Obesity and Coronary Artery Disease: Role of Vascular Inflammation

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Abstract

Obesity is becoming a global epidemic. Around 1.1 billion adults and 10% of the world's children are currently overweight or considered obese.

Generally associated with risk factors for cardiovascular disease, such as Diabetes Mellitus and systemic arterial high blood pressure, the obesity has been more and more seen as an independent risk factor for Coronary Artery Disease (CAD).

Coronary arteriosclerosis comprises a series of inflammatory responses at cellular and molecular level, whose reactions are stronger in obese patients.

In the past, the adipose tissue was regarded as a mere fat deposition. Now it is seen from a totally different standpoint, as an active endocrine and paracrine organ that produces several inflammatory cytokines, such as the adipokines.

This article aims to raise awareness about obesity as an increasingly significant public health issue over the past decades, as well as to relate the intense inflammatory process in obese individuals with an increased tendency for this group of individuals to develop CAD.

Obesity as a health public issue

The obesity is currently considered as a global epidemic – an important health public issue, mainly to Western countries[1]. According to data recently published in the United States, 67% of adult individuals are overweight, while 34% % present obesity, representing an increase of 75% versus 1991 (Figure 1)[2]. For the first time in the History of mankind, the number of people who are overweight surpassed the people with malnutrition, amounting to more than one billion one hundred million people overweight people around the world.

Overweight is associated to an increasing morbidity and mortality. For instance, in the United States, for the first time since the Civil War, estimates are for a decrease in life expectancy arising out of diseases and disorders related to obesity - including high blood pressure, dyslipidemia, cardiovascular disease and some types of cancer[3].

Key words

Obesity; coronary artery disease; inflammation; protein C.

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In Brazil, data from the 2003 Brazilian Household Budget Survey revealed that the overweight affects 41.1% of men and 40% of women. Out of this percent, 8.9% of adult men and 13.1% of adult women are considered obese[4]. Thus, we may consider obesity as the most common risk factor found in industrialized and developing countries (Figure 2).

Obesity as a risk factor for coronary artery disease

The association with classic risk factors for cardiovascular disease, such as arterial high blood pressure, Diabetes Mellitus, dyslipidemias and metabolic syndrome, is known for very long time now. However, more recent findings reveal that, even after the control of these associated diseases, the risk of cardiovascular events remains high, which makes obesity to be considered an independent cardiovascular risk factor[5].

The association of obesity with clinically significant coronary artery disease is blatant in two classical prospective studies highly consulted: the Framingham Heart Study[6] and the Nurses Health Study[7].

The relative risk for Coronary Artery Disease (CAD) for adults with body mass index (BMI) of 21 kg/m² increased from 1.19 for patients with BMI from 21 to 22.9 kg/m², and to 3.56 in patients with BMI higher than 29 kg/m² (Table 1).

The Asia Pacific Cohort Collaboration Study[8], with segment higher than 7 years and involving 430,000 adults, found an increase of 9% in ischemic cardiac events for each unit of change in BMI.

Relationship between obesity and death due to cardiovascular disease is even more conspicuous when concerning patients with abdominal obesity. In the Tandolapril Cardiac Evaluation (TRACE) study, a database analysis showed an increase in mortality around 23% compared to patients without abdominal obesity. This study disregarded Diabetes and arterial high blood pressure influences[9].

When patients with diagnosed cardiovascular disease or after acute myocardial infarction are analyzed, the increase in BMI is inversely correlated to the increase of mortality[10].

The overweight associated to fat accumulation in mesenteric region refers to a central, visceral or androgenic obesity[11]. The so-called visceral obesity is well-known as associated to a higher mortality than the peripheral obesity. The cause of this difference lies in the fact that the visceral adipose tissue visceral is more metabolically active than the subcutaneous adipose tissue, causing, for instance, a higher glucose production and, consequently, type 2 Diabetes Mellitus and hyperinsulinism. This higher insulin secretion causes sodium retention, resulting in systemic arterial high blood pressure[12]. These conditions

