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Adipocytokines in Severe Sepsis and Septic Shock

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1. Introduction

Among the different conditions of critical illness leading to admission to an Intensive Care Unit (ICU), sepsis remains the leading cause of death at the non-coronary medical ICU [1]. Even with optimal therapy, mortality rates of severe sepsis and septic shock are about 40 to 50% [2, 3]. Although there are numerous studies with varying methods from different countries, the incidence of severe sepsis is constantly approximately one out of ten admissions to all ICUs worldwide [4]. With millions of individuals concerned every year, worldwide sepsis is one of the major healthcare problems today. The proportion of severe sepsis, and case fatal outcomes increased during the last years [2]. It is crucial to establish the diagnosis sepsis as early as possible and to identify its origin, in order to initiate an appropriate therapy permitting to achieve the best possible outcome [5].

Sepsis is defined as a systemic inflammatory response syndrome (SIRS) caused by an infection. The association with organ dysfunction or sepsis-induced hypotension is termed severe sepsis. Septic shock, as a subset of severe sepsis, is characterized by sepsis-induced hypotension, persisting despite adequate fluid resuscitation [6]. Early differentiation between sepsis and SIRS is a considerable problem in the treatment of patients on ICU. Due to the early systemic release of inflammatory cytokines as compared with synthesis of acute-phase-proteins, cytokines have been widely investigated for their diagnostic potential in predicting sepsis [7]. Nevertheless, until now the perfect biomarker for differentiation of sepsis and SIRS has not been found yet and ongoing research focuses on identification of appropriate diagnostic biomarkers for sepsis [8].

Despite a growing number of studies, the physiopathology of sepsis is not satisfyingly understood. Data show that physiopathology is characterized by a large number of pro- and anti-inflammatory cytokines and mediators of inflammation with complex interactions [9]. For instance, the application of a single bolus i.v. infusion of endotoxin to a healthy individual leads to the expression of 3147 genes, (> 10% of the human genome) [10]. These mediators and cytokines lead to endothelial dysfunction and activation of inflammatory and coagulation pathways as reaction to the invasion of a pathogen [11]. In order to reduce the sepsis-related high mortality, a better understanding of common pathogenic mechanisms of sepsis and other critical diseases is needed, potentially resulting in more effective treatment options.

2. Obesity in critical disease

At present, obesity is regarded as a low-grade proinflammatory state with oxidative stress caused by glucose and macronutrient intake. In this setting various proinflammatory cytokines and acute phase reactants are induced, e.g. TNF-α and IL-6, which are mainly derived from the macrophages as part of the white adipose tissue [11, 12]. Oxidative stress leads to the production of reactive oxygen species (ROS) with NADPH oxidase as major vascular source of ROS [13]. ROS are particularly important for endothelial dysfunction and can cause cellular injury [14]. For these reasons the reaction to sepsis in obese individuals is different than those in individuals without chronic inflammatory state [11].

Obesity has been suggested as a prominent risk factor for mortality in critically ill patients, especially in sepsis [15, 16]. Singer et al. hypothesized that continuous low-grade chronic inflammation primes blood and endothelial cells to reply more rapidly to any additional inflammatory stimulus, such as sepsis [17]. However, recent publications on critical disease, only reported an influence of obesity on morbidity, but not on mortality [18, 19]. This means that obese and very obese patients acquired more frequently ICU-associated infections and had a longer length-of-stay, but there was no evidence for a higher 60-day in-hospital mortality compared with normal weighted patients in the study of Sakr et al. [19] .

3. Hyperglycemia and insulin resistance in critical disease

As in obesity, hyperglycemia, impaired glucose tolerance and insulin resistance are common findings in critically ill patients after surgery or with sepsis [20]. This feature has also been termed "diabetes of injury" [21, 22]. Hyperglycemia in hospitalized patients is known to lead to various adverse effects (e.g. fluid imbalance, alterations of immune function and inflammation), which are commonly improved by glucose control [23] (Table).

