to an activation stimulus such as modified lipoproteins, pro-inflammatory cytokines or coagulation cascade proteases like thrombin, induction and expression of cell adhesion molecules (CAMs) on the surface of the endothelium increasing their interaction with circulating leukocytes can occur. Among them, we highlight the vascular cell adhesion molecule-1 (VCAM-1), the intercellular adhesion molecule-1 (ICAM-1), members of the selectin family (P-selectin and E-selectin) and MCP-1 chemokine.<sup>11,12</sup>

Studies indicate high levels of circulating CAMs in obesity, especially in obesity characterized by accumu-

lation of visceral adipose tissue.<sup>9,13,14</sup> However, studies linking these molecules and anthropometric markers of obesity are still controversial and inconclusive.<sup>15-20</sup> For some molecules, weight loss in obese individuals, whether achieved by dietary or surgical intervention, has positive relation to their levels,<sup>18,21,22</sup> but unlike it was expected, Keogh et al.<sup>23</sup> observed a small but significant increase in VCAM-1 after 8 weeks of dietary intervention, which demonstrates that other factors may be involved in the reduction of these concentrations.

In parallel, the connection between dietary patterns and effects on inflammatory response, and consequently, on levels of CAMs and chemokines has been discussed.<sup>21,24,25</sup> Diet macronutrient distribution and the amount of micronutrients can affect oxidative stress and cause inflammatory changes, which together with a model of chronic excessive intake could induce a pro-inflammatory process.<sup>25,26</sup> High calcium diets, for example, can reduce levels of MCP-1.<sup>27</sup> In addition, components of the diet such as trans fatty acids and high glycemic load are considered pro-inflammatory, while a suitable ratio of  $\omega$ -3 and  $\omega$ -6 polyunsaturated fatty acids is considered anti-inflammatory.<sup>21,26,28,29</sup> On the other hand, low-calorie diets have contradictory relation to levels of cell adhesion molecules. For P-selectin and ICAM-1,<sup>22,30</sup> such diets have positive influence reducing their levels, while VCAM-1 levels can increase depending on macronutrients distribution.<sup>23</sup>

Similarly, the relation of cell adhesion molecules and biochemical parameters such as fasting glucose, insulinemia, triglycerides, total cholesterol and fractions and presence of metabolic syndrome (MS) is also not fully elucidated and for some molecules, such relations are rare.<sup>17,31,32,33</sup>

In this context, the objective of this review was to describe and discuss the role of P-selectin, E-selectin, ICAM-1, VCAM-1 and MCP-1 in inflammation and their relation to anthropometric, body composition, dietary and biochemical markers.

## Methods

This review was conducted using electronic scientific databases, including Medline, PubMed and SciELO, using the following key words in English, Spanish and Portuguese: inflammation, obesity, cell adhesion molecules, VCAM-1, ICAM-1, E-selectin, P-selectin, CCL2 and MCP-1 chemokines, adipose tissue, anthropometry, body composition, diet(ary) pattern. The articles were selected after reading the abstract and regardless of their year of publication.

## Obesity and inflammation

Obesity is the most prevalent chronic metabolic disease in the world. In 2005, over 1.6 billion adults

were overweight, of which at least 400 million were obese.<sup>34</sup> This disease results from a positive energy balance in med/long term. Excess energy is stored in adipose tissue and, if this process is prolonged, the individual develops obesity. The balance between food intake and energy expenditure is influenced by a complex interaction of genetic, environmental and social factors<sup>35</sup> and it is associated with numerous comorbidities that affect individuals life quality, such as T2DM, CVD and some types of cancers.<sup>36</sup>

Obese individuals may develop insulin resistance (IR) and MS, and these changes may lead to T2DM. Not only excess body fat, but distribution and type of body fat exert different effects. Evidence has shown a causal relation between obesity and T2DM due to the fact that visceral adipose tissue is more metabolically active than subcutaneous and gluteal-femoral adipose tissue, causing increased production of free fatty acids, IR, hyperglycemia and consequently hyperinsulinemia<sup>9</sup>. Moreover, infiltration of inflammation-related cytokines and white adipose tissue immune cells produces a chronic low-grade inflammation and it is, in part, responsible for the pathogenesis of insulin resistance in obese.<sup>4,37</sup>

Adipocyte hypertrophy that occurs in obesity causes an increased production of a number of pro-inflammatory cytokines and chemokines by the same cells and stromal vascular cells, such as TNF- $\alpha$ , IL-6, IL-1 $\beta$ , resistin, MCP-1, among others.<sup>5,6,7,10</sup> The increased production of these molecules triggers local effects on the endothelium, leading to an increased production of CAMs and vascular permeability, which ultimately are translated into an increase in monocyte infiltration and accumulation of macrophages.<sup>7,9</sup> Thus, the mechanism by which obesity may trigger a chronic inflammatory process is clear.

However, the inverse relation has been suggested, that is, obesity as a consequence of chronic inflammation, also known as subclinical.<sup>3,38,39</sup> According to Das<sup>38</sup> and Engström et al.,<sup>39</sup> inflammatory cytokines IL-6, IL-1 $\beta$  and TNF- $\alpha$  are involved in metabolism regulation and food intake by regulating insulin action in adipose tissue and modulating release of leptin by this tissue, and these effects can be enhanced by the polymorphism of the TNF- $\alpha$  receptor-2 gene that is associated with leptin resistance and obesity. Thus, it is believed to be a vicious cycle between obesity and inflammation induced by changes in adipose tissue.<sup>40</sup>

### Migration of leukocytes in inflammatory response

The inflammatory response is the body's first defense against tissue damage which aims to remove the response inducing stimulus and to initiate local tissue recovery. This response is coordinated by cellular mediators categorized according to their biochemical properties, such as vasoactive amines, vasoactive peptides, lipid mediators, cytokines, chemokines and proteolytic enzymes.<sup>41</sup>

Initially, after tissue damage caused by injury or infection, there is a production of inflammatory mediators such as IL-1 $\beta$ , TNF- $\alpha$  and IL-6, chemokines, as well as the expression of CAMs that produce exudate composed of large molecules as albumin and fibrinogen. After that, other plasma proteins migrate to the extravascular space together with leukocytes, which start to circulate along the endothelium through the post-capillary venules.<sup>42</sup> These changes support a key role of activated vascular endothelium, which is to promote the mobilization and recruitment of leukocytes to the inflammatory site.<sup>43</sup>