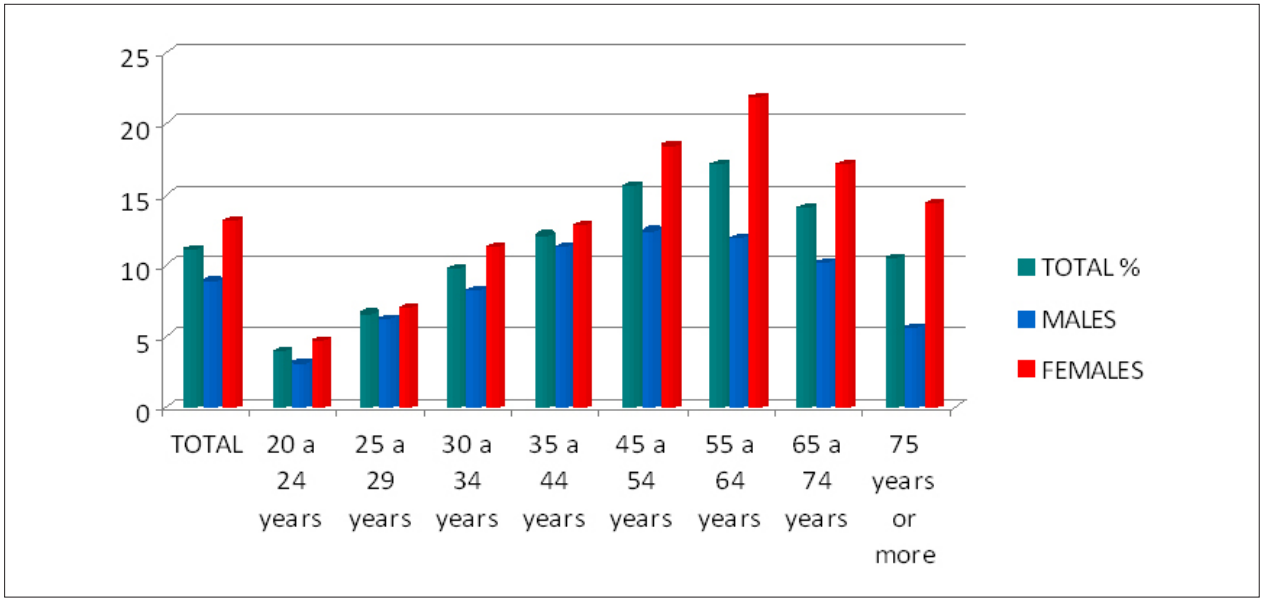

Figure 1 - Prevalence of obesity, in 20-year-old individuals or more, per gender, according to age groups on Brazil in 2003 (%)[4].

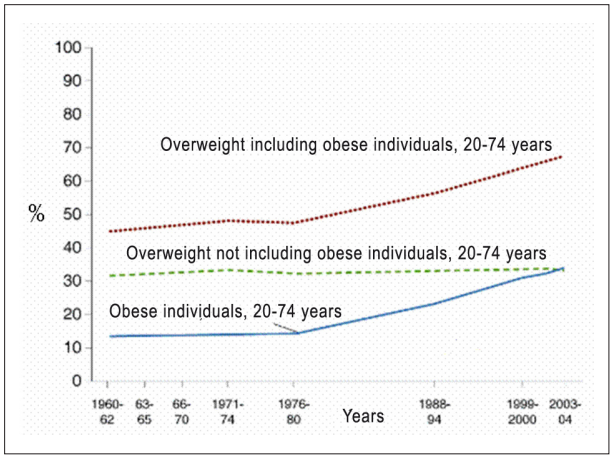

Figure 2 - Overweight and obesity: Increase of 75% since 1991 in the United States.

Table 1 - The risk increases for diseases related to obesity insofar as the Body Mass Index (BMI, kg/m²)[4] increases

Disease	BMI <25	BMI 25-29,9	BMI 30-34,9	BMI ≥35
Type 2 diabetes	1.00	2.42	3.35	6.16
Biliary calculi	1.00	1.97	3.30	5.48
High blood pressure	1.00	1.92	2.82	3.77
Arthritis	1.00	1.56	1.87	2.39
CVA	1.00	1.53	1.59	1.75
Cardiovascular disease	1.00	1.39	1.86	1.67

characterize metabolic syndrome, considering currently a challenge for public health, once it represents a substantial increase in the risk of Diabetes Mellitus (twice), as well as of cardiovascular disease (twice to thrice)[13].