Adverse effects of Acute Hyperglycemia
Blood-flow abnormalities
Increase of vascular permeability
Electrolyte disturbances
Fluid shifts
Acid-base disturbances
Proinflammatory gene expression
Immune dysfunction
Impairment of complement activity
Inhibition of opsonization
Catabolism

Table 1. Adverse effects of Acute Hyperglycemia in critical illness (modified from [23])

In case of critical disease or trauma hepatic gluconeogenesis is increasing despite hyperglycemia and high insulin levels, whereas insulin-dependent glucose uptake in skeletal muscle and heart is impaired. In critically ill patients the overall glucose-uptake is elevated but mainly in tissues which do not depend on insulin for glucose uptake [24]. Hyperglycemia in critically ill patients has been related to mediators of stress, but there is growing evidence for causative defects in glucose metabolism [25] (Fig.1). Moreover,

proinflammatory cytokines can affect glucose metabolism by changing insulin receptor signaling and by boosting counterregulatory hormone secretion [21, 26]. Likely, adipocytokines link hyperglycemia and insulin resistance to inflammation in sepsis.

Acute Stress Response

Endogenous factors

Increased counterregulatory hormones
   glucagon, epinephrine, cortisol,
   growth hormone, norepinephrine

Increased cytokines
   ↑ *oxidative metabolism*
   ↓ *nonoxidative metabolism*

Increased insulin resistance
   adipocytokines?
   (↑ *resistin*)
   (↓ *adiponectin*)

Exogenous factors

Medications
   glucocorticoids
   catecholamines

Nutrition
   total parenteral nutrition
   enteral nutrition

Other
   dialysis/CVVH substrates
   immobilisation
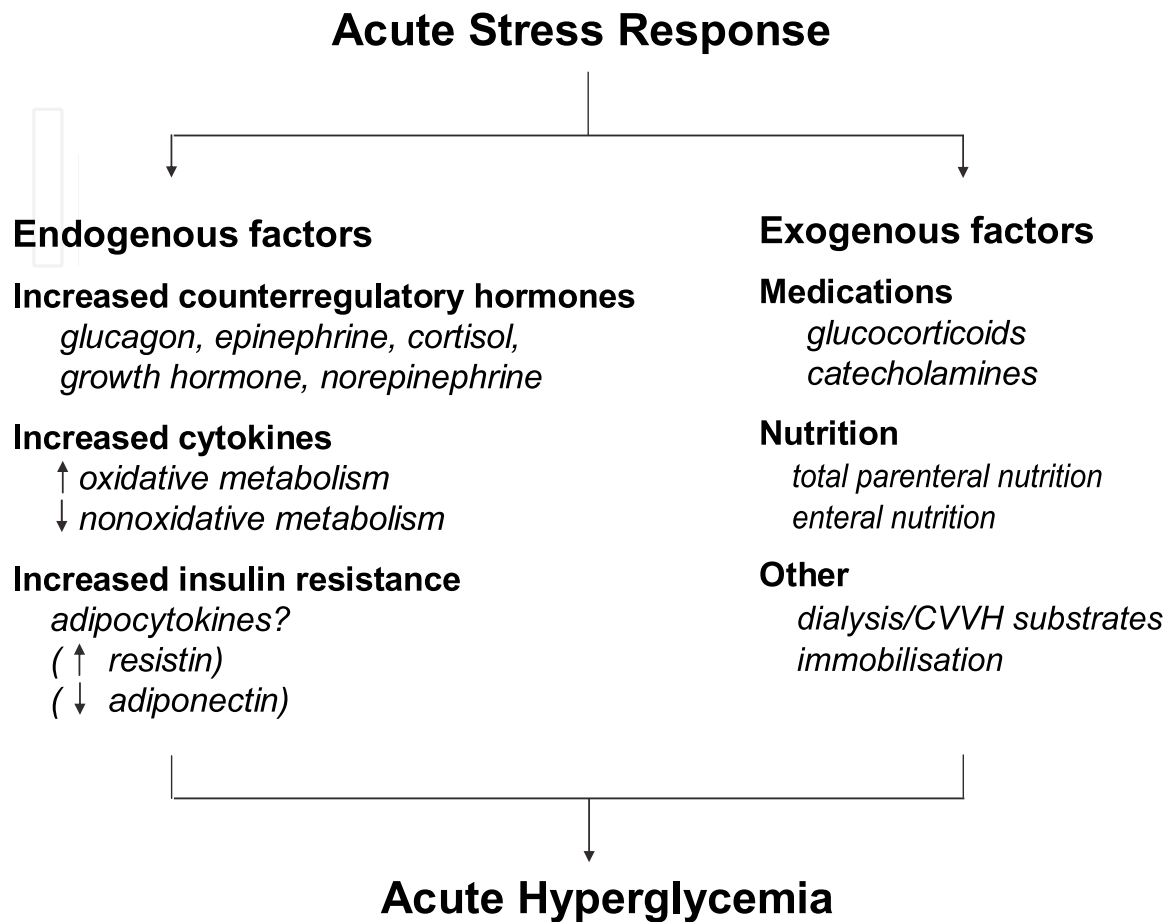
Acute Hyperglycemia

