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Review Article

Obesity: Role of Tumor Necrosis Factor-α and of Other Adipocytokines Involved in the Chronic Inflammation and the Immune and Metabolic Dysregulation

Tania Beatriz Romero-Adrián*

Graduate Studies in Immunology, Faculty of Medicine, University of Zulia, Venezuela, Institute of Biological Research, Faculty of Medicine, University of Zulia, Venezuela

***Corresponding Author:** Tania Beatriz Romero- Adrián, Physician, Pediatrician, Parasitologist, Magister Scientiarum in Clinical Immunology and Doctor of Medical Sciences, Graduate Studies in Immunology, Faculty of Medicine, University of Zulia, Institute of Biological Research, Faculty of Medicine, University of Zulia, Venezuela.

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Abstract

Obesity has been declared by the World Health Organization (WHO) as a "global epidemic" due to its high prevalence. It known that genetic, nutritional, metabolic and immunological factors predispose to the obesity. This pathology is considered a chronic inflammatory condition of low grade, which affect the immune and metabolic homeostasis, and is one of the critical processes associated with development of insulin resistance, diabetes and related diseases. Prolonged caloric overload leads to adipose expansion with adipocyte hypertrophy. Tumor necrosis factor-α (TNF-α) induces the gene expression of various inflammatory cytokines and chemokines. The secretion of monocytes chemoattractant protein (MCP-1), and cytokines, such as TNF-α, interleukin-1 (IL-1) and interleukin-6 (IL-6), cause infiltration of the immune cells and adipocyte dysfunction. The over-nutrition, smoking, physical inactivity and the ageing appear to contribute to the development of vascular dysfunction. Endothelial dysfunction associated with TNF- α in pathophysiological conditions is linked to excess production of reactive oxygen species and a decrease in nitric oxide bioavailability. TNFα is involved in the regulation of the carbohydrate and lipid metabolism among other biological actions and have important influence on others adipocytokines, such as: adiponectin and leptin produced by the white adipose tissue. TNFα inhibits to the adiponectin that is anti-inflammatory and stimulates to the leptin that is proinflammatory which reveal its harmful effect in obesity. When a cytokine as TNF-α is in high concentrations cause immune and metabolic dysregulation since make up a network with other elements of the system, and the adverse consequences only could demonstrate by scientific studies.

The prevention of the obesity is the key element that includes: exercise, a complete, harmonic, sufficient and adequate nutrition guided by a specialist and regular medical control to maintain health and to avoid organic consequences that limit the time of life.

Keywords: *Obesity; Adipose Tissue; TNF- α; Adipocytokines; Adiponectin; Leptin; Dysregulation*

Introduction

Obesity is a pathological clinic condition in which intervene genetic, nutritional, metabolic and immunological factors, also, plays an important role in the development of health problems. The high prevalence of obesity is a global public health problem due to, its association with several pathologic conditions such as: arterial Hypertension, dyslipidemia, atherosclerosis, type 2 diabetes, insulin resistance, psychosocial alterations, apnea obstructive of sleep, cancer and other entities [1] that reduced lifespan [2].

WHO defines obesity as "a condition in which percentage body fat (PBF) is increased to an extent in which health and well-being are impaired, and, due to the alarming prevalence increase, declared it as a "global epidemic" [3]. WHO report that "Every year at least 2.8 million people die of obesity or overweight. Although previously was considered a problem confined to high-income countries, obesity is currently prevalent in low and middle income countries" [4].

The current classification of Obesity proposed by the WHO is based on the Body Mass Index (BMI), which relate the weight expressed in kilos and the square of height, expressed in meters. When the BMI calculation is equal to or greater than 30 kg/m^2 are in presence of obese people. Based on the above, the classification is as follows: Normo Weight 18.5 - 24.9 (kg/m^2) Risk associated with health: Average. Excess Weight ≥ 25 (kg/m^2). Overweight or Pre-Obese 25 - 29.9 (kg/m^2), Risk associated with health: increased. Obesity Grade I or moderate 30 - 34.9 (kg/m^2), Risk associated with health: moderate increase. Obesity Grade II or severe 35 - 39.9 (kg/m^2), Risk associated with health: severe increase. Obesity Grade III morbid ≥ 40 (kg/m^2) Risk associated with health: very severe increase [3]. Researchers consider necessary to classify obesity condition on the basis of body fat composition and distribution, rather than simply on the increase of body weight. The body mass index (BMI) of a subject, used to easily approximate body fat percentage and stratify people into categories, leads to a misclassification [5].

