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Obesity and Its Influence on Mediators of Inflammation: Clinical Relevance of C-Reactive Protein in Obese Subjects

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Abstract

The rising prevalence of overweight and obesity in the world has been described as a global pandemic, with marked variations across countries in the levels and trends in overweight and obesity with distinct regional patterns. Concern about the health risks associated with rising obesity has become nearly universal. In this chapter, a systematic review that was conducted in four databases (Web of Science, MEDLINE, Scopus, CINAHL), using the MeSH terms [obesity, inflammation, disease management, C-reactive protein (CRP)] is presented. Based on the above, the aims of this work are to provide information on the relationship between obesity and circulating levels of CRP, to describe the basic chemical structure and functions, and to analyze its clinical usefulness in obese patients. The available scientific evidence justifies the need to include determining the values of high-sensitivity C-reactive protein (hs-CRP) among clinical screening tests on obese subjects to evaluate the cardiovascular risk, among other risks.

Keywords: obesity, inflammation, C-reactive protein, clinical relevance, cardiovascular risk

1. Introduction

The rising prevalence of overweight and obesity in the world has been described as a global pandemic at all stages of life worldwide [1]. Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health with serious health complications and increases the risks of morbidity and the prevalence of several health complications, such as type-2 diabetes, hypertension, atherosclerosis, dyslipidemia, prothrombotic state, insulin

resistance, cardiovascular disease, metabolic syndrome, and various types of cancers [2]. A complex interaction between the environmental factors, genetic predisposition, and human behavior is the cause of the current obesity pandemic [3]. Obesity has been linked strongly with metabolic abnormalities including increased blood pressure [4], increased blood sugar [5], and lipid profile abnormalities [6]. Furthermore, obesity has been predisposed to metabolic abnormalities via inflammatory process [7]. In the state of obesity, the pro-inflammatory adipokines, derived from adipose tissue, are overexpressed, increased production, and secretion of inflammatory mediators: interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF- α) [8, 9]. The increased circulatory levels of inflammatory mediators particularly IL-6 have been associated with hepatocyte stimulation to synthesize and produce a low-grade systemic inflammation marker C-reactive protein (CRP) [8]. This protein was discovered in 1930 by Tillet and Francis, being insulated in the serum of patients with acute inflammatory processes. Upon its discovery, it was thought that C-reactive protein levels could be a pathogenic secretion for its high levels in patients with multiple pathologies. Finally, the discovery of its synthesis and secretion in the liver closed this discussion [10]. Currently, PCR serum represents an effective clinical indicator of infectious and inflammatory processes in the body, and therefore, it can be used to determine the risk of heart disease and to predict metabolic syndrome and diabetes mellitus [11]. In this sense, the systemic inflammation represented by increased level of high-sensitivity CRP (hs-CRP) has been classified as a characteristic feature and an essential cause of many illness conditions including metabolic syndrome [12], atherosclerosis [13], coronary heart disease [14], and cancers [15]. Based on the above, the aims of this work were to provide information on the relationship between obesity and circulating levels of CRP, to describe the basic chemical structure and functions, and to analyze its clinical usefulness in obese patients.

2. Overall structure

CRP is a protein of the pentraxins group, which is distinguished by its conformation in the space, presenting pentameric form of annular disc (see **Figure 1**). Structurally, it is composed of five identical subunits unglycosylated and linked by noncovalent bonds that depend of calcium binding to exert their action [16]. From a functional perspective, the active forms of PCR are the pentameric or native structure (p-n-PCR or PCR) and the monomeric isoform (m-PCR). This latter is formed by a dissociation process of the p-PCR. The monomeric isoform may appear linked to membranes or free in plasma, changing their functions in each case [17]. The pentameric isoform has two faces, one with ability to adhere to the phosphatidylcholine in the presence of calcium ions [18], while the other presents adhesion sites for complement component C1q and Fc receptors. The existence of five subunits with capacity to bind together phosphatidylcholine determines its high avidity for phosphatidylcholine [18]. This interaction occurs during the identification of microorganisms such as bacteria, fungi, and parasites showing phosphatidylcholine in their membrane [19]. Once identified pathogens, adherence to C1q occurs on the other side of the pentamer, activating partially the complement pathway and adhering to factor H [17]. This mechanism is a first defensive barrier in our organism against certain pathogens.