Fig. 1. Etiology of acute hyperglycemia. Acute stress response is characterized by complex interactions of counter-regulatory hormones, cytokines and insulin sensitivity (modified from [23]).

In 2001 a milestone study from van den Berghe et al. showed that tight control of hyperglycemia during critical illness in a cohort of cardiac surgery patients significantly improved outcome in terms of morbidity and mortality. Adjustment of hyperglycemia resulted in less severe nosocomial infections, renal and hepatic dysfunction, critical illness polyneuropathy, muscle weakness, and anemia [27, 28]. Increasing hyperglycemia paralleled increase in rates of mortality in critical illness [27]. Nevertheless, consecutive studies in medical ICU patients demonstrated higher mortality for intensive insulin therapy, potentially due to severe hypoglycemia [29]. Therefore, control of hyperglycemia by insulin therapy in a moderate range of blood glucose levels of 140-180 mg/dL is at present part of standard therapy in critically ill patients.

4. Adipose tissue as a hormonally active organ

Historically, adipose tissue was solely considered to store excess energy. Most recent data emphasize the role of adipose tissue as a hormonally active system, influencing

inflammation, metabolism, body weight, and lipid and glucose metabolism [30]. Proteins mainly secreted by adipocytes are called adipokines [11]. Matsuzawa and colleagues reported that approximately 30% of all genes expressed in visceral fat encode secretory proteins [31]. An increasing number of soluble mediators ("adipocytokines") mainly derived from adipocytes itself or other cell types from adipose tissue (e.g. stromavascular fraction, adipose precursor cells and macrophages in the adipose tissue) have been identified. Adipocytokines are important mediators linking chronic inflammatory conditions to systemic insulin resistance in obesity and diabetes mellitus type 2 [18, 32] (Fig.2).
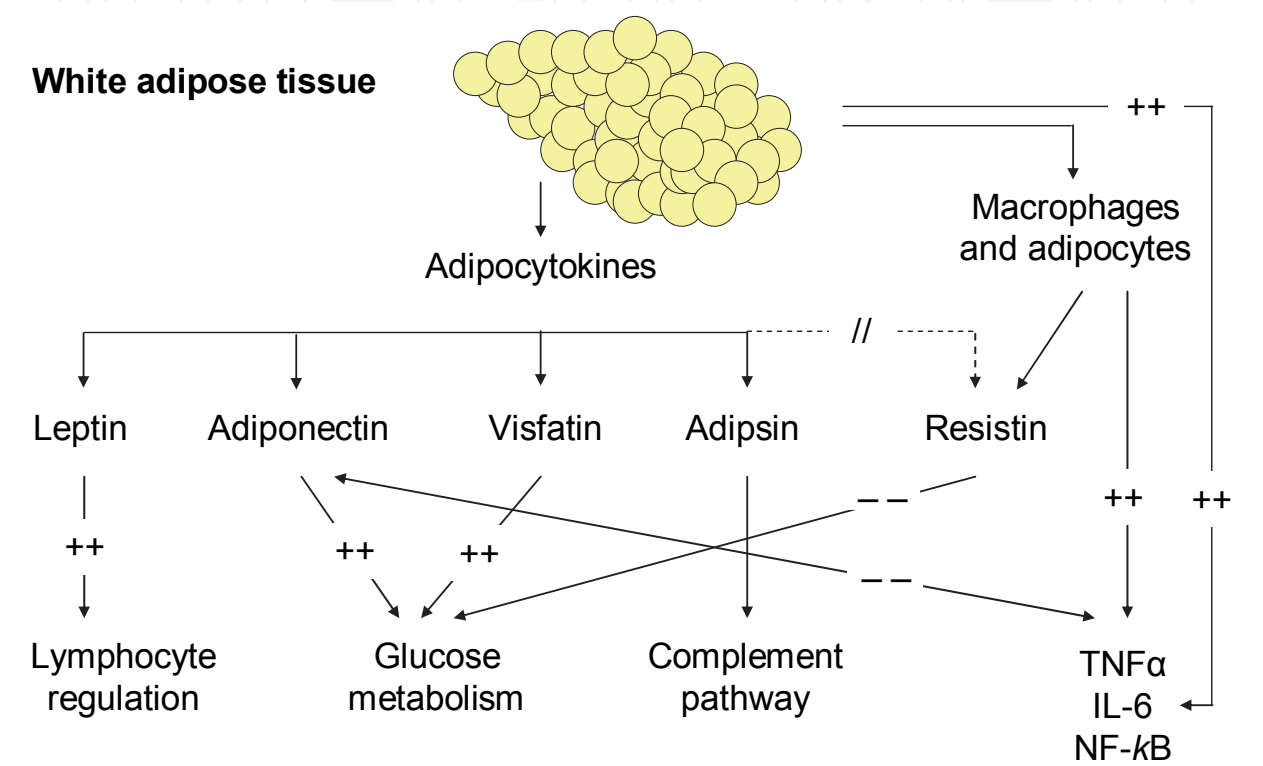