The migration of leukocytes into tissues depends on the binding that occurs between these cells and CAMs. Then, signals within the endothelial cells are activated, allowing the opening of narrow vascular passages that are small intercellular gaps. The movement of leukocytes through these passages is stimulated by chemokines produced by the endothelium and tissue. The majority of these cells migrate through these intercellular gaps, but in severe inflammation conditions, a small percentage of leukocytes can transcellularly migrate.<sup>44</sup>

The leukocytes migration process into the extravascular space during inflammatory response is regulated by reactive oxygen species (ROS). This process, known as adhesion cascade, involves some steps that typically include: rolling of leukocytes on the endothelial cell surface followed by arrest of leukocytes on the endothelium for adhesion and high affinity and subsequent transmigration into the inflammation tissue site (fig. 1).<sup>43,45</sup>

The rolling leukocytes express integrins in a low affinity that, after being activated by chemokines produced by activated vascular endothelium, lead to increased affinity. Subsequently, integrins stabilize selectin-mediated binding, reduce the rolling speed favoring the adhesion of leukocytes to the endothelium and promote their passage from the blood to the tissues.<sup>46</sup>

The transient and reversible interactions of leukocytes rolling on the endothelium are mediated by weak binding between selectins propagated on the endothelium and on leukocytes and by a firm adhesion interceded primarily by VCAM-1 and ICAM-1, which bind to integrins 1 and 2 expressed on leukocytes.<sup>47,48</sup>

If inflammatory response persists, qualitative changes, characterized by replacement of leukocytes by macrophages and chronicity of the process, occur. The chronicity of the inflammatory state is a matter of scientific research since little is known about causes and mechanisms involved in such state and its involvement in development of chronic diseases.<sup>49</sup>

### Cell Adhesion Molecules (CAMs)

The CAMs are membrane receptors glycoproteins that play an important role in the adhesion of cells to extracellular matrices and to endothelial surfaces<sup>50</sup>.

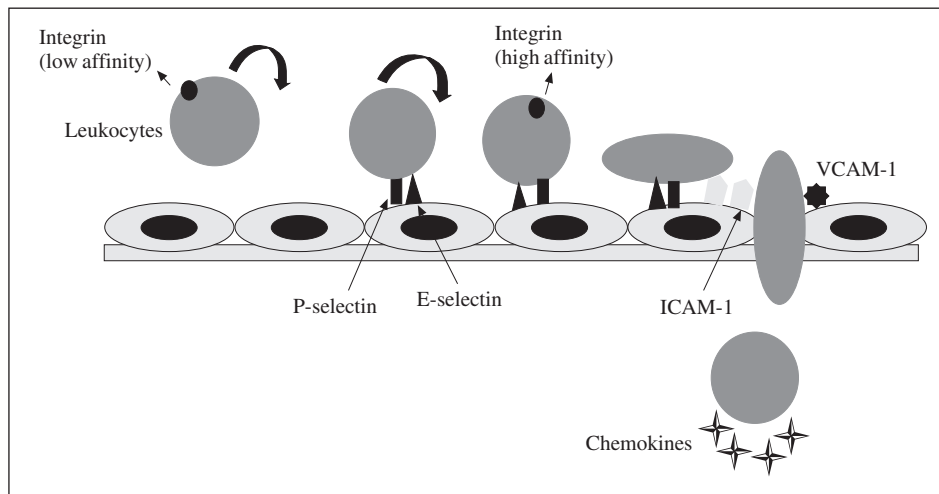


Fig. 1.—Leukocytes migration process. The rolling leukocytes express integrins of low affinity that, after their activation by chemokines, acquire high affinity for endothelial cells. Then the selectin mediated binding is stabilized, the rolling speed is reduced, promoting leukocyte adhesion to vascular endothelium interceded by VCAM-1 and ICAM-1 and promoting the opening of intercellular passages, allowing leukocytes to pass from blood to tissues.

They are known to mediate cell-endothelium interactions of leukocytes and platelets with a critical role in many processes, including inflammation and vascular wall integrity, in addition to being essential for maintaining health and being involved in development of chronic diseases.<sup>51</sup>

Based on their structure and role, CAMs can be divided into three main families: integrins, selectins and immunoglobulin superfamily. Among them, P-selectin, E-selectin, ICAM-1 and VCAM-1 are relevant in chronic inflammatory process, and therefore have a prominent role in CVD.<sup>41,52,53</sup> The distribution and roles of these molecules in the inflammatory process are presented in table I.

### Selectins

Selectins are binding protein molecules that mediate the initial low affinity interaction between leukocytes

and endothelial cells and manifest as rolling leukocytes. This transient binding, despite the low affinity, results in increased leukocyte recruitment to the periphery and subsequent firm adhesion and transendothelial migration of these cells.<sup>41</sup>

In contrast to most of the other CAMs, the role of selectins is restricted to interactions between leukocytes and vascular endothelium, and P-selectin and E-selectin are the most important molecules in this process. Soluble forms of selectins can be detected in plasma, where high concentrations have been reported in animals and patients with inflammatory diseases.<sup>55</sup>

### P-Selectin

P-selectin is identified and stored in alpha granules of platelets and in Weibel-Palade bodies of endothelial cells from where it can be rapidly mobilized to the cell

**Table I**  
Adhesion molecules and chemokine: their cellular role and distribution

Adhesion molecules/chemokine	Distribution	Role
P-selectin	Platelets, endothelium	Interaction between platelets and endothelium, adhesion, rolling and recruitment of leukocytes to the endothelium
E-selectin	Endothelium	Adhesion, rolling and recruitment of leukocytes to the endothelium
VCAM-1	Endothelium, mild atherosclerotic injury in muscle cells	Adhesion of leukocytes to endothelial cells
ICAM-1	Endothelium, leukocytes, fibroblasts, mild atherosclerotic injury in muscle cells	Adhesion and transmigration of leukocytes
MCP-1	Epithelial, endothelial and immune cells	Leukocyte recruitment

ICAM-1: Intercellular adhesion molecule-1; VCAM-1: Vascular adhesion molecule-1; MCP-1: Monocyte chemoattractant protein-1. Adapted from Hope and Meredith<sup>50</sup> and Calder et al.<sup>54</sup>



surface in response to a variety of inflammatory agents such as cytokines and free radicals.<sup>53,56</sup>

The expression of P-selectin on the surface of endothelial cells is usually of short duration, so this makes it an ideal candidate for mediating early leukocyte-endothelial interactions. It has an agile kinetics that reveals its important role in recruitment of neutrophils in the early stages of inflammatory reaction.<sup>57</sup>

Few studies have reported high concentrations of P-selectin in the plasma of obese patients<sup>22,58</sup> and its relation to fat distribution has not been well established. Its concentration is directly related to body mass index (BMI), waist-hip ratio (WHR) and waist circumference (WC).<sup>22,59,60</sup> However, Pou et al.<sup>59</sup> showed that both visceral and abdominal subcutaneous fat have also been associated with P-selectin concentrations. When adjusted for BMI and WC, though, this relation did not remain significant (table II). Thus, this suggests that the relation between P-selectin and visceral adiposity is independent of BMI and WC. This is probably justified by the fact that BMI does not assess obesity itself, understood as excess adipose tissue and WC, used in clinical practice as a marker of visceral fat, also takes into consideration the abdominal subcutaneous fat. Therefore, obese patients may not have very representative visceral fat, proportionally, in relation to total fat and consequently maintain homeostasis in relation to inflammatory process.