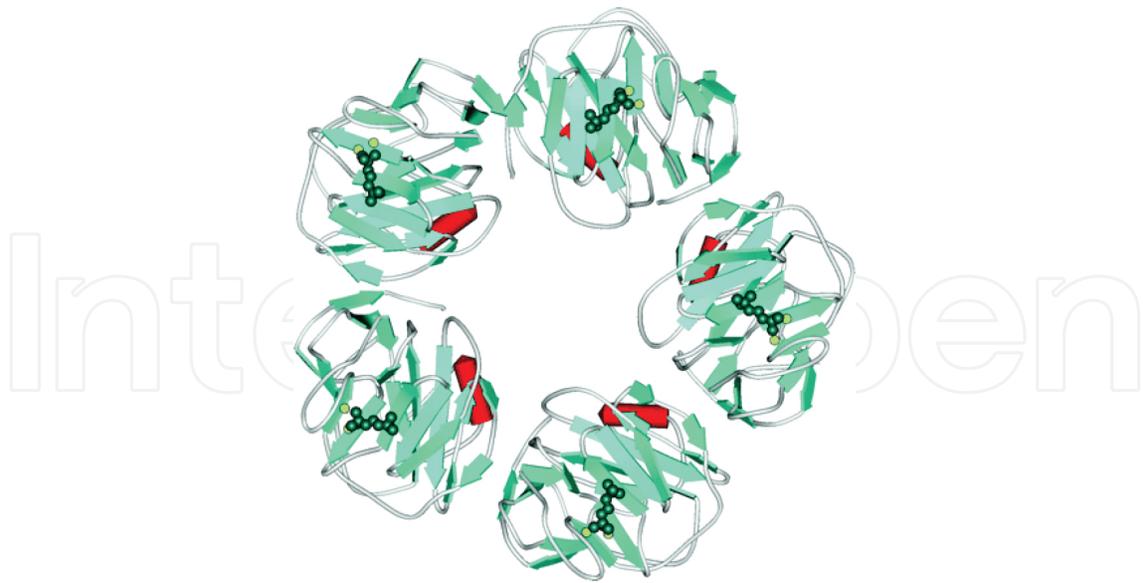


Figure 1. Crystal structure of C-reactive protein complexed with phosphocholine from Thompson et al. [50].

3. Functions and clinical significance in obese subjects

CRP is synthesized in hepatocytes in response to stimulation of interleukin 6 (IL-6) [20], being their serum concentrations higher among obese subjects [21]. It is an acute phase reactant protein whose plasma levels are elevated rapidly during a tissue damage or aggression and according to the intensity, reaching its peak in 24–48 h. This increase is due to an increase in the plasma concentration of IL-6, which is produced by macrophages [22], endothelial cells, T cells, and adipocytes [23]. When the inflammatory process ceases, within a period of 3–7 days, the CRP returns to normal values.

