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Review

Adipokines in critical illness: A review of the evidence and knowledge gaps

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ABSTRACT

Adipose tissue products or adipokines play a major role in chronic endocrine and metabolic disorders; however, little is known about critical conditions. In this article, the experimental and clinical evidence of alterations of adipokines, adiponectin, leptin, resistin, visfatin, asymmetric dimethylarginine (ADMA), and ghrelin in critical illness, their potential metabolic, diagnostic, and prognostic value, and the gaps in the field have been reviewed.

The results showed considerable changes in the concentration of the adipokines; while the impact of adipokines on metabolic disorders such as insulin resistance and inflammation has not been well documented in critically ill patients. There is no consensus about the circulatory and functional changes of leptin and adiponectin. However, it seems that lower concentrations of adiponectin at admission with gradual consequent increase might be a useful pattern in determining better outcomes of critical illness. Some evidence has suggested the adverse effects of elevated resistin concentration, potential prognostic importance of visfatin, and therapeutic value of ghrelin. High ADMA levels and low arginine:ADMA ratio were also proposed as predictors of ICU mortality and morbidities. However, there is no consensus on these findings.

Although primary data indicated the role of adipokines in critical illness, further studies are required to clarify whether the reason of these changes is pathophysiological or compensatory. The relationship of pathophysiological background, disease severity, baseline nutritional status and nutrition support during hospitalization, and variations in body fat percentage and distribution with adipokines, as well as the potential prognostic or therapeutic role of these peptides should be further investigated in critically ill patients.

1. Introduction

Critical illness is a condition that requires indispensable support of failing vital organs for survival. The underlying cause may be trauma, major surgery or severe illnesses [1]. Limited available studies showed some changes in morphologic, physiologic, and metabolic functions of adipose tissue. It has been reported that adipose tissue in critical illness has higher number and smaller size of adipocytes [2], along with increased capacity to store glucose and lipid metabolites [3]. Adipogenesis and pre-adipocyte markers are also increased in this condition [2]. Considerable stimulation of sympathetic nervous system and systemic inflammation [4], and infiltration of macrophages to adipose tissue [2] are seen in critical illness; however, M2 macrophages that alternatively activated and accumulated in adipose tissue during critical illness, tend to be anti-inflammatory and have insulin sensitizing properties [5]. Adipose tissue might play a major role in metabolic alterations of critical illness and adaptation to stress through structural and also functional changes. Adipose tissue was exclusively recognized as a fat storage organ up to mid-1990s that the dynamic endocrine function of adipose tissue and its potential to affect whole body homeostasis has been recognized [6]. The adipose tissue products, adipokines or adipocytokines, act through an endocrine, autocrine or paracrine manner. They are supposed to be involved in a wide range of processes including dietary intake and appetite regulation, energy expenditure, insulin resistance, lipid metabolism, immunity, inflammation and acute-phase responses, vascular homeostasis, endothelial function, and angiogenesis [7–10]. In recent decades, role of adipokines has been studied substantially in health and many chronic disorders. Additionally, with the aim of improving metabolic dysfunction and better clinical outcome, the effects of different pharmacological, nutritional and medical interventions have been extensively investigated on adipose tissue biology and adipokines. However, the precise role of adipokines in critical

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illness is sometimes conflicting and largely unknown.

The gene expression and circulatory levels of adipokines and acute-phase proteins might change in different stages of critical conditions, which could affect insulin resistance and other disorders during critical illness [11]. Given the obesity epidemic [12], a large proportion of patients with critical illness might be already exhibiting altered circulating adipokine concentrations due to their excess body weight. The relationship between adipokines and percentage body fat, their alterations in different phases of critical illness, and their association with survival and other comorbidities have not been well documented. In this review, we have discussed the alterations in the behaviour of major adipocytokines, with more recognized physiological and metabolic functions, and their potential metabolic, diagnostic, and prognostic value in determining clinical outcomes in critical illness.

2. Study selection and data extraction

Relevant experimental and clinical articles were identified based on searches in PubMed, Scopus, and the bibliographies of related publications. Search strategies included standardized terms and keywords, which covered the concepts of critical illness and adipokines. All studies describing the changes of adipokines in critical illness and their relationship with mortality and other outcomes were extracted. A qualitative analysis was performed to summarize the most relevant evidence, and the uncertainties were discussed.

3. Adiponectin

Adiponectin (ADPN) or gelatin binding protein 28 is a 30-kD peptide that is almost exclusively synthesized by adipocytes and has high circulatory concentrations. ADPN has pleotropic effects on different cell types and endocrine functions. ADPN is well recognized as an insulin-sensitizing, anti-atherogenic, and anti-inflammatory agent [13]. It could play a major role in both chronic and critical illnesses [14,15]. Considering the extensive beneficial effects of ADPN as an insulin-sensitizing adipokine and inflammation modulation, and regarding its negative feedback on tumor necrosis factor alpha (TNF-α) [16], it may potentially be an important determinant of metabolic disorders and severity of inflammation and multiple organ dysfunction in critical illness.

