Acta Scientific Cardiovascular System

Volume 1 Issue 7 December 2022

Review Article

Obesity and the Genesis of Cardiovascular Risk: A Review

Carcagnì Addolorata*

Department of Cardiology, Centro Cuore Carcagnì, Campobasso, Italy

***Corresponding Author:** Carcagnì Addolorata, Department of Cardiology, Centro Cuore Carcagnì, Campobasso, Italy.

Received: November 16,2022

Published: November 23, 2022

Abstract

Obesity has been growing at an alarm rate worldwide Several evidence highlights the role of obesity in the development cardiovascular risk and ischemic diseases. Visceral fat contributes to a systemic inflammatory state and circulating mediators of inflammation participate in the mechanisms of vascular damage in obese patients. Moreover, these inflammatory proteins cause insulin-resistance leading to FRC appearance and cardiovascular disease

This review shows how the obesity causes inflammatory state and insulin resistance enhancing cardiovascular risk.

Keywords: Obesity; Inflammation; Insulin-Resistance; Cardiovascular Risk

Introduction

Obesity is a pathological condition that has been growing at an alarm rate worldwide [1]. The World Health Organization (WHO) has reported that it has tripled in the last 40 years. Its etiology is multifactorial and may be due to genetic and hormonal factors, but it is mainly caused by an increased calories intake associated to sedentary life [1].

Fat tissue is 20% visceral and 80% superficial [2]. The superficial adipocytes have high sensitivity to insulin and a greater ability to store excess fatty acids, protecting other tissues from lipotoxic effects in obesity. Visceral cells, instead, have a greater endocrine activity. When visceral adipose tissue increases in obesity, it produce many metabolites playing an important role in the onset of the inflammation and insulin-resistance; and it is frequently associated with cardiovascular risk factors (FRC) [2]. Central obesity frequently cause the onset of diabetes mellitus type II, dyslipidemia, and hypertension [3-6]. The coexistence of these FRC in subjects with central obesity seems to have an exponential effect in determining cardiovascular diseases, and not simply an additive effect [7]. The strengthening condition the effect of FRC is insulin-resistance, which correlates with the volume of the visceral adipose tissue but not with superficial fat [2,6]. Therefore, it is important not only the presence of obesity, but also how adipose tissue is distributed [3,4].

The aim of this review is to highlight how obesity determines the inflammatory and insulin-resistance state that cause the onset of major FRC and cardiovascular disease.

Visceral fat, inflammation and insulin resistance

Adipocytes increase in volume because the accumulation of fatty acids in obesity. However, although fat has the ability to store excess fatty acids by hypertrophying, visceral fat shows less of this ability and tends to present more colliquative phenomena when it increases in volume [2].

In initial phase, the adipocyte hypertrophy is associated with an increased number of adequate local capillaries, but subsequently the angiogenesis is insufficient and tissue ischemia may appear [3,6,8]. Tissue ischemia determines oxidative-stress of the adipocytes with consequent production of reactive oxygen

species (ROS), that leads to cell damage and apoptosis [8]. Furthermore, the activation of intracellular pathways, linked to the stress of the endoplasmic reticulum, facilitate the production of pro-inflammatory cytokines that activate the immune system. Quiescent macrophages are present in adipose tissue, mainly in visceral fat. In normal condition, these "resident" macrophages produce anti-inflammatory cytokines, such as interleukin-10 (IL-10) and control the activation of adipocyte inflammatory pathways [8]. In presence of visceral obesity, instead, the adipocyte cytokines activate the "resident" macrophages that change phenotypically, transforming themselves into "recruited" macrophages capable of producing substances such as Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6) [6,8]. Adipocyte and macrophages cytokines recruit circulating monocytes into the visceral fat and contribute to the amplification of inflammation. When cytokines enter the bloodstream of the portal vein and reach the liver, systemic inflammation onset [3,6,8].

Therefore, in the first phase the inflammation is local and aims to repair/destroy damaged adipocytes; but over time, local inflammation can become systemic.

High levels of circulating adipocytokines, such as TNF-α, IL-6, leptin, resist in and adiponectin, play a central role in the pathogenesis of obesity-related insulin resistance [3,6]. The increased plasma levels of these substances and free fatty acids (FFAs) cause alterations in the structure or expression of the cellular receptor insulin: the lipoprotein lipase (LLp) [3]. Reduced LLp-activity of peripheral tissue leads to that high quantities of glycerol and FFAs reach the liver. Here, the more insulin-sensitive lipase (HLp) promotes the synthesis of triglycerides that leads not only to an increased production of endogenous VLD-lipoproteins (VLDLs), but also to their accumulation into the hepatocytes [3,6,9]. The liver becomes steatosis [9].