PCR is deposited in anatomical locations in which inflammatory processes occur, as in the intima of arteries [24]. In this location, PCR could participate in LDL capture by macrophages in atherosclerotic plaque and thus be related to the development of atherosclerosis [25, 26]. Also, it is known that CRP directly induces the production of other inflammatory cells and decreases the expression of nitric oxide synthase [27], participating actively in the atherogenic process. The first evidence of the relationship between circulating CRP levels and the development of coronary artery disease were published in 1954, showing an elevated CRP levels in patients with acute myocardial infarction [28]. However, it will be during the decade of the nineties when studies show the independent prognostic value of CRP in primary and secondary prevention of coronary artery disease [29, 30]. Currently, by the ultrasensitive method [31], it can be detected levels of hs-CRP required to the prediction of cardiovascular risk [32]. Based on this method, the American Heart Association (AHA) [33] recommends the following ranges for predicting cardiovascular risk: <1.0 mg/L low risk, 1.1–3.0 mg/L moderate risk, and 3.1–10.0 mg/L high risk. hs-CRP values in the above ranges have shown sensitivity and specificity for early detection of vascular events, not just in coronary arteries, also in the peripheral circulation and brain in obese subjects [34]. Thus, in the study by Jager et al. [35] on

a population of 2484 individuals, researchers concluded that CRP was an important predictive value for cardiovascular mortality, especially in association with other risk factors such as obesity. Other recent studies have shown a direct association between elevated plasma levels of hs-CRP and the occurrence of cardiovascular accidents, both in individuals without cardiovascular disease [36, 37], and in individuals with previous cardiovascular disease [38]. In this sense, hs-CRP has demonstrated to be a sensitive and specific marker for early identification of individuals with cardiovascular risk, especially among obese subjects [39]. On the other hand, prospective studies show that CRP levels in the general population and especially in obese subjects is a strong predictor of future coronary events, stroke, peripheral artery disease, congestive heart failure, and cardiovascular mortality in general [40], with a continuous gradient of cardiovascular risk over the whole of their serum levels. In addition, serum levels of CRP may be an indicator of subclinical atherosclerosis, correlating its concentration with intima-media thickness [41] and with the calcification degree of the coronary arteries [42]. Pande et al. [43], in their study with a population of 3000 patients, described higher levels of CRP in patients with peripheral arterial disease. Ridker et al. [44], from a population greater than 13,000 subjects and assessing different inflammatory markers, including CRP, also found a statistically significant correlation between CRP levels and the risk of peripheral arterial disease. In addition, in a five-year follow-up in a small cohort of 150 patients, the authors conclude that those subjects who developed peripheral artery disease had higher average CRP values during the monitoring period. In this sense, Vainas et al. [45], in a sample greater than 300 patients with peripheral arterial disease, they conclude that the severity of peripheral arterial disease was correlated with serum CRP levels.

In the recent study, Gaillard et al. [46] were studied 1116 pregnant women with obesity. The study was developed during the second trimester of pregnancy and evaluated the serum levels of CRP in the mothers and fetus's fat mass. The authors concluded that higher second-trimester maternal CRP level was associated with higher mid-childhood overall and central adiposity.

Other studies have shown that the obesity is a negative prognostic factor after diagnosis of breast cancer [47]. There are evidences that propose a greater amount of adipose tissue will increase the susceptibility of the patients to metastasis development [48]. Several mechanisms have been proposed to explain the adverse effect of obesity on survival among women with breast cancer, including alteration in cytokines profiles such as CRP [49]. In this sense, alteration in acute phase proteins such as CRP in obese patients may exaggerate the inflammation status [47]. Owing to the fact that the inflammation has the potential to prone the patients toward later distant metastasis, it is necessary to regulate and control the levels of CRP among other cytokines. Nevertheless, the exact mechanisms in which obesity and CRP levels may influence breast cancer are not well known and need more research for its clarifying [47].

4. Conclusions

In conclusion, the available scientific evidence justifies the need to include determining the values of hs-CRP among clinical screening tests on obese subjects to evaluate the cardiovas-

cular risk, among other risks. CRP is an important clinical parameter in the early detection of atherosclerotic disease and thus for the prevention of cardiovascular disease in people with obesity. Its possible influence as an inflammation marker in the prognosis of cancer patients is another important aspect that needs further study. However, even considering the scientific evidence, new prospective studies are necessary with larger populations to acquire solid and extrapolable results to citizenship.

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