3.1. Animal studies

In a mouse model of cecal ligation and puncture (CLP), mortality risk elevated significantly in ADPN knockout (KO) mice [17]. Uji and colleagues [18,19] showed that in a murine model of CLP, ADPN KO mice were more prone to polymicrobial sepsis with higher concentrations of inflammatory cytokines and decreased survival compared with wild-type mice. An inverse correlation was observed between plasma ADPN concentration with plasma endotoxin and TNF-a levels in rats with induced polymicrobial sepsis [20]. However, in a thioglycollate-induced inflammation model, after administration of recombinant trimeric ADPN to ADPN KO mice, intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM) expression did not change significantly [17]. Pini et al. [21] also reported a reduction in plasma ADPN in acute inflammatory response to zymosan-induced peritonitis in wild-type mice. Nevertheless, they failed to find any significant difference in blood cytokines between ADPN KO and wild-type mice. Thus, in experimental models of critical illness ADPN might exert survival benefits through mechanisms other than anti-inflammatory pathways. Administration of different types of recombinant ADPN in vitro, strain related differences in ADPN KO mice and differences in composition of microbiota might influence the role of ADPN [22]. In addition, it is not clear that which form of ADPN (bacterial or mammalian, globular or full-length) and which oligomers (trimeric, hexameric and high molecular weight forms) have anti-inflammatory properties [13,23,24].

3.2. Human studies

Some studies have reported reduced levels of ADPN in critically ill patients upon admission to ICU [11,15,25,26]. Additionally, the down regulation of ADPN receptor mRNA in white blood cells in endotoxemia [27], negative correlation between ADPN and Sequential Organ Failure Assessment (SOFA) score [25], and higher levels of ADPN during recovery compared to ICU stay [11] have been stated previously. These reports could advance the argument that ADPN modulation during critical illness might ameliorate the inflammatory responses, improve glucose tolerance and reduce need to vasopressors [28].

However, there are controversial data on metabolic role of ADPN in critically ill patients. For example, Koch et al. reported an inverse relationship between ADPN and BMI, preexisting diabetes, hemoglobin A1c and insulin concentration in critically ill patients. They found that hypo-adiponectinemia was related to insulin resistance in these patients [29]. In contrast, Hillenbard et al. reported positive correlation between ADPN and insulin demand in septic patients [30].

Moreover, Walkey et al. [31,32] have reported that higher mortality rate in patients with acute respiratory failure was associated with higher ADPN concentrations. Higher plasma ADPN levels were related to the development of acute respiratory distress syndrome and higher 30-day mortality in patients with severe sepsis [33]. In patients with severe brain injury, higher plasma ADPN was associated with higher in-hospital mortality, higher 6 month mortality and undesirable consequences such as Glasgow outcome scale score of 1–3 [34]. Koch et al. [29] have observed elevated mortality rate in ICU patients with higher baseline ADPN levels, independent of BMI. Similarly, in a septic shock cohort of pediatric patients, ADPN levels were increased and directly associated with higher mortality rate [35]. Venkatesh et al. reported a positive weak correlation between ADPN levels at day 3 of ICU admission and disease severity [15].

A strong positive correlation has been observed between plasma ADPN and cortisol both in critically ill patients [15] and healthy people [36,37]. Thus, it could be speculated that in critically ill patients higher ADPN levels at admission could reflect the severity of illness and the level of stress induced to adipocytes, which might disrupt the adipose tissue function and cause an imbalance of adipokines.

A biphasic pattern of circulating ADPN has been reported in critical illnesses, which in some extent might explain the conflicting data. There is an initial transient decrease in ADPN levels, which is followed by a gradual increase during the late phase of illness. This increase may be interpreted as a recovery index [11,26,32]. ADPN has an inhibitory effect on inflammatory cytokines like TNF-α, interleukin (IL)-6 and C-reactive protein (CRP) [27]. Probably, the reduction of ADPN concentrations in the early phase of critical illness may allow appropriate pro-inflammatory responses in this phase, while ADPN increase during the late phase of disease might mediate its anti-inflammatory responses to suppress the over activation of the immune system and improve recovery [38]. Thus, high ADPN levels at admission might reflect worse condition and prognosis, and probably patients with high ADPN levels in the early phase of the critical illness lose some compensatory mechanisms. Lower ADPN concentrations in obese patients might be one of the probable mechanisms linked to a better survival of obese patients in critical illness [39]. Further studies are needed to investigate the precise role of ADPN in the pathophysiology of critical illness and also its probable prognostic and therapeutic functions.

4. Leptin

Leptin, the product of the *ob* gene, is a 16-kD adipose derived peptide with extensive biologic functions from determining the appetite and energy expenditure [40] to the regulation of reproduction, angiogenesis, hematopoiesis, glucose homeostasis and wound healing [41]. Circulatory level of leptin is directly correlated with body fat mass and increases in obesity while starvation and malnutrition reduce its