Obesity, coronary artery disease, and vascular inflammation

For many years, the physiopathology of arteriosclerosis was considered merely as an accumulation of lipids on the arterial wall. However, over the two past decades, the growing development in the field of vascular biology has been elucidating the nature of atherosclerotic lesions: in fact, they correspond to a series of cellular and molecular responses highly specific and dynamic, with an inflammatory character[14,15].

In vulnerable patients, arteriosclerosis develops through the influence of stress conditions to the endothelium, such as aging, systemic arterial high blood pressure, hypercholesterolemia, Diabetes, tobacco addiction and obesity itself. These factors damage the endothelium and spur on an inflammatory/proliferative reaction on the vascular wall. Such reaction increases the secretion of primary proinflammatory cytokines, such as interleukin (IL)-1 and the tumoral necrosis factor-alpha (TNF-A). They are responsible for the expression of leukocyte adhesion molecules, by the intercellular adhesion molecule (ICAM)-1 and P-, E-, and L-selectins, and by the increase of chemotactic substances (monocyte chemotactic protein-1 [MCP-1] and the macrophage colony-stimulating factor [M-CSF], both amplifiers of the inflammatory cascade)[16,17] (Table 2).

Obesity is characterized as an excess of adipose tissue, with consequent weight gain, and associated with several comorbidities[18]. Regarded as a mere deposition of triacylglycerol and free fatty acids in the past, now the adipose tissue is seen as

an important endocrine and paracrine organ, which produces several proinflammatory substances[19].

In the process of differentiation of preadipocytes into mature adipocytes, the latter began capable of producing a number of proteins: enzyme, cytokines, growth factors and hormones involved in several metabolic events[20].

Components of adipogenesis include the lipoprotein lipase, angiotensinogen, adipsin, adiponectin, IL-6, prostaglandin, TNF-A and nitric oxide. These molecules have modulating action of lipid depositions and body fat distribution[21].

More recently, the adipose tissue is being regarded as a source of proinflammatory mediators which contribute to vascular injury, insulin resistance and atherogenesis. The adipokines, as known nowadays, include: TNF-A, IL-6, leptin, plasminogen activator inhibitor 1 (PAI)-1, angiotensinogen, resistin and C-reactive Protein (CRA). Some of them have a protective role against vascular inflammation and insulin resistance, namely: the adiponectin and the nitric oxide, among others[18].

The adipokines are found high in obese patients and in patients with insulin resistance, and are more produced by the abdominal adipose tissue than in other places. The weight loss is associated with the decrease of these substances[22].

Main inflammatory markers in obesity

C-reactive protein

The CRA is an acute phase protein (APP) synthesized in the liver and regulated by the circulating levels of IL-6. In their turn, IL-1 and TNF-A may induce expression of messenger RNA for production of CRA. Recently, high levels of CRA in plasma were considered as independent predictors of Coronary Artery Disease[23]. Circulating plasma levels of CRA are high in obese and are directly related to the amount of body fat, estimated by means of body mass index, visceral obesity, abdominal circumference, insulin resistance, metabolic syndrome and Diabetes Mellitus[24].

The CRA is not a mere marker of inflammatory activity: it participates directly in the process of atherogenesis and modulates the endothelial function. It also induces the expression of several molecules (ICAM-1, VCAM-1, MCP-1 and selectins). It acts as regulator of the production of nitric oxide in the endothelium and coordinates the production and secretion of several cytokines, increasing the proinflammatory activity of several adipokines[25].