Adipose tissue (AT) is divided into white adipose tissue (WAT) responsible for the storage of fat and the secretion of cytokines and brown adipose tissue (BAT), which is responsible for thermogenesis. In rodents, BAT is a heat-producing adipose tissue located in interscapular, subscapular, axillary, perirenal, and periaortic regions [6]. The supraclavicular and paravertebral BAT distribution seen in adults appears to develop with puberty in boys and girls [7,8]. BAT cells differ from white adipose tissue (WAT) cells [9,10]. The BAT cells contain numerous small lipid vacuoles and a large number of well-developed mitochondria, whereas WAT cells are characterized by a single large lipid vacuole and a few mitochondria. Histologically, "beige" cells demonstrate an intermediate phenotype between classical BAT and WAT adipocytes [10]. Many studies have demonstrated that adipose tissue macrophages (ATMs) are responsible for increased proinflammatory cytokines and may contribute to obesity associated inflammation, insulin resistance, and metabolic dysfunction [11]. The accumulation proinflammatory immune cells in obese adipose tissue exacerbates the immunometabolic dysfunction and could be a potent stimulus for accelerating ageing in obesity [12]. The growth and function of tissues is dependent of their vascularization. The factors associated with adipose tissue angiogenesis are: angiopoietin-like 4, hepatocyte growth factor, placental growth factor, fibroblast growth factor-1, leptin, adiponectin and others. In obesity, impaired vascularization is associated with adipose tissue malfunction and metabolic disease risk [13].

We discuss the role of a proinflammatory adipocytokine known as TNF-α and other factors in obesity and its influence to systemic level which determine important alterations, conditioned by events interne or extern, to the establishment and development of diseases. This review provide very important guidelines and reflection, since this cytokine is an acute phase reactant together with Interleukin-1 and Interleukin-6 and its increase upsets all the organic systems, especially in obese patients with co-morbidities.

TNFα: Biological actions and its interconnection with other relevant factors in obesity

Prolonged caloric overload leads to adipose expansion with adipocyte hypertrophy. TNF-α induces the gene expression of various inflammatory cytokines and chemokines. Then, there is a secretion of monocytes chemoattractant protein (MCP-1), and cytokines, such as TNF-α, IL-1, and IL-6, causing infiltration of the immune cells [14]. Increased secretion of proinflammatory cytokines, including MCP-1 and TNF-a, induces additional macrophage recruitment and adipocyte dysfunction [15,16]. These serial inflammatory changes in AT induce a chronic state of inflammation strongly implicated in the metabolic dysregulation. Obesity is considered a state of chronic low grade inflammation which is one of the critical processes associated with development of insulin resistance, diabetes and related diseases [17].

Clinical observations and basic research have indicated a potential link between inflammation and alterations of the lipid and carbohydrate metabolism in obesity. One of cytokines or regulating proteins with a close relationship is TNF-α which belongs to the superfamily of the TNF. The members of this superfamily participates in inflammation, proliferation, invasion, angiogenesis, apoptosis, metastasis and

morphogenesis. The relation with immunologic, cardiovascular, pulmonary, neurologic and metabolic diseases is evident. However, other regulating proteins or cytokines can, act in pleiotropic, synergist, antagonist and redundant form, make up a network with unpredictable results [17].

Tumor necrosis factor-α (TNFα) is a cytokine predominantly produced by activated macrophages and to a lesser by other cell types. Activated TH1 cell that secreted TNF-α and TNF- β activate endothelium to induce macrophage binding and exit from blood vessel at site of infection. TNFα is involved in the inflammation, cellular proliferation, apoptosis and morphogenesis with important participation in the regulation of the carbohydrate and lipid metabolism [17]. Studies in mice have demonstrated increase of cytokine release in obesity and identified increase of the expression of TNFα in the adipose tissue of obese mice. The levels of the cytokine correlate with degree of adiposity and the associated insulin resistance [18]. In insulin resistant states, the cytokine acts mostly in an auto- and paracrine manner in adipose tissue [19] and skeletal muscle [20]. TNF-α is highly overexpressed in the AT of obese humans and rodents, and their blockade leads to increases in insulin sensitivity [18,19].

Risk factors such as by over-nutrition, smoking, physical inactivity and aging appear to contribute to the development of vascular dysfunction. TNF- α mediated signaling initiates and accelerates vascular oxidative stress, the vascular inflammation and cell infiltration, increases atherosclerosis, vascular remodeling, thrombosis and endothelium apoptosis. Exercise and diet supplement reduce the risk of vascular dysfunction by inhibiting of TNFα production [21]. TNF receptor signaling via the TNFR1 and TNFR2 appears to mediate the effects of exercise on cognitive-like behaviors [22]. Also, the exercise appears to suppress other pro-inflammatory factors such as reactive C protein and Interleukin-6, and augment anti-inflammatory factors as Interleukin-4, Interleukin-10, transforming growth factor-β and adiponectin [23]. Endothelial dysfunction associated with TNF- α in pathophysiological conditions is linked to excess production of reactive oxygen species and a decrease in nitric oxide bioavailability. It have demonstrated that TNF-α participates in the disruption macrovascular and microvascular circulation both *in vivo* and *in vitro* [21].