Weight loss is a method that is likely to improve concentrations of inflammatory markers and endothelial dysfunction in obese subjects. Thus, the kind of intervention, dietary or surgical, can influence the reduction of P-selectin concentrations. Roberts et al.<sup>61</sup> studying weight loss in obese men after 3 weeks and Ziccardi et al.<sup>22</sup> in obese women after one year, both resulting from dietary intervention and physical activity, showed decreased P-selectin concentrations (table III). This decrease was also observed after the fourth month of weight loss following surgery in morbidly obese<sup>62</sup>. This is possibly due to reduction of adiposity, which results in improved endothelial activation and is related to reduction of this adhesion molecule.

However, it is unclear whether diets varying in macronutrient composition can affect inflammatory responses differently. Sharman and Volek<sup>30</sup> compared a low calorie diet with very low carbohydrate levels (< 10% carbohydrate) and low fat levels (25% fat, < 10% saturated fat and < 300 mg cholesterol) on inflammatory markers in overweight men. After 6 weeks of intervention there was no significant reduction in absolute concentration of P-selectin for both diets. However, when inflammatory values were normalized with reduction of 1kg of body weight, there was a significant reduction of P-selectin for both treatments and it was higher for the very low carbohydrate level diet (table IV). The results of this study suggest that in a short period of time, weight loss and not diet composition seems to be the underlying driving force in reducing these inflammatory markers.

Besides adiposity and macronutrient composition, biochemical parameters also influence concentrations of CAMs. Studies have shown that concentrations of P-selectin were positively associated with fasting glucose,<sup>17</sup> triglycerides and total cholesterol and inversely associated with high-density lipoprotein (HDL-c)<sup>16,60</sup> in apparently healthy individuals. This association of triglycerides and HDL-c was found by Miller and Cappuccio<sup>19</sup> after adjustment on age and sex (table V).

This way, it is becoming clear that P-selectin is an essential component in cardiovascular disease and therefore is a potential therapeutic target. A longitudinal monitoring of apparently healthy women for 3.5 years showed that concentrations of P-selectin were significantly higher in the beginning of the study among participants who subsequently developed a first cardiovascular event than those who had no event. In this study, relative risk of future events increased by 25% for each quartile increase in basal level of P-selectin.<sup>63</sup>

Therefore, concentrations of P-selectin are directly related to obesity markers and weight loss. However, as to body composition, unlike what was expected, its relation is not yet well established, since there was no association of P-selectin with visceral or subcutaneous fat. The macronutrient distribution or a healthy eating pattern also need to be elucidated, since studies indicate a reduction in concentrations of P-selectin resulting from weight loss induced by diet and not due to its composition. Similarly, the relation of this molecule with biochemical parameters should be more studied, since these are all contributing factors to cardiovascular events through its inflammatory effects on vascular endothelium.

### *E-Selectin*

E-selectin is expressed on endothelial cells specifically and strongly stimulated by inflammatory molecules such as TNF- $\alpha$  and IL-1 $\beta$ , and it is widely expressed in vasculature on sites of inflammation.<sup>64</sup>

Its relation to the occurrence and type of obesity, as well as to anthropometric markers is established. The concentrations of E-selectin were significantly associated with BMI and WHR.<sup>16,17,19,33</sup> When compared, the concentrations of E-selectin in obese and nonobese individuals, they are significantly higher in obese, and visceral obesity is more strongly related than total fat.<sup>14,33</sup> This could be explained by production of TNF- $\alpha$  and IL-6 derived from visceral adipocytes on which they induce increased expression of this molecule.<sup>33</sup>

Studies also point to reduction in concentrations of E-selectin with weight loss, whether due to dietary or surgical intervention. Ito et al.<sup>18</sup> when studying obese women after 3 months of nutritional intervention and physical activity, showed a significant reduction of this molecule. Similar results were found by Pontiroli et