Table 2 – Effects of adipokines in vascular homeostasis

Adiponectin	Inhibits the expression of ICAM-1, VCAM-1 and E-selectin. Inhibits the transformation of macrophages in foam cells.
Angiotensinogen	Diminishes the proliferation and migration of vascular smooth muscle cells. Diminishes the availability of nitric oxide. Inhibits the angiogenesis. Stimulates the expression of ICAM-1, VCAM-1, MCP-1 and M-CSF.
C-reactive Protein	Diminishes the availability of nitric oxide. Increases the release of IL-6. Stimulates the expression of ICAM-1, VCAM-1, MCP-1, selectins in endothelial cells. Inhibits the angiogenesis. Increases the collection of LDL-C in endothelial cells. Stimulates apoptosis of endothelial cells. Increases the proliferation and migration of smooth muscle cells and restenosis.
IL-6	Stimulates the expression of ICAM-1, VCAM-1, MCP-1, and E-selectin. Increases the proliferation and migration of smooth muscle cells.
Leptin	Increases production of nitric oxide. Increases proliferation and migration of smooth muscle cells and endothelial cells. Increases the apoptosis of smooth muscle cells. Increases the angiogenesis. Increases the release of MCS-F. Increase the accumulation of cholesterol in hyperglycemic conditions.
PAI-1	Increases the thrombogenesis. Increases the restenosis.
Resistin	Increases the release of endothelin-1. Increases the expression of adhesion molecules.
TNF-A	Diminishes the bioavailability of nitric oxide. Diminished vasodilation. Stimulates the expression of ICAM-1, VCAM-1, MCP-1, selectins in endothelial cells and smooth muscle cells. Increases the apoptosis of endothelial cells.

PAI - plasminogen activator inhibitor; TNF - tumor necrosis factor; ICAM - intercellular adhesion molecule; VCAM - vascular cell adhesion molecules; MCP - monocyte chemotactic protein; M-CSF - macrophage colony-stimulating factor; IL-interleukin; LDL-C - low-density cholesterol lipoprotein[21].

Leptin

The leptin is a specific adipocyte hormone, which functions as a signaling molecule in the brain, which makes it complete the negative feedback of the lipostatic theory of weight control[26]. The knowledge that obese individuals are not mostly leptin-deficient, rather, to the contrary, they have high serum concentrations of these substances, set the stage for the leptin resistance theory[2].

In this vein, resistance to leptin may be explained by a low sensibility to the action of the hormone or by the high leptin serum levels that could lead to an improper response (relative leptin deficiency).

The leptin resistance theory became noticeable after a dose scaling study of recombining leptin, randomized and placebo-controlled, obtained disappointing results while trying to evaluate the weight loss after injecting recombining leptin. Serum concentration twenty to thirty times higher were necessary for the weight loss[27]. It is not clear why high serum concentrations of endogenous leptin are found in obese individuals and in individuals resistant to leptin. One knows, however, that these high levels and exogenous supplements of leptin are not sufficient to keep a healthy weight.

There are several theories that explain this mechanism, but none was scientifically proved: genetic mutation, self-regulation, tissue access limited by the blood-brain barrier and the action of molecules in cellular and circulatory levels.

There are many therapeutic implications of fighting resistance to leptin, insomuch this condition seems to be associated to various risk factors for CVD and other pathological conditions, such as obesity, metabolic syndrome, resistance to insulin, type 2 Diabetes Mellitus, systemic arterial high blood pressure, atherothrombosis and myocardial disease.

TNF-A

High amounts of secretion of inflammatory cytokine produced by obese individuals and by insulin-resistant patients not only give rise, but spread the formation of atherosclerotic lesion. The TNF-A participates in the acceleration of atherogenesis by inducing the expression of VCAM-1, ICAM-1, MCP-1 and E-selectin. It also reduces the bioavailability of nitric oxide in endothelial cells and impairs endothelium-dependant vasodilation, promoting the endothelial dysfunction. Besides this, is causes apoptosis in endothelial cells, contributing for endothelial injury[28].

Resistin

It is a hormone specific of the adipose tissue recently discovered, which directly induces the insulin resistance in muscles and liver. The resistin induces the expression of messenger RNA producer of endothelin-1 in endothelial cells, thus contributing to endothelial dysfunction. It also significantly increases the expression of the cellular adhesion molecule VCAM-1 and the MCP-1, hey factors in formation of early atherosclerotic lesion[29].

It was recently demonstrated the proinflammatory action of resistin in smooth muscle cells: it induces the proliferation of such cells, suggesting the action of these hormones is restenosis of coronary lesions in patients with Diabetes[30].

Angiotensinogen

It is a precursor of angiotensin II, expressed and produced in adipocytes. The angiotensin II directly stimulates the expression of ICAM-1, VCAM-1, MCP-1 and M-CSF in vascular cells. The increased production of angiotensinogen by the adipose tissue is associated with high blood pressure and angiogenesis, both related to endothelial dysfunction. Similarly, the angiotensin II acts in the formation of oxygen-derived free radicals, decreasing the availability of nitric oxide and causing damages to the vascular tissue[31].