The accumulation of lipids in hepatocytes leads to cell damage with mechanisms similar to those already described for adipocytes [9,10]. Also, in the liver the ischemia tissue causes hypoxia and oxidative-stress with activation of cellular pathways leading to the production of large quantities of ROS. Moreover, hepatocytes produce and release multiple inflammatory cytokines including IL-8, TGF-beta, MCP-1 and TNF-α. [10]. The production of local ROS and cytokines favors the development of further liver damage and over time contributes to the progression of steatosis, that may lead to the appearance of tissue fibrosis typical of non-alcoholic liver disease and cirrhosis [9,10]. Over time, the persistence of ischemia transforms local inflammation into a systemic inflammatory response, such as occurs in visceral fat, and increases the systemic inflammatory state [3,6,9].

Central obesity, therefore, is associated with a systemic inflammatory state due to the production of high quantity of cytokines by adipocytes, activated monocytes/macrophages and also hepatocytes. These inflammatory substances enter the bloodstream and reach various parts of the body, amplifying insulin resistance and causing the onset of FRC and cardiovascular disease (Figure 1).

Figure 1: Adipocytes, activated monocytes/macrophages and also hepatocytes produce cytokines and cause inflammation and insulin resistance.

The cardiovascular risk

Insulin is the hormone that controls the metabolism of carbohydrates, lipids and proteins; with insulin-resistance appearance all of these metabolic controls are altered (Figure 2).

Figure 2: Insulin -resistance and the cluster of FRcs associated.

- **Diabetes**: In the first stage of insulin resistance, pancreatic insulin secretion increased both in fasting and in the post-prandial phase. Therefore, normal blood glucose levels are achieved by increasing serum insulin concentrations, typical of the pre-diabetic phase [10,11]. Over the time, the reduced production of this hormone by the pancreas lead to the reduction in circulating insulin levels and the onset of fasting hyperglycemia, typical of diabetes type II [6,11].
- **Dyslipidemia:** Iinsulin resistance is associated also to a peripheral lipolysis due to the effect of glucagon activity. Accumulation of FFA and glycerol in the bloodstream and subsequently in hepatocytes is accompanied by increased production of very low-density lipoprotein (VLDLs) by the liver [9-10]. These lipoproteins are rich in triglycerides and are the precursors of low-density lipoprotein (LDLs). Normally LDLs are reuptake into the liver by HLp, but HLp activity is reduced in insulin-resistance and consequently the LDLs increases in the bloodstream [9-10]. At the same time, high-density lipoproteins (HDLs) are reduced by increase kidney elimination of Apo-A proteins. Therefore, insulin resistance due to central obesity is associated with hyperglycemia, hypertriglyceridemia, an increase in cholesterol, especially LDL, and a reduction in HDLs [6,10].
- **Hypeuricemia:** Insulin controls not only the glucose or lipid metabolism, but also the protein metabolism. This hormone, in fact, facilitates the entry of amino acids into the muscle and plays an important role in protein synthesis. The frequent finding of high uric acid levels in patients with insulin-resistance is due to hyperinsulinemia [13]. High serum levels of insulin reduce the renal excretion of uric acid and facilitate its increase in the blood. This leads to the activation of pathways that transform uric acid in oxidated uric acid. Therefore, oxidated uric acid becomes a molecular capable to damage the vessels endothelium and in particular the capillaries of the kidney [14].
- **Hypertension:** Hypertension is common in obese patients [3,5,6]. Also, the mechanisms that favor hypertension in these patients are related to hyperinsulinemia [15,16]. Insulin-resistance associated with hyperinsulinemia causes an increase in the activity of the sympathetic nervous system to limit the increase in body weight [15]. Insulin stimulates the production of catecholamines directly through a baroreceptor reflex. Plasma norepinephrine is increased in patients with insulin-resistant and hypertension [16]. The increased activity of the sympathetic system leads to the activation of the renin-angiotensin system with sodium retention and hypervolemia. A greater renal sodium reuptake, not compensated by natriuresis, can also be favored in these obese patients by the coexistence diabetic nephropathy [15]. In addition, hyperinsulinemia causes the release of norepinephrine from sympathetic system and increase intracellular Ca ++ and vasoconstriction [15]. Moreover, insulin is an important growth-factor and stimulates the smooth muscle cells of vessels [15]. Insulin can stimulate smooth muscle cell proliferation directly or by increasing levels of other growth factors such as PDGF and IGF-1. Therefore, hyperinsulinemia is associated to higher peripheral resistance at rest because hypertrophy and hyperplasia of the vessels muscle cells.

All these insulin-mediated mechanisms contribute to the onset of hypertension in subjects with obesity and insulin resistance.