Fig. 2. Secretion of adipocytokines and 'classic' inflammatory cytokines by white adipose tissue. Although regarded as an adipokine resistin is in humans mainly derived from macrophages. TNF, tumor necrosis factor; IL, interleukin; NF, nuclear factor (modified from [11]).

Potentially relevant factors released from fat tissue include hormones, adipocytokines, chemokines, growth factors, transcription factors, enzymes and participants of the coagulation cascade [33]. Many of these factors signal to organs of metabolic importance and the immune system and thus contribute to the phenomenon of insulin resistance [30] as proved for TNF-α and IL-6 [34, 35]. A recent study demonstrated similar high adipocytokine profiles in septic patients as well as in morbidly obese [36]. Most validated data are available for Interleukins-1,-6,-8 and -10, TNF-α, Resistin, Adiponectin, Leptin, Leptin-Rezeptor, RBP4, Osteopontin, Visfatin, Omentin, Adipsin, Sfrp5, Adipophilin and VASPIN (visceral adipose-tissue-derived serine protease inhibitor).

In critically ill patients adipocytokines seem to be involved in the regulation of inflammation and metabolism and by this directly influence the clinical outcome of ICU patients. For critical illness, especially severe sepsis and septic shock, most valid data are available for resistin, leptin, leptin-receptor, and adiponectin.

5. Resistin

Up to now, resistin is the most widely studied adipocytokine in critical illness. Human resistin is mainly derived from macrophages and neutrophils as recently reported [37] and not from adipocytes (like in mice [38]) and has been implicated in glucose metabolism and insulin sensitivity. It is named for mediating resistance to insulin through the exacerbation of the adipose tissue inflammation in humans [39]. In a knock-out mouse model it has been demonstrated that the lack of resistin protects against diet-induced insulin resistance and type 2 diabetes mellitus [40].

Elevated resistin serum levels have been found in critically ill patients with significantly higher concentrations in sepsis than in non-sepsis patients and peak values in septic shock [37, 41]. Likely, resistin seems to act as an acute-phase protein and might be part of the systemic inflammatory response, as it has been correlated to IL-6, IL-10, TNF-α, C-reactive protein and procalcitonin [42].

Data concerning the correlation between resistin, obesity, insulin resistance, hyperglycemia and diabetes mellitus are controversially discussed at present. Several studies found a positive correlation between resistin serum levels and hyperinsulinemia, hyperglycemia and insulin resistance in patients who suffer from obesity and type 2 diabetes [43, 44], but these findings could not be confirmed in other studies [45, 46]. Interestingly, resistin levels have been recently found to be independent of pre-existing diabetes mellitus or body-mass index (BMI) in critically ill, especially in septic patients [41, 42].