It known that is necessary the expression of cell membrane receptors for that TNF-α interacts with them. When an undifferentiated T cell is activated expresses several proteins besides cluster of differentiation 28 (CD28) that has a support or modifies the costimulatory signal that drives clonal expansion and differentiation. It have described transmembrane TNFα receptors in humans, TNFR1 (p60) and TNFR2 (p80). The number of TNF receptors, major histocompatibility complex (MHC) class II molecules, B7 molecules, CD40 on the macrophages surface can increase, making the cell more effective at presenting antigen to fresh T cells. Mice lacking of TNF receptor show increased susceptibility to pathogens. Soluble forms of those receptors (sTNFR1 and sTNFR2) are present in plasma and it is supposed that their concentrations, especially sTNFR2, might reflect local action of TNFα in tissues [24]. Soluble TNFR might neutralize TNFα at high levels and stabilize its bioactivity [25]. Adipose tissue TNFR2 mRNA, the protein and plasma levels of sTNFR2 are increased in obesity and related to insulin resistance [24,26]. However, there were no differences in relation to TNFR1 levels. Other authors reported an increase of adipose tissue expression [27] and plasma levels [28] of both receptors in obese subjects. Plasma TNFα values are usually low and do not give the precise information about its auto- and paracrine action. However, there are contradictories results. Soluble TNFR2 might serve as the best predictor of local TNFα system activity [24].

Studies have demonstrated that TNFα might to be an important factor determining plasma cholesterol levels. The cytokine induces an increase in serum cholesterol and in hepatic hydro-3-methyl-glutaryl coenzyme A reductase activity in mice [29]. TNFα also induces maturation of sterol regulatory element binding protein-1 (SREBP-1), an important transcription factor in cholesterol biosynthesis [30]. There is an evidence that *TNFR2* gene polymorphism is associated with hypercholesterolemia [31] and coronary artery disease [32].

TNFα levels correlate significantly with the concentrations of very-low-density lipoprotein (VLDL), triglyceride (triacylglycerol) and cholesterol, and negatively with high density lipoprotein (HDL) cholesterol [33]. Atorvastatin and simvastatin decrease TNFα levels in patients with hyperlipidemia and hypercholesterolemia [34-36]. Patients with type IIa and IIb dyslipidemia have an abnormal pattern of TNFα [37]. TNFα blockade could significantly affect lipid metabolism. This have been demonstrated with the administration of anti-TNF-monoclonal antibody as adalimumab and infliximab in patients with active rheumatoid arthritis [38,39]. TNF-α is a key cytokine in the metabolic syndrome which is characterized by abdominal obesity, hypertension, diminish level of HDL, elevated triacylglycerols and high fasting glucose. Also, constitutes an important risk factor in atherosclerosis and type 2 diabetes [23].

Many investigations have demonstrated the influence of TNFα on others adipocytokines as adiponectin and leptin. In the first case, the TNFα inhibit la adiponectin and this inhibit to TNFα. Adiponectin has regulatory functions in the carbohydrate and lipid metabolism. Also, stimulates fatty acids oxidation, reduces plasma triglycerides, improves glucose metabolism and increase the insulin sensitivity and reduces macrophages to foam cell transformation. In general terms, the factors that diminish the plasma levels of adiponectin in human are: obesity, age , male sex, indo-Asian ethnic group, circadian rhythm (night), size of adipocytes, insulin resistance, type 2 diabetes, arterial coronary disease, gestational diabetes, TNF-α, IL-6, catecholamine, glucocorticoids among other factors. The augment of adiponectin it is noted in: female sex, Caucasian ethnic group, loss of weight by hypocaloric diet or gastric bypass. This adipocytokine has a mayor expression in the adipocyte and its encounter in plasma levels of 5 - 30 ug/ml [40].

Other adipocytokine is the Leptin that is produced by adipocytes and stimulated by TNF-α. Regulates the control of appetite and body weight, the metabolism and the energetic homeostasis, decreases the secretion of insulin stimulated by glucose, augment the blood pressure, the heart rate and actives immune cells among other biological actions. After eating, augment the leptin which decreases the appetite. The obese people or with overweight are resistant to the effect of leptin reason why they gain weight. The influence of TNF-α is evident since it inhibits adiponectin and stimulates leptin when its concentrations are high and affects the functions of the adipocytokines cited [40,41].

Studies recent demonstrate that the Obesity is associated with down response to anti-TNF, therapy in patients with rheumatic diseases, but not in patients with inflammatory bowel disease [42]. More investigations are required due to the systemic and metabolic complexity of obesity

Conclusions

The inflammation, the production of reactive oxygen species, endothelial apoptosis and dysfunction, lipid and carbohydrate metabolism alterations, metabolic and immune dysregulation, as consequences of the augment of TNF-α in obesity are key elements in the chronic affectation of the health of subjects with over-nutrition and co-morbidities that aggravate its condition. The prevention of the obesity, with adequate diet, exercise, contention of stress, is determinant to avoid consequences adverse organic that limit the time of life. Despite the government politics and of the programs of the WHO, the obesity it has converted in a global epidemic and "Every year at least 2.8 million people die of obesity or overweight".

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