**Table II**  
*Association of adhesion molecules and chemokine with anthropometric markers and body composition*

<i>Subject</i>	<i>n (sex)</i>	<i>Type of study</i>	<i>Methods</i>	<i>Association</i>	<i>Reference</i>
Obese	56(M)	Transversal	Sedentary individuals. Anthropometric and body composition data were collected. This by computed tomography.	BMI: ↑ E-selectin, ICAM-1, ↔ VCAM-1 WC: ↔ E-selectin, ICAM-1, ↑ VCAM-1 WHR: ↑ E-selectin, VCAM-1, ↔ ICAM-1 SAT: ↔ E-selectin, VCAM-1, ↑ ICAM-1 VAT: ↑ E-selectin, VCAM-1, ↔ ICAM-1	14
Healthy	316 (M/F)	Cohort	Monitoring of medical history, smoking, alcohol consumption and anthropometry over 5 years.	BMI: ↑ E-selectin, ↔ ICAM-1, VCAM-1	15
Healthy	592 (M/F)	Transversal	Evaluated lifestyle and anthropometry.	WHR: ↑ P-selectin, E-selectin, ICAM-1, VCAM-1	16
Healthy	493 (M/F)	Transversal	Evaluated lifestyle and anthropometry.	BMI: ↑ P-selectin, E-selectin, ICAM-1	17
Obese	46 (M)	Transversal	Consisted of a 3 month follow-up with lectures on diet, exercise and behavioral modification.	BMI, WC: ↑ E-selectin, ICAM-1	18
Healthy	664 (M/F)	Transversal	Individuals of different ethnicities. Evaluated clinical and anthropometric parameters.	BMI: ↑ E-selectin, ↔ P-selectin, ICAM-1, VCAM-1 WHR: ↑ E-selectin, ICAM-1, VCAM-1, ↔ P-selectin	19
Healthy	1577 (M/F)	Transversal	Different ethnic groups, conducted anthropometric, biochemical and clinical measures.	BMI: ↑ E-selectin, ↔ P-selectin, ICAM-1, VCAM-1 WHR: ↑ E-selectin, ICAM-1, VCAM-1, ↔ P-selectin	20
Obese and non obese	96 (F)	Transversal	Dietary intervention and exercise over 12 months and liposuction for women candidates.	BMI: ↑ P-selectin, VAM-1, ICAM-1 WHR: ↑ P-selectin, VAM-1, ICAM-1	22
Obese and non obese	100 (M/F)	Transversal	Conducted medical evaluation, physical examination and anthropometry.	BMI, WC: ↑ MCP-1	31
Obese and non obese	87 (M/F)	Transversal	Conducted anthropometric measures and body composition by computerized tomography.	BMI, WHR, VAT: ↑ E-selectin SAT: ↔ E-selectin	33
Healthy	1250(M/F)	Transversal	Conducted anthropometric measures and body composition by computerized tomography.	BMI: ↑ P-selectin, ICAM-1, MCP-1 WC: ↑ P-selectin, ICAM-1, MCP-1 SAT: ↔ P-selectin, ICAM-1, MCP-1 (after adjustment for BMI and WC) VAT: ↔ P-selectin, ICAM-1, MCP-1 (after adjustment for BMI and WC)	59
Healthy	3013 (M/F)	Transversal	Monitored by Framingham and Omni Study, through medical history and lifestyle habits.	BMI: ↔ P-selectin, ICAM-1, ↑ MCP-1 WC: ↑ P-selectin, ↔ ICAM-1, MCP-1	60
Healthy	27.158 (M)	Transversal	Evaluated anthropometric data, lifestyle and physical activity.	BMI: ↑ ICAM-1	75
Healthy	145 (M)	Transversal	Women without breast cancer. Anthropometric measures and biochemical parameters were evaluated.	BMI: ↔ ICAM-1, ↓ VCAM-1 WHR: ↔ ICAM-1, VCAM-1	81
Obese mice	40	Transversal	Obesity was induced by high lipid diet from the time they were 9 weeks old.	Adiposity: ↑ MCP-1	91
Obese and non obese	20 (M/F)	Transversal	Individuals were submitted to surgery, and the obese were submitted to placement of adjustable silicone gastric band by laparoscopy. From this, adipocytes were isolated.	BMI, VAT: ↑ MCP-1	92
Obese	90 (M/F)	Cohort	Adipose tissue was obtained by biopsy performed in volunteers undergoing abdominal surgery for gastric banding, gastric weight reduction surgery, or laparotomy.	VAT: ↑ MCP-1	93
Obese	23 (M/F)	Transversal	Lifestyle intervention for 12 weeks consisting of hypocaloric diet combined with physical activities for at least 2 hours/day.	BMI: ↑ MCP-1	94
Obese and non obese mice	12	Transversal	Knockout mice for the MCP-1 receptor were put on a high fat diet to determine obesity.	Adiposity: ↑ MCP-1	95

↑ positive association; ↔ no association; ↓ negative association; ICAM-1: Intercellular adhesion molecule-1; VCAM-1: Vascular adhesion molecule-1; MCP-1: Monocyte chemoattractant protein-1; BMI: body mass index; WC: waist circumference; WHR: waist-hip ratio; SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue; M- male; F: female.

**Table III**  
*Effect of weight loss on adhesion molecules and chemokine*

Subject	n (sex)	Intervention period	Methods	Effect	Reference
Obese	46 (F)	3 months	Consisted of lectures on diet, exercise sessions and behavioral modification. Emphasis on themes of calorie restriction, increasing consumption of vegetables and grains and replacing saturated fats with unsaturated.	↓ E-selectin, ICAM-1	18
Obese and non obese	96 (F)	12 months	Intervention with hypocaloric diet, exercise and liposuction for women candidates. Diet composition: 1300 kcal, 55% carbohydrate, 22% protein, 23% fat and 25 g fibers.	↓ P-selectin, VCAM-1, ICAM-1	22
Obese	99 (M/F)	8 weeks	Intervention with two types of hypocaloric diet: a low-carbohydrate and high in saturated fat (4% carbohydrate, 61% lipid, 20% saturated fat) and low in saturated fat (46% carbohydrate, 30% lipid, <8% saturated fat).	↓ P-selectin, E-selectin, ICAM-1 ↑ VCAM-1	23
Obese and SM	31 (M)	3 weeks	Dietary intervention and daily exercise. Diet: 12-15% fat, 15-20% protein and 65-70% mainly from complex carbohydrates, >40 g of dietary fiber.	↓ P-selectin, ICAM-1	61
Morbid obese and non obese	49 (M/F)	4 months	Weight loss was due to bariatric surgery.	↓ P-selectin, E-selectin, VCAM-1, ↔ ICAM-1	62
Obese and non obese	126 (M/F)	12 months	The intervention was adjustable gastric band or diet and physical activity. Hypocaloric diet: 1000 for men and 1100 kcal / day for women, 48% carbohydrate, 33% protein and 19% fat (olive oil).	↓ E-selectin, ICAM-1	65
Obese mice	40	18 weeks	Weight loss was due to feed restriction.	↓ MCP-1	91
Obese	23 (M/F)	12 weeks	Intervention with low-calorie diet combined with physical activity for at least 2 hours/day.	↓ MCP-1	94

↑ increased; ↔ no effect on; ↓ decreased; ICAM-1: Intercellular adhesion molecule-1; VCAM-1: Vascular adhesion molecule-1; MCP-1: Monocyte chemoattractant protein-1; CHO: carbohydrate; PTN: protein; LIP: lipid; M- male; F: female.

al.<sup>65</sup> in surgical weight loss in individuals with morbid obesity. This suggests a reduction of endothelial activation and an important role of adipose tissue in this pathophysiological mechanism.

Diet macronutrient composition can directly affect concentrations of E-selectin. When comparing different meals overloaded with glucose, fat or in combination, in healthy individuals, it was found an increase in these levels after high fat and glucose meals, and when combined, there were more pronounced effects on E-selectin.<sup>21</sup> This increase is due to hyperglycemia and postprandial hypertriglyceridemia, which have independent but cumulative effects and promote an atherogenic profile.