Resistin serum levels have been correlated to renal and liver functions [47, 48], implicating renal and hepatic elimination or degradation of resistin. Resistin is considered as a part of the systemic inflammatory response from adipocytes, but in the critical illness response, resistin seems to be mainly derived from macrophages and not from adipocytes [42].

For critically ill, non-septic patients, high resistin serum concentrations have been identified as an adverse prognostic indicator for the ICU- as well as overall survival. Potentially, high resistin levels could indicate an excess of inflammatory reaction that might be of considerable harm, even in the absence of infection [42].

6. Leptin and leptin-receptor

Since its identification in 1994 leptin has been known for its role in controlling body weight and food intake through hypothalamic pathways [49, 50]. The name leptin derived from the Greek language, as the word leptos means thin [51]. In mouse models, deficiency of leptin or leptin-receptor resulted in a hyperphagic, morbidly obese, and lethargic phenotype with significantly reduced macrophage phagocytic activity [52-54]. Circulating leptin levels directly reflect adipose tissue mass in non-critically ill subjects [55]. The same result applies in critical disease, in which leptin has also been found to closely correlate with adipose tissue mass; moreover, an inverse association between circulating leptin-receptor and the BMI in critically ill patients has been reported [56].

Little is known about the mechanisms of leptin expression. It is secreted not only from white adipocytes, but also from placenta and stomach [57]. In not critically ill individuals leptin serum concentrations correlate with impaired insulin sensitivity, increased inflammatory markers, and coronary artery disease [58]. Various central and peripheral effects of leptin via leptin-receptors in brain and leptin-receptors in pancreas, liver, adipose tissue, and in the immune system, especially in human peripheral blood mononuclear cells, have been

described [59]. Therefore, leptin is not only involved in control of body weight and energy expenditure, but also in glucose homeostasis and immunoregulation. Leptin is able to modulate the immune response by proliferation and activation of the mononuclear cells. Moreover, it activates the production of proinflammatory cytokines in cultured monocytes, protects monocytes against apoptosis and influences RNA metabolism. The leptin-receptor itself is similar to members of the class I cytokine family and exists in six isoforms [60]. Leptin is regarded as a proinflammatory cytokine itself [61], whose action in the central nervous system is necessary for an adequate systemic immune response [62].

In animal and human studies administration of endotoxin and TNF-α as inducers of severe systemic inflammation resulted in significant elevation of serum leptin levels [63]. Yousef and colleagues also reported increased values for IL-6, CRP, TNF-α and leptin at admission to ICU, with leptin threshold values of 38 μg/l for distinguishing between SIRS and sepsis [7]. Controversially, among other studies, a study from Denmark revealed low leptin levels - and also low adiponectin and RBP4 levels - at admission to the ICU, possibly due to an acute stress response [64]. The absence of increasing leptin levels in these studies may be due to the short duration of the experiments, given that a delay is needed to observe an increase of leptin following a LPS-stimulation [65]. Another study in critically ill patients, including septic and non-septic groups didn't report differences in leptin and leptin-receptor serum concentrations as compared with healthy controls [56].

Besides the suggested potential role as a diagnostic parameter leptin and leptin-receptor seem to have a prognostic impact, as high leptin-receptor serum concentrations at admission to ICU have been identified as an adverse prognostic indicator for survival [56]. Bornstein and colleagues noticed earlier that low levels of leptin might indicate a poor prognosis in septic patients [66]. Other studies had similar findings with exogenous leptin administration as a protective factor in leptin-deficient mice [67, 68]. These results are in conflict with observations from other investigators. Shapiro et al. reported a decrease in survival rates after application of exogenous leptin in murine sepsis models, whereas leptin-receptor deficient mice showed a better outcome with higher survival rates [60].

Despite the strong evidence that leptin takes part in the cell-mediated immunity response and in cytokine crosstalk [69] additional studies for clearing the role of leptin and its receptors in sepsis and SIRS are warranted.