Adiponectin

Opposed to what happens to other adipokines already referred to, the levels of adiponectin are lower in obese patients, functioning and an inhibitor agent of the inflammatory process[32]. Clinical and experimental studies suggest that low levels of adiponectin contribute for the development of diseases related to obesity, including cardiovascular diseases[33].

Levels of adiponectin in plasma generally range from 3 to 30 μg/ml in healthy individuals. In obese individuals, these levels are significantly reduced, with negative correlation between BMI and adiponectin levels in plasma[34]. The reason for the reduction of the levels of adiponectin in obese individuals seem to be related with proinflammatory cytokines, such as the IL-6, which, due to the fact they increase in obese individuals, may cause a reduction in the expression of the messenger RNA producer of adiponectin and its release by adipocytes[35].

In vascular levels, actions of the adiponectin comprise reduction in expression of ICAM-1, VCAM-1 and E-selectin. They also inhibit the transformation of macrophages in foam cells and the proliferation and migration of smooth muscle cells[36].

Qasim et al., in a sub-analysis of the database of SIRCA (*Study of Inherited Risk of Coronary Atherosclerosis*), examined the association between leptin and adiponectin and the risk factor for CVD and coronary arterial calcification (CAC). The plasma leptin associated positively with the CAC after adjustment for age, gender, traditional risk factor and Framingham risk score (Tobit regression relationship of 2.42 [IC 95%: 1.48 – 3.95; p=0. 002]). In their turn, the levels of plasma adiponectin did not associate to the CAC[37] (Figure 3).

Endothelial dysfunction present in obesity: cardiovascular worsening factor

The coronary endothelial dysfunction is considered an early stage of the coronary arteriosclerosis and may occur in epicardic vessels, resistance vessels or both[38]. Suwaidi et al[39] assessed the impact of obesity in coronary endothelial function in patients with normal coronary or slightly sick coronary when examined with angiography. A total of 397 consecutive patients with such characteristics were subject to coronary vascular reactivity using intracoronary adenosine, acetylcholine and nitroglycerin. The patients were divided

into three groups, based on the Body Mass Index (BMI), since the one considered normal (BMI < 25 kg/m²), until the overweight group (BMI from 25 to 30 kg/m²) and the obese patients (BMI > 30 kg/m²). The increase in coronary flow as a response to acetylcholine was significantly lower than in the group of obese patients than in the of patients with normal BMI (see Figure 4). By means of multivariate analysis, the group of overweight and obese patients was independently associated to coronary endothelial dysfunction. The study demonstrated that the obesity is independently associated to coronary endothelial dysfunction in patients with normal coronaries under angiography exam or else with mild coronary artery disease.

Therapeutic implications

The overweight leads not only to changes in the development of insulin resistance, but also influences the process of endothelial dysfunction by means of proinflammatory and prothrombotic effects of adipokines. The treatment which aims at reducing the percent of body fat, as well as the visceral fat, tends to reduce such effects[40].

The magnitude of the protective effect seems to be related with the reduction of the body mass index. In overweight women who experience slight weight loss (>10%), a reduction of up to 20% % in premature mortality was found, also associated to the control of risk factors, such as Diabetes Mellitus, dyslipidemia and systemic arterial high blood pressure[41].

The current knowledge that the production of adipokines is increased in obesity and insulin resistance conditions leads to a new field of research aiming at developing treatments that interfere in this situation.

Measures not related to use of drugs, such as change of life style, are still the crux of the treatment. Drugs such as glitazons, estatins, acetylsalicylic acid, angiotensin converter enzyme inhibitors and angiotensin receptor blockers are being tested and seem to be active in the decrease of anti-inflammatory adipokines[2] (Table 3).