Moreover, a healthy dietary pattern, characterized by consumption of fruits, vegetables, fish, poultry and whole grains was associated with decreased concentrations of E-selectin after adjustment for age, BMI, physical activity, smoking and alcohol consumption in apparently healthy women. At the same time, a Western dietary pattern characterized by higher intakes

of red meat, sweets, fries and refined grains was associated with increase in these concentrations.<sup>66,67</sup>

The type of lipid in the diet may also differentially influence endothelial activation. The w-3 alpha-linolenic fatty acid consumption in overweight individuals with hypercholesterolemia significantly reduces E-selectin concentrations, since it activates mechanisms that beneficially affect both lipids/lipoproteins and CAMs on which they inhibit endothelial activation<sup>68</sup>. The intake of trans fatty acids is directly associated with increased concentrations of E-selectin, due to vasodilatation, and consequent increase of CAMs and reduced HDL-c, which can cause oxidation of low density lipoproteins (LDL-c). This indicates that dietary factors may influence the cardiovascular risk through modulation of endothelial function.<sup>24</sup>

The concentrations are also related to biochemical parameters. Fasting glucose, fasting insulin and triglycerides were positively associated with E-selectin,<sup>17,19,33</sup> while HDL-c had a negative association<sup>19,33</sup> in healthy individuals. As for individuals with

**Table IV**  
*Qualitative and quantitative effect of diet on adhesion molecules and chemokine*

<i>Subject</i>	<i>n (sex)</i>	<i>Intervention period</i>	<i>Methods</i>	<i>Effect</i>	<i>Reference</i>
Type 2 diabetics and healthy	50 (M/F)	4 weeks	All participants ate three different diets on different days: a high fat meal (75g fat, 5 g of carbohydrate and 6g of protein per m <sup>2</sup> of body surface), a meal with only 75 g of glucose and the third meal was rich in fat and contained 75 g of glucose. Blood samples were collected at 0, 1, 2, 3, and 4 h.	High fat diet: ↑ E-selectin, VCAM-1, ICAM-1 High glucose diet: ↑ E-selectin, VCAM-1, ICAM-1 High fat and glucose diet: ↑ E-selectin, VCAM-1, ICAM-1 (more pronounced than isolated diets)	21
Healthy	730 (F)	Transversal	Food intake was registered using a validated semiquantitative FFQ. Detailed information about the type of fat or oil used for frying (cooking and table), brand, type and year of consumption of margarine.	Intake of trans fatty acids: ↑ E-selectin, VCAM-1, ICAM-1	24
αP2-agouti transgenic mice	30 (M)	3 weeks	Mice were divided into three groups with different diets: one group on control diet (0.4% calcium carbonate), one group with a high concentration of calcium (1.2% calcium carbonate) and the third group consumed a high calcium diet derived from dairy products (1,2% nonfat dry milk).	Diet rich in calcium and dairy: ↓ MCP-1	27
Overweight	15 (M)	6 weeks	Comparison of two hypocaloric diets: a very low-carb diet (<10% carbohydrate, 60% of fat and 30% of protein) and a low-fat diet (20% protein, 25% fat, <10% saturated fat and <300 mg cholesterol, 55% carbohydrate). All volunteers consumed both diets.	Low-carb diet: ↔ P-selectin, ↓ ICAM-1 Low-fat diet: ↔ P-selectin, ↓ ICAM-1	30
Healthy	732 (F)	Transversal	Healthy dietary pattern was characterized by higher intake of fruits, vegetables, fish, poultry and whole grains, and Western dietary pattern was characterized by higher intake of red and processed meats, sweets, desserts, fries and refined grains.	Healthy dietary pattern: ↓ E-selectin, ↔ VCAM-1, ICAM-1 Western dietary pattern: ↑ E-selectin, VCAM-1, ICAM-1	66
Healthy	486 (F)	Transversal	Healthy dietary pattern: rich in fruits, vegetables, tomatoes, poultry, tea, fruit juices and whole grains. Western dietary pattern: rich in refined grains, red meat, butter, processed meats, high fat dairy products, sweets and desserts, pizza, potatoes, eggs, hydrogenated fats and sodas.	Healthy dietary pattern: ↓ E-selectin, VCAM-1, ICAM-1 Western dietary pattern: ↔ E-selectin, ↓ VCAM-1, ICAM-1	67
Hypercholesterolemic individuals	23 (M/F)	6 weeks	Three diets: a standard diet (13% saturated, 13% MUFA and 9% PUFA), a diet rich in PUFA and ALA (8% saturated, 12% MUFA and 17% PUFA) and a diet rich in PUFA and LA (8% saturated, 12% MUFA and 16% PUFA).	Diet Rich in ALA: ↓ E-selectin, VCAM-1, ICAM-1 more pronounced than the other diets	68
Overweight and obese	11 (M/F)	6 hours after eating	Subjects consumed three high-fat shakes: one rich in saturated fat, the other rich in monounsaturated and the third rich in w-3 polyunsaturated fat. Blood samples were collected at 0, 1, 2, 4 and 6 after eating.	High in saturated fat: ↑ VCAM-1, ↔ ICAM-1 High in monounsaturated: ↔ VCAM-1, ICAM-1 High in polyunsaturated: ↔ VCAM-1, ICAM-1	76
Individuals with coronary artery disease	60 (M/F)	6 weeks	Individuals divided into three groups fed with 700 g/week of Atlantic salmon in different ways: the first with 100% fish oil, the second with 100% canola oil and the third with 50% of each oil, resulting in fillets with high, medium and low levels of w-3 PUFAs.	Fish oil: ↓ VCAM-1 compared with the other oils	82
Obese and non obese mice	12	Transversal	Knockout mice for the receptor of MCP-1 were fed a high saturated fat diet.	High intake of saturated fat: ↑ MCP-1	95

↑ increased; ↔ no effect on; ↓ decreased; ICAM-1: Intercellular adhesion molecule-1; VCAM-1: Vascular adhesion molecule-1; MCP-1: Monocyte chemoattractant protein-1; FFQ: food frequency questionnaire; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids; ALA: α-linolenic acid; LA: linoleic acid; CHO: carbohydrate; PTN: protein; LIP: lipid; M- male; F: female.