7. Adiponectin

Adiponectin is the most abundant adipocytokine in humans with high serum concentrations, normally accounting for about 0.01% of total plasma protein [70]. There are three different molecular forms of circulating adiponectin [30]. It is exclusively secreted by adipocytes with higher serum concentration in females [71]. Interestingly, despite sole adipocytic origin, adiponectin has been found to be inversely correlated to the BMI in healthy individuals and in critically ill patients as well [72]. Until now, this so called "adiponectin paradox" – exclusive synthesis in adipocytes but low adiponectin levels in obesity - has not been solved yet [73]. Secretion of adiponectin is boosted several folds by insulin [70], but interestingly in type 2 diabetes - as in obesity - adiponectin serum concentrations are reduced [74]. Reduced adiponectin levels and an association with pre-existing diabetes mellitus have been reported in critically ill patients as well [72].

Adiponectin has been found as an anti-atherogenic agent with positive correlation to high-density lipoprotein cholesterol and inverse correlations to low-density lipoprotein cholesterol, triglycerides, insulin resistance, and diastolic blood pressure. Moreover,

adiponectin seems to exert direct anti-atherogenic effects on the endothelial cells [75]. Studies in rodents also demonstrated protective functions of adiponectin in obesity and insulin resistance [76]. In a study with nondiabetic, but obese patients with varying degrees of insulin resistance, the presence of adiponectin resulted in an increase of insulin-sensitivity. Concomitantly to higher adiponectin serum concentrations in lean individuals, serum levels of TNF-α are decreased [74]. As TNF-α is presently known for its implication in insulin resistance, reduced serum concentrations might affect higher insulin sensitivity as well [77].

Additionally, adiponectin seems to have anti-inflammatory functions in animal models of sepsis. It has been reported as a potent inhibitor of cytokine production in porcine macrophages [78]. Furthermore, adiponectin-knockout mice had significantly higher mortality rates and serum levels of inflammatory markers in polymicrobial sepsis [79]. In a study of Teoh and colleagues the administration of adiponectin to adiponectin-knockout mice led to an improved outcome in experimentally generated sepsis. As concluded by the authors, low adiponectin levels potentially link obesity and the (discussed) worse outcome of obese patients in sepsis [80]. Glucocorticoids, inflammation, and oxidative stress – commonly associated with critical disease – are known for reducing adiponectin synthesis [81]. Matching these facts, some studies reported low adiponectin levels in patients with critical disease of pulmonary origin and also in rats with sepsis (without analyzing the impact of the measured low values on mortality or outcome) [64, 82]. Nevertheless, there are conflicting data concerning the role of adiponectin in critical illness. In a large monocenter clinical study there was no difference in adiponectin serum levels in critically ill patients compared to healthy controls and furthermore no difference between septic and non septic patients. In the same study low adiponectin serum concentrations at admission to ICU have been found as a positive prognostic indicator for ICU and overall survival in contrast to the above mentioned theory of low adiponectin levels worsening the outcome of critically ill patients [72].

Interestingly, no correlation of adiponectin with cytokines or mediators of inflammation have been reported in critically ill patients [64, 72]. The mechanisms of adiponectin excretion and biodegradation in critical disease are presently unclear. Due to a reported correlation between adiponectin levels and markers of cholestasis and cystatin C as a marker of renal function, hepatic and renal elimination have been discussed in critically ill patients [72]. Other studies in non-ICU patients with liver cirrhosis, animal models and uremic patients confirm the theory of partially biliary and renal excretion of adiponectin [83, 84]. Yuan et al. reported a direct suppression of adiponectin gene expression by C-reactive protein in a concentration- and time-dependent manner [85], which might be an important finding for understanding adiponectin in critical disease, especially in sepsis, in which extremely high CRP levels are frequently found.

As a result of the entirety of conflicting data, up to now it remains unclear whether circulating adiponectin is pathogenetically involved in mechanisms of critical disease leading to higher mortality rates. Maybe it is an epiphenomenon of variables such as adiposity, yet unknown functions of adipose tissue or metabolic alterations in critical illness [72].

8. Retinol binding protein 4 (RBP4)

Retinol binding protein 4 is secreted by adipose tissue and liver. Although it is named an adipocytokine for its derivation of adipocytes, the main source of RBP4 in humans is the

liver [86]. Besides serving as a transport protein for vitamin A (retinol), RBP4 has been implicated in the development of insulin resistance in rodent models and in humans [87, 88]. Von Eynatten et al. found elevated