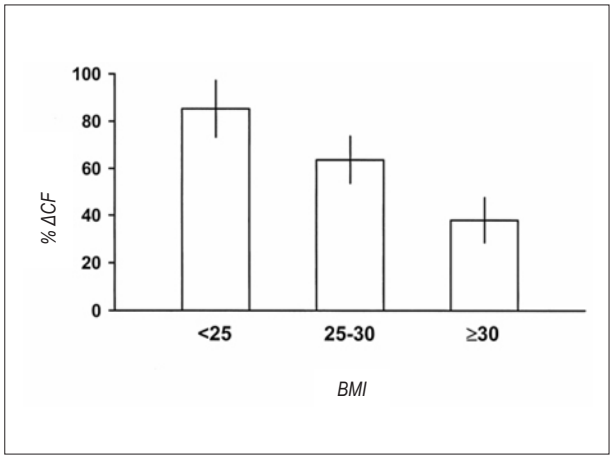

Figure 4- Average (± SD) of the percentage alterations of coronary flow (% ΔCF) as a response to acetylcholine in the studied patients. BMI: Body Mass Index (kg/m²)[29].

Table 3 - Therapeutic interventions that possibly interfere in the adipokine metabolism[22]

Diet
Physical exercise
Estatins
Acetylsalicylic acid
Inhibitors of angiotensin-converting enzyme
Angiotensin receptor blockers
Tiazolidinediones

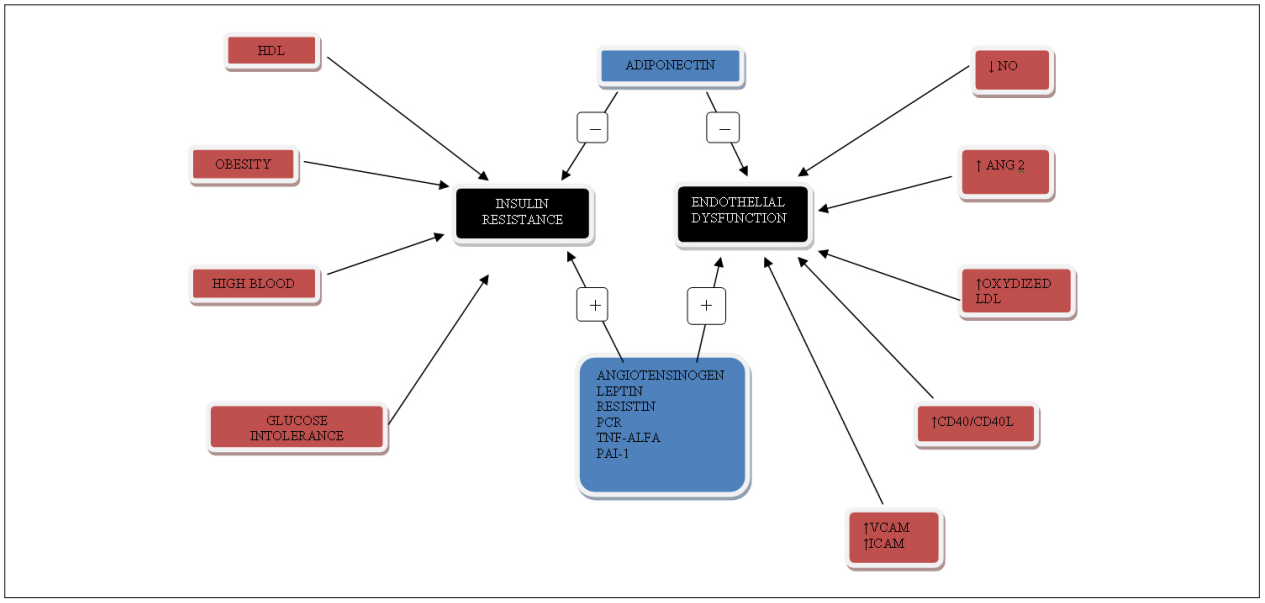

Figure 3 - Role of adipokines in insulin resistance and endothelial dysfunction.

Conclusions

The obesity is a chronic metabolic disorder associated to the CAD, with increase indexes of morbidity and mortality. The inflammatory process causes not only endothelial dysfunction, but also triggers cellular proliferation and migration, oxidative stress, apoptosis, thrombus and cellular necrosis. The adipokines have an important role in this process, mainly in endothelial dysfunction. The weight loss, although not scientifically proven to decrease mortality, seems to reduce risk for CAD and Diabetes Mellitus, mainly in obese individuals.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any post-graduation program.

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