

## Editorial

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# Obesity Induced Inflammation – A Complex Condition

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The occurrence of overweight and obesity has risen around the world. This rate will increase in the future without appropriate interventions. Obesity is a condition with increased percentage of fat mass. Evidence based studies indicate that excess adiposity is accompanied with a proinflammatory state. This low grade chronic inflammation could initiate and progress the metabolic disorders such as insulin resistance, type 2 diabetes, endothelial dysfunction, atherosclerosis and several types of cancers.<sup>1</sup> There are outstanding differences between obesity induced inflammation and classic inflammation. Classic inflammation originates from the intense immune system response to an insult, results in Basal Metabolic Rate (BMR) increase and usually diminishes over time. In contrast, obesity induced inflammation is chronic, metabolic, moderate, and is associated with a reduced BMR. Some studies suggested the term “metaflammation” for this inflammatory condition.<sup>2</sup>

Adipokines are bio factors, which secreted from white adipose tissue. Variety physiologic and pathophysiologic roles of adipokines have been recognized in inflammation, immunity and metabolism.<sup>3</sup> The interplay between adipokines and inflammatory response may elucidate the process of diseases. In the obese state, the dysregulation of proinflammatory and anti-inflammatory adipokines could partly explain the inflammatory mechanism of obesity and its related consequences.<sup>4</sup> Furthermore, adipokines could play a potential role in physiopathology of many inflammatory and autoimmune diseases through their endocrine, paracrine and autocrine activities.<sup>5,6</sup>

A wide spectrum of proinflammatory adipokines ranging from the well-recognized classic ones such as IL-6 and TNF- $\alpha$ , to recently discovered peptides including resistin, lipocalin 2, RBP4 (retinol-binding protein 4) and ANGPTL 2 (angiopoietin-like protein) have been identified to be involved in metabolic disorders, insulin resistance and endothelial dysfunction.<sup>4</sup> On the other hand, anti-inflammatory adipokines including adiponectin, omentin, Zinc- $\alpha$ 2-glycoprotein (ZAG), Secreted Frizzled-Related Protein 5 (SFRP5), Interleukin-10 (IL-10), C1q/TNF-Related Protein (CTRP) family, Interleukin-1 Receptor Antagonist (IL-1RA), Transforming Growth Factor  $\beta$  (TGF- $\beta$ ), Growth Differentiation Factor 15 (GDF15) potentially could counteract with these disorders.<sup>7,8</sup>

To achieve a therapeutic strategy for various obese complications increasing the production of anti-inflammatory biomarkers is of special importance. The imbalance between proinflammatory and anti-inflammatory adipokines could be resolved to some extent by different interventions. Various pharmacological, lifestyle and dietary interventions have been examined as anti-inflammatory therapies in the obese state. However, there are controversies regarding the effectiveness of these interventions in altering the adipokines and more importantly insulin resistance in obesity. Among dietary interventions weight loss, omega-3 fatty acids and their metabolites Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) are the most studied examples. Others include investigating the effects of dietary patterns (Mediterranean, low fat diet, etc.), tomato juice, grape seed oil, nuts (walnut, almond, and hazelnut), green tea, rice bran, etc.

The point that should be noted is that despite the emphasis on the importance of increasing anti-inflammatory factors<sup>8</sup> and targeting the root causes of inflammation rather than merely inhibiting inflammatory factors,<sup>2</sup> most studies have focused primarily on suppression of well-known inflammatory mediators such as Interleukin-6 (IL-6) and Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ). This is a great disappointment that these interventions could not remarkably improve the major inflammation associated disorders including glucose homeostasis.<sup>9</sup>

To interpret the results it is required to respond to this basic challenging question that whether there is any benefit of suppressing metaflammation. In fact, despite the destructive effects of inflammation on insulin resistance and the metabolism of fat tissue, there may be potential benefits of inflammation in obesity, which has not been considered enough. Expanding evidence propose the essential role of proinflammatory cells and mediators in providing sufficient blood flow of adipose tissue through angiogenesis, regulation of metabolism, adipose tissue remodeling, and adipocyte differentiation,<sup>9</sup> however, these beneficial effects are the matter of discussion.

Proinflammatory cytokines including TNF- $\alpha$ , IL-6 and Interleukin-18 (IL-18) may exert different and even favorable effects in the obese state.<sup>9</sup> The proinflammatory factor IL-15 might be an example of the positive function of inflammation in obesity. According to recent studies, IL-15 lessens weight gain and lipogenesis probably by enhancing energy expenditure and activating brown fat. It has affirmative effects on improving insulin sensitivity and glucose metabolism too. IL-15 activates inflammation-associated pathways including IKK/NF- $\kappa$  B, JAK/STAT and PI3K/Akt.<sup>10</sup>

Accordingly, it seems that one of the reasons that many anti-inflammatory therapies did not show expected efficacy might be the simultaneous reduction of the advantages of inflammation.<sup>9</sup> Thus, we need to know whether the advantages of the suppression of this metabolic inflammation outweighs disadvantages. Moreover, to what extent we are allowed to neutralize the inflammation to prevent the inhibition of compensatory effects of inflammation and damage to the organism. Another interesting question would be whether we could perform purposive interventions with the aim to distinguish between positive and negative effects of inflammation.

In summary, future studies aimed at identifying inflammatory and anti-inflammatory adipokines and mediators, or evaluating the effectiveness of interventions on inflammation suppression should consider both the detrimental and potentially beneficial effects of inflammation. We require to further experimental and clinical studies, which improve and equilibrate our perspective on obesity-induced inflammation. Since we need to know how much the inflammation associated with obesity is compensatory and how much is destructive.

#### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

#### ACKNOWLEDGMENT

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