Diabetes & Metabolic Syndrome: Clinical Research & Reviews xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Review

Complement 3 serum levels as a pro-inflammatory biomarker for insulin resistance in obesity

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
C3
C3a-desArg
ASP

ABSTRACT

Introduction: Obesity is frequently characterized by chronic inflammation and insulin resistance (IR). Obesity-associated inflammation is responsible for the complement system activation of which the third component (C3) plays the central role.
Objective: to discuss several aspects of the central component of the complement system in relation to obesity and obesity-associated IR.
Methods: A critical review of the relevant published English articles from 2003- 2014 was carried out using several search engines including PubMed, Google Scholar, and ScienceDirect. Keywords were used, including complement system, C3, obesity-induced inflammation, IR, ASP, and adipose tissue.
Conclusion: The defect in the adipose tissue secretory function during obesity may result in different metabolic disorders including IR. The C3 role during obesity-associated inflammation in IR is emerging. More longitudinal studies are warranted to evaluate the role of C3 among other pro-inflammatory biomarkers for IR.

Contents

1. Introduction

Obesity is one of the most emerging health problems throughout the world. The prevalence of the disease has increased in the last decades, reaching epidemic proportions along with obesity-related non-communicable diseases [1,2]. In 2014, the World Health Organization's global database (2015) revealed that 1.9 billion adults were overweight; of them nearly 600 million were diagnosed with obesity contributing to 13% of adults aged 18 years and older.

Accumulated evidence indicated that obesity is associated with chronic, low grade inflammation, characterized by macrophage infiltration and elevated levels of pro inflammatory biomarkers [3,4]. Remarkably, obesity-induced subclinical inflammation is responsible for the activation of the complement system [4]) of which the third component (C3) is the central component [5] C3 has been found to have a positive association with various measures of body fat (BF) [5,6] It has also been linked with insulin resistance (IR) or hyperinsulinemia, metabolic syndrome, and type 2 diabetes mellitus (T2DM) [5,7,8]. Therefore, the objective of this review is to discuss several aspects of the main component of the

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http://dx.doi.org/10.1016/j.dsx.2016.12.036
1871-4021/

complement system (C3) in relation to obesity and obesity-associated IR.

2. Etiology of obesity

Obesity is a complex multifactorial chronic disease that can also become manifest in childhood and adolescence [9]. Obesity results mainly from an imbalance between the energy ingested in food and the energy expended as the excess energy is stored in adipocytes that enlarge in size (hypertrophy) and/or increase in number (hyperplasia) [10]. The etiology of obesity can be categorized into three main categories: (1) factors that affect caloric and nutrient intake, (2) physical activity levels or intensity, and (3) genetic factors [11]. Although the three domains are definitely playing a role in the development of obesity, Al-Domi [10] mentioned that the underlying mechanisms that lead to a failure in the adaptation mechanisms remain not clear.

3. Obesity-induced inflammation

White Adipose tissue (WAT) is an active tissue, which exerts systemic endocrine effects by expressing many pro-inflammatory cytokines such as, tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), interleukins (IL) (such as IL1, IL6, IL10 and IL8), plasminogen activator inhibitor-1 (PAI-1), fibrinogen, monocyte chemoattractantprotein-1 (MCP-1) and anti-inflammatory factors such as adiponectin [3]. AT is a heterogeneous tissue that besides adipocytes contains connective tissue matrix, nerve tissue, stromovascular cells (i.e. preadipocytes, fibroblasts, endothelial cells, histiocytes and macrophages), and immune cells [12,13].

During obesity, adipocytes undergo hypertrophy and hyperplasia followed by progressive macrophages and other immune cell infiltration, hypoxia, angiogenesis, death of adipocyte cells, free fatty acids (FFA) release and extracellular matrix overproduction [12,14]. Consequently, abnormal production of pro-inflammatory adipokines and reduced production of other adipokines with anti-inflammatory properties are observed, which in turn will result in low grade, chronic inflammation [14]. Adipocytes and macrophages regulate the subclinical inflammation in AT in a paracrine fashion, macrophages start to secrete pro-inflammatory cytokines with their receptors on the surface of adipocytes, a condition that will enhance more lipolysis, and thus more FFA will bind toll like receptor-4 (TLR-4) on the surface of macrophages enhancing them to produce more pro-inflammatory biomarkers [3]. Moreover, adipocytes will begin to secrete low levels of pro-inflammatory biomarkers, such as TNF-α that will stimulate pre-adipocytes and endothelial cells to produce MCP-1 attracting more macrophages to AT [14,15].