FRCs play an important role in causing endothelial damage and thus trigger the mechanisms that lead to the atherogenesis [3,6,10]. The alteration of the endothelium, however, is only one of the process phases. The atheroma begins when LDLs enter into the intima of the vessel wall after endothelial damage, activating the monocytes of the blood (Figure 3). To do this the LDLs must be oxidized. The LDL oxidation process can take place in the bloodstream or directly into the vessel wall [18]. Certainly, high LDLs blood concentration is a favorable condition for plaque process; but the oxidation of LDLs (LDLox) and their transformation into free-radicals is the fundamental condition. In the inflammatory state associated with obesity, the presence of elevated circulating ROS has the ability to activate the oxido-reductase present on circulating leukocytes, endothelium and smooth muscle cells of vessels with production of LDLox [18].

Vessel narrowing caused by atheroma is associated with the most common cardiovascular diseases; but the most feared event is atherothrombosis.

Atherothrombosis is caused by a sudden rupture/erosion of an atheromatics plaque because high concentrations of ROS and

Figure 3: Atheromatic plaque formation.

cytokines due to systemic inflammation, and can cause acute events such as myocardial infarction and stroke.

Conclusions

Central obesity cause a dysmetabolic state associated to a cluster of FRCs capable of developing cardiovascular problems. The coexistence of central obesity with these FRCs seems to have an exponential and not simply additive effect in determining cardiovascular problems. Insulin-resistance is the strengthening factor in this type of patient.

Furthermore, visceral adipose tissue plays an important role in the development of the systemic inflammatory state. The circulating inflammatory factors participate not only in the vascular damage and in the onset of the atheroma; but also play an important role in the plaque destabilization favoring atherothrombosis and acute syndromes.

Therefore, the cardio-metabolic risk has been always evaluated in patients with central obesity and insulin resistance must be prevented.

Bibliography

1. WHO: Obesity and overweight.
2. Walker GE., *et al.* "Obesity modifies expression profiles of metabolic markers in superficial and deep subcutaneous abdominal adipose tissue depots". *Endocrine* (2014): 99-106.
3. Carcagnì A. "Obesity, inflammation and cardiovascular risk: the genesis of atheroma". *Outpatients Cardiology* (2021): 31-42.
4. Karastergiou K., *et al.* "Sex differences in human adipose tissues - the biology of pear shape". *Biology of Sex Differences* (2012): 3-13.
5. Andersen GF., *et al.* "Confronting Chronic Disease in Countries". *New England* (2007): 209-2011.
6. Berg AH., *et al.* "Adipose Tissue, Inflammation, and cardiovascular disease". *Circulation Research* (2005): 939-949.
7. Pencina MJ., *et al.* "Predicting the 30-year risk of cardiovascular disease: the Framingham heart study". *Circulation* (2009): 3078-3084.
8. Cottam DR., *et al.* "The chronic inflammatory hypothesis for the morbidity associated with morbid obesity: implications and effects of weight loss". *Obesity Surgery* (2004): 589-600.
9. Lomonaco R., *et al.* "Effect of adipose tissue insulin resistance on metabolic parameters and liver histology in obese patients with nonalcoholic fatty liver disease". *Hepatology* (2012): 1389-1397.
10. Schaffler A., *et al.* "Mechanisms of disease: adipocytokines and visceral adipose tissue--emerging role in nonalcoholic fatty liver disease". *Nature Clinical Practice Gastroenterology and Hepatology* (2005): 273-280.
11. Bray GA., *et al.* "Clinical evaluation of the overweight patient". *Endocrine* (2000): 167-186.
12. DeFronzo RA., *et al.* "Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease". *Diabetes Care* (1991): 173-179.
13. Yu W and Ji-Dong Cheng. "Uric Acid and Cardiovascular Disease: An Update from Molecular Mechanism to Clinical Perspective". *Frontiers in Pharmacology* (2020).
14. Yuri YS and Johnson RJ. "Uric Acid: the oxidant-antioxidant paradox". *NN Nucleic Acids* (2008): 608-619.
15. Novo G., *et al.* "Impact of insulin resistance on cardiac and vascular function". *International Journal of Cardiology* (2016): 1095-1099.

16. Reaven GM., *et al.* "Hypertension and associated metabolic abnormalities. The role of insulin resistance and the sympathoadrenal system". *The New England Journal of Medicine* (1996): 334-374.

17. Fuster V., *et al.* "Atherothrombosis and High-Risk Plaque: Part I: Evolving Concepts". *Journal of the American College of Cardiology* (2005): 937-954.

18. Violi F., *et al.* "Role of NADPH oxidase in atherosclerosis". *Future Cardiology* (2009): 83-92.