**Table V**  
*Association of biochemical parameters, adhesion molecules and chemokine*

Subject	n (sex)	Type of study	Association	Reference
Obese	56(M)	Transversal	E-selectin: ↑ total cholesterol, triacylglycerols, LDL-c, fasting insulin, HOMA, ↔ HDL-c, fasting blood glucose ICAM-1, VCAM-1: ↔ total cholesterol, triacylglycerols, LDL-c, fasting insulin, HOMA, HDL-c, fasting blood glucose	14
Healthy	316 (M/F)	Cohort	E-selectin: ↑ triacylglycerols, ↔ LDL-c, ↓ HDL-c ICAM-1, VCAM-1: ↔ triacylglycerols, LDL-c, HDL-c	15
Healthy	592 (M/F)	Transversal	P-selectin, E-selectin, ICAM-1, VCAM-1: ↑ total cholesterol, HDL-c	16
Healthy	493 (M/F)	Transversal	P-selectin, ICAM-1: ↑ triacylglycerols, ↔ fasting blood glucose E-selectin: ↔ triacylglycerols, ↑ fasting blood glucose	17
Obese	46 (F)	Transversal	E-selectin: ↑ triacylglycerols, ↔ total cholesterol, HOMA ICAM-1: ↔ triacylglycerols, total cholesterol, HOMA	18
Healthy	664 (M/F)	Transversal	P-selectin, ICAM-1, VCAM-1: ↑ triacylglycerols, ↔ fasting insulin, ↓ HDL-c E-selectin: ↑ triacylglycerols, fasting insulin, ↓ HDL-c	19
Healthy	1577 (M/F)	Transversal	E-selectin: ↑ total cholesterol, triacylglycerols, fasting insulin, fasting blood glucose, ↓ HDL-c P-selectin: ↔ total cholesterol, triacylglycerols, fasting insulin, ↑ fasting blood glucose, ↓ HDL-c ICAM-1: ↑ total cholesterol, triacylglycerols, ↔ fasting insulin, fasting blood glucose, ↓ HDL-c VCAM-1: ↔ total cholesterol, ↑ triacylglycerols, ↔ fasting insulin, fasting blood glucose, ↓ HDL-c	20
Obese and non obese	100 (M/F)	Transversal	MCP-1: ↔ total cholesterol, triacylglycerols, LDL-c, ↓ HDL-c	31
Individuals with MS	37 (M/F)	Transversal	ICAM-1, VCAM-1: ↑ MS, HOMA-IR	32
Obese and non obese	87 (M/F)	Transversal	E-selectin: ↔ total cholesterol, LDL-c, ↑ triacylglycerols, ↓ HDL-c	33
Healthy	3013 (M/F)	Transversal	P-selectin: ↑ triacylglycerols ICAM-1, MCP-1: ↔ triacylglycerols	60
Obese and non obese	126 (M/F)	Transversal	E-selectin, ICAM-1: ↑ insulin, HOMA	65
Healthy	30 (M)	Longitudinal	E-selectin: ↔ fasting and postprandial blood glucose, fasting and postprandial triacylglycerol, fasting and postprandial insulin ICAM-1: ↔ fasting and postprandial blood glucose, fasting and postprandial triacylglycerol, fasting insulin, ↑ postprandial insulin VCAM-1: ↔ fasting and postprandial blood glucose, fasting triacylglycerol, ↑ postprandial triacylglycerol, ↔ fasting and postprandial insulin	78
Healthy, hypercholesterolemic and hypertriglyceridemic individuals	40 (M/F)	Transversal	E-selectin: ↑ total cholesterol ICAM-1: ↑ total cholesterol, triacylglycerols VCAM-1: ↑ triacylglycerols	83

↑ positive association; ↔ no association; ↓ negative association; ICAM-1: Intercellular adhesion molecule-1; VCAM-1: Vascular adhesion molecule-1; MCP-1: Monocyte chemoattractant protein-1; MS: metabolic syndrome; HOMA-IR: Homeostatic model assessment insulin resistance; LDL-c: low-density lipoprotein; HDL-c: high-density lipoprotein; M- male; F: female.

visceral adiposity, E-selectin is related to hyperinsulinemia and IR,<sup>14</sup> which was expected since this adipose tissue is highly lipolytic and has a late interference in post-insulin receptor mechanisms, resulting in inefficient glucose uptake causing such effects.

Thus, E-selectin, may play a role in atherogenesis model centered on inflammation.<sup>69</sup> The concentrations were significantly associated with coronary artery disease (OR: 1.54, 95% CI: 1.27-1.86) and occurrence of atherosclerosis of the carotid artery (OR: 1.36, 95%

CI: 1.09-1.70). The risk of coronary artery disease in individuals with high levels of E-selectin was 2.98 times higher (95% CI: 1.74-5.10).<sup>15</sup>

Therefore, E-selectin is well grounded as to the occurrence and type of obesity and visceral obesity is strongly related to these concentrations. Similarly weight loss is positively associated with its reduction. Macronutrient distribution, healthy eating pattern and type of lipids are also clearly related to E-selectin, since dietary factors can influence modulation of

endothelial function. Along with these factors, total cholesterol and fractions, triglycerides, fasting insulin and fasting glucose are also associated with E-selectin. Thus, E-selectin can be considered a classic molecule for obesity and cardiovascular risk factors.

#### *The immunoglobulin superfamily (IgSF)*

The IgSF is the most abundant family of cell surface molecules, representing 50% of all leukocyte surface glycoproteins.<sup>70</sup> IgSF members are diverse, comprising soluble and membrane-bound immunoglobulin and monomeric adhesion molecules.<sup>56</sup>

These molecules are expressed on endothelial cell membranes, they are also involved in leukocyte adhesion and are induced by TNF- $\alpha$ , interferon- $\gamma$  (IFN- $\gamma$ ) and IL-1 $\beta$ . The main molecules of this family are: ICAM-1 and VCAM-1, which are relevant in chronic inflammatory process, with highlights to CVD.<sup>56</sup>

#### *Intercellular Adhesion Molecule-1 (ICAM-1)*

ICAM-1 is a transmembrane glycoprotein that binds to integrins in order to facilitate transmigration of leukocytes through vascular endothelium. Intercellular adhesion function has been attributed to ICAM-1 as a result of this binding capacity. Its expression is regulated by agents such as TNF- $\alpha$  and thrombin.<sup>70, 71, 72</sup>

The firm adhesion of leukocytes to the endothelium via ICAM-1 causes an increase in intracellular free Ca<sup>2+</sup>, contractility of myosin and activation of p38 kinase. The activation of these signaling pathways results in extensive remodeling events of the cytoskeleton that alter the contractility of endothelial cells, thereby facilitating transmigration and weakening bindings of junctional adhesion molecules.<sup>73, 74</sup>

Its relation to anthropometric markers has been explored, but with controversial results. A study involving apparently healthy women observed a positive and significant relation between BMI and ICAM-1, and showed that women in the highest BMI quintile had 14% higher concentrations than those in lower quintiles.<sup>75</sup> As to obese women, a significant positive association with BMI and WHR was found.<sup>22</sup> However, Ponthieux et al.<sup>17</sup> and Miller and Cappuccio<sup>19</sup> when studying healthy individuals of different ages and ethnicities, respectively, could not observe significant association with BMI after adjustment for age, sex, smoking status and ethnicity. This may have been observed because BMI does not measure, as it was previously mentioned, body composition, which is common among the adjustment variables.

Regarding body composition, however, both subcutaneous and visceral abdominal fat were not associated with ICAM-1 concentrations, when adjusted for BMI and WC. Thus, the concentration of this molecule also seems to be independent of these two anthropometric

markers.<sup>59</sup> This shows that there may be alternative mechanisms to alteration of such cell adhesion molecule, besides type of adiposity, as possibly reduction of HDL-c and subsequent oxidation of LDL-c, which can be a risk factor for modification of the endothelium regardless body composition.

Weight loss was related to ICAM-1 concentrations. Ito et al.<sup>18</sup> and Ziccardi et al.<sup>22</sup> studied weight loss in obese women submitted to hypocaloric dietary intervention after 3 and 12 months, respectively, and observed a positive association with this molecule. Thus, this suggests an important role of adipose tissue in reduction of endothelial activation.

Not only the caloric value, but also qualitative characteristics of the diet may be associated with concentrations of this molecule and therefore with endothelial activation. Studies with women showed that a dietary pattern characterized by higher intakes of red and processed meats, sweets, desserts, fries and refined grains reduces ICAM-1 concentrations.<sup>66, 67</sup> At the same time, consumption of a high glucose load and fat,<sup>21</sup> particularly saturated fat<sup>76</sup> and trans fatty acid<sup>24</sup> produces a significant increase in ICAM-1. Thus, it is suggested that inappropriate food intake plays an important role in endothelium functional changes caused by oxidation of LDL-c, which is the initial step in development of atherosclerosis.

Prospective studies indicate ICAM-1 concentrations as a predictor of future cardiovascular events.<sup>15, 77</sup> Biochemical parameters considered risk factors for development of CVD such as total cholesterol, triglycerides and HDL-c were associated with concentrations of this cell adhesion molecule, and HDL-c had an inverse association.<sup>19, 20</sup> Furthermore, ICAM-1 is positively related to insulin, postprandial glucose<sup>78</sup> and IR.<sup>17</sup>

Kressel et al.<sup>32</sup> used the homeostasis model assessment for definition of IR (HOMA-IR), and showed that individuals who had HOMA-IR  $\geq 5.03$  had higher concentrations of this marker when compared with those who had HOMA-IR  $\leq 1.32$ . Therefore, these results reinforce the idea that associations between systemic and vascular inflammation may help explain predisposition for IR in obese patients.

This way, studies on the relation of ICAM-1 with nutritional and dietary parameters present controversial results for anthropometric markers when adjusted for age, sex, smoking status and ethnicity, and further research is required, particularly related to body composition, in order to elucidate its relation with obesity per se and/or the distribution of body fat. However, this molecule is directly related to weight loss, with inadequate dietary pattern, high intake of saturated and trans fat and biochemical parameters, and has an inverse relation with HDL-c.

#### *Vascular Cell Adhesion Molecule-1 (VCAM-1)*

VCAM-1 is a type I transmembrane glycoprotein expressed primarily in activated endothelial cells and

binds mainly to  $\alpha 4\beta 1$  integrin which is constitutively expressed on lymphocytes, monocytes and eosinophils.<sup>79</sup>

VCAM-1 can mediate both rolling and firm adhesion. Although it is structurally similar to ICAM-1, VCAM-1 has a unique pattern of regulation. It is not expressed in basal conditions, but is rapidly induced by pro-atherosclerotic conditions.<sup>47,79</sup> It is induced by IL-4 and high concentrations of ROS oxidized LDL-C.<sup>80</sup>

The relation of VCAM-1 concentrations with anthropometric markers is also controversial. Some researches show a positive correlation with BMI,<sup>15,16,17,22</sup> WC and WHR,<sup>14</sup> while Miller and Cappucio<sup>19</sup> did not show any significant results between VCAM-1 and BMI after adjustment for age, sex, smoking status and ethnicity. Recently, Souza et al.<sup>81</sup> observed an inverse correlation between VCAM-1 and BMI, when studying apparently healthy women, and showed that for every increase of 1 kg/m<sup>2</sup> in BMI, there was a reduction of 1,7 ng/mL in its concentrations. Thus, there is still a gap in understanding the mechanisms that explain pathophysiological changes that make obesity a risk factor for increased CAMs.

Results that point to a decrease in concentrations of VCAM-1 as a result of weight loss are also contradictory. Ziccardi et al.<sup>22</sup> demonstrated significant reduction of VCAM-1 after a year of nutritional intervention with low-calorie diet in obese women, while Keogh et al.<sup>23</sup> observed a slight increase (5%) in concentrations for 8 weeks with two types of hypocaloric diet, one low in carbohydrates and high in saturated fat and the other high in carbohydrates and low in saturated fat. Although weight loss reduces adiposity and consequently reduces this molecule, this result may be due to the effect of excess fat or carbohydrate in both diets on endothelial function, since such excesses may cause lipogenesis.

Besides distribution of macronutrients, dietary patterns may also influence concentrations of VCAM-1. Individuals whose diets were based on processed foods, high glycemic index, few fruits and vegetables had significantly higher concentrations than those who had higher intake of fish, poultry, fruits, vegetables and whole grains.<sup>66,67</sup> Moreover, supplementation of w-3 polyunsaturated fatty acids significantly reduced this molecule in hypercholesterolemic individuals<sup>68</sup> with coronary artery disease.<sup>82</sup>

Biochemical parameters show little evidence of the relation with concentrations of VCAM-1 in healthy or obese individuals. Positive association of this molecule with triacylglycerols,<sup>83</sup> IR<sup>32</sup> and total cholesterol and negative association with HDL-c<sup>16</sup> were observed. Nevertheless, evidences indicate that VCAM-1 is one of the major CAMs involved in atherosclerotic lesions and it is the first CAM to be expressed before the development of atherosclerotic plaques.<sup>45</sup> Its high concentration increases the risk by 2.8 times for future cardiovascular events.<sup>84</sup>

Therefore, contrary to the expected, some studies show that VCAM-1 may have an inverse relation to BMI and weight loss, which suggests that other factors may be involved in its stimulation and/or depression. However,

dietary factors such as adequate food pattern and supplementation of w-3 polyunsaturated fatty acids positively influence the reduction of its concentrations. Similarly, total cholesterol, triglycerides, and IR show a positive correlation and HDL-C is inversely correlated with this molecule, being this the first CAM to be altered in the development of atherosclerotic plaques.

## Chemokines

Chemokines constitute a family of small chemotactic cytokines composed of heparin binding proteins that drive the migration of circulating leukocytes to sites of inflammation or injury.<sup>85,86</sup> These cytokines not only regulate cell chemotaxis by concentration gradients, but also adhesion.<sup>87,88</sup>

According to Lezama Asencio,<sup>88</sup> chemokines are involved in metabolic disorders. The main motivation for examining chemokines is how easily their expression can be documented in disorders associated with leukocyte infiltration.<sup>89</sup> The monocyte chemotactic protein (MCP-1), also named chemokine ligand 2 (CCL2), is a key chemokine in regulation of migration and infiltration of monocytes/macrophages involved in chronic inflammatory diseases.<sup>90</sup>

### *Monocyte chemoattractant protein-1 (MCP-1/CCL2)*

MCP-1 or CCL2 was the first human chemokine to be discovered. It is produced by many types of cell, including endothelial cells, fibroblasts, epithelial cells, smooth muscle cells, monocytes and microglial cells, constitutively or in response to extracellular stimuli such as oxidative stress, cytokines or growth factors. MCP-1/CCL2 and its receptors play a central role in development of inflammatory responses and are crucial for the recruitment of immune cells to sites of inflammation.<sup>90</sup>

In obese humans and rodents, MCP-1/CCL2 is expressed by adipose tissue and increases proportionally to adiposity.<sup>6,7,91,92</sup> A study of two independent cohorts with obese individuals showed that concentrations of MCP-1/CCL2 increased with obesity, especially with intra-abdominal visceral fat,<sup>93</sup> which is expected since this fat deposit is highly lipolytic. Thus, its concentrations are associated with BMI, visceral fat and WC.<sup>31,59</sup>

Moreover, its reduction is related to weight loss in individuals with severe obesity. A weight loss of 12% in obese individuals resulted in a reduction of 20% in its concentrations ( $p < 0,001$ ).<sup>94</sup> Thus, it is suggested the importance of reducing adipose tissue in improvement of endothelial activation.

Simultaneously with changes in anthropometric measures as a result of obesity, MCP-1/CCL2 is negatively correlated with HDL-C and positively with IR. These findings indicate that MCP-1/CCL2 can be a potential candidate linking obesity with metabolic complications, such as atherosclerosis and diabetes.<sup>31</sup>

The relation of MCP-1/CCL2 with diet has been poorly described. In humans, a study by Zemel and Sun<sup>27</sup> using diets rich in calcium and dairy products resulted in significant suppression when comparing with low calcium diet. The reason for this is probably because the decrease in intracellular calcium concentration induced by high levels of this nutrient in the diet reduces the synthesis of fatty acid synthase and consequently reduces lipogenesis and increases lipolysis. This is a possible mechanism for the effect of dietary calcium in modulating adiposity. In rats, a high fat diet increases the expression of MCP-1/CCL2. Thus, it is suggested that there is an influence of diet composition on the expression of this chemokine.<sup>95</sup>

MCP-1/CCL2 also plays a key role in the pro-inflammatory pathways in vascular endothelium and development of atherosclerosis, situation in which its concentration is high. By using MCP-1/CCL2 in knockout mice to examine atherosclerosis, studies have shown that the absence of this chemokine significantly reduces deposition of lipids in arteries and formation of atherosclerotic lesions.<sup>86,90</sup>

This way, the relation of MCP-1/CCL2 with anthropometric markers and body composition is well established, especially with intra-abdominal visceral fat, being reduction in its concentrations influenced by weight loss. In parallel, diets rich in calcium are also related to its concentration, but more studies should be conducted in order to understand if dietary pattern and macronutrient distribution also influence positively the reduction of MCP-1/CCL2 once this chemokine is a strong link between obesity and its metabolic complications.

## Conclusion/perspectives

The importance of CAMs and chemokines in subclinical inflammation, which can lead to development of metabolic syndrome, obesity and other chronic diseases, is well understood, being this a bidirectional process.

All molecules reviewed here relate positively with an anthropometric marker as BMI, WC, WHR, but studies also show that there is no relation of ICAM-1 with BMI after adjustment for age, sex, smoking status and ethnicity, while for VCAM-1 there may be an inverse relation, its concentrations may be higher in those with lower BMI. As for the body composition, both E-selectin and MCP-1/CCL2 are positively associated with type of fat, being the visceral one more strongly related to its concentrations. However, for P-selectin, VCAM-1 and ICAM-1, both subcutaneous and visceral abdominal fat were not associated with its concentrations.

Weight loss, whether due to hypocaloric diets with different macronutrient distribution or surgical, influences positively the reduction in concentrations of all CAMs and chemokines studied, except for VCAM-1 in which distribution of macronutrients can influence more than calorie reduction, which suggests that other

factors may be involved in its stimulation and/or depression.

Besides distribution of nutrients, high consumption of trans fatty acids, saturated fat and a Western dietary pattern are associated with increased concentrations of CAMs. In contrast, individuals that supplement w-3 fatty acid in diet, have a healthy dietary pattern and a diet rich in calcium and dairy products and have lower concentrations of these molecules and MCP-1/CCL2.

Regarding biochemical parameters, all molecules and the chemokine have inverse relation of their concentrations with HDL-C and positive relation with total cholesterol and triglycerides. In addition, all molecules have positive relation with fasting glucose, fasting insulin and IR, being the ICAM-1 also related to postprandial glycemia.

Therefore, although there were significant progress in understanding the involvement of E-selectin, P-selectin, VCAM-1, ICAM-1 and the chemokine MCP-1/CCL2 in regulating subclinical inflammation, studies linking these CAMs to anthropometric markers, body composition, biochemical and dietary parameters in healthy and obese individuals are still needed to elucidate these associations and mechanisms, since these are contributing factors for cardiovascular events due to its inflammatory effects on vascular endothelium.

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