Interestingly, AT contains large numbers of T cells, but during the progression of obesity more $CD8^+$ (cytotoxic T cells) infiltrate in AT than $CD4^+$ (T helper cells). This increment of $CD8^+$ T cells will induce more macrophage infiltration in AT, and hence amplifying the local inflammation [16]. Nevertheless, macrophages show heterogeneity in function, modified by local environmental factors. M1 or "classically activated" and M2 or "alternatively activated" are the two separate polarization states of macrophages [3]. M1 macrophages enhance pro-inflammatory cytokine production (e.g. TNF-α, IL-6, IL-12) and reactive oxygen species (e.g. NO) [17]. whereas M2 macrophages are involved in the repair or remodeling of tissue as they enhance anti-inflammatory cytokine production (e.g. IL-10 and IL-1) and arginase enzyme, which blocks NO production by a variety of mechanisms [17,18]. During the course of AT expansion, M1 phenotype macrophages will recruit in the AT while the dominant macrophages of lean AT are M2 [3]. Fig. 1 illustrates obesity-induced inflammation.

4. The complement system

The complement system is an integral part of both the innate and acquired immune response, consisting of a network of proteins that integrate with each other in cascades of stepwise proteases activation [19]. Its role in the defense against infectious microbes, disposal of cellular debris, synapse maturation, getting rid of immune complexes, angiogenesis and linking between innate and adaptive immune responses in the body are well known, but recently, the role of improbable management of the complement system against health is emerging [20].

Activation of any of the three pathways of the complement system (classic, alternative, and lectin pathways) leads to the cleavage by the convertase enzyme of the multifunctional protein

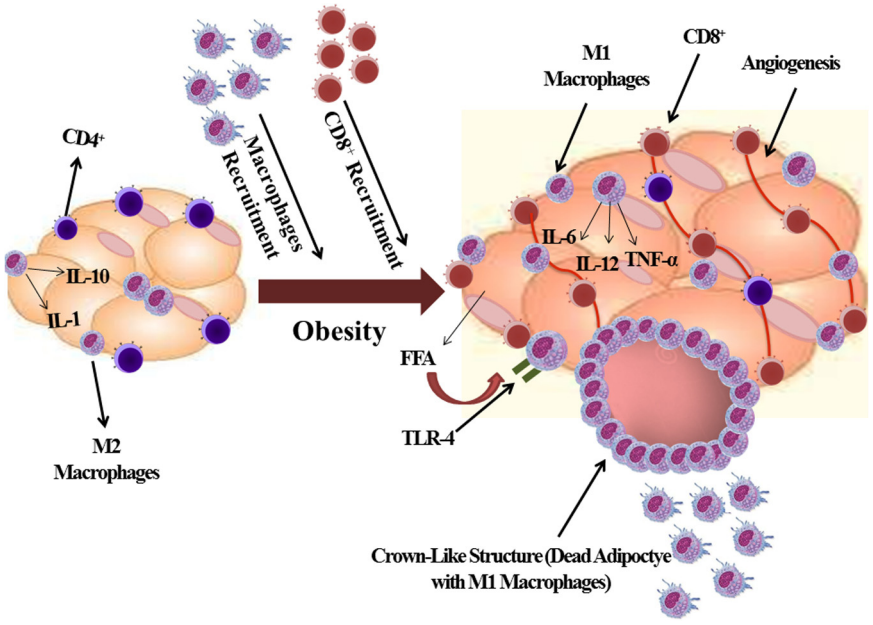

Fig. 1. Obesity-induced inflammation.

Please cite this article in press as: R.M. Al Haj Ahmad, H.A. Al-Domi, Complement 3 serum levels as a pro-inflammatory biomarker for insulin resistance in obesity, Diab Met Syndr: Clin Res Rev (2016), http://dx.doi.org/10.1016/j.dsx.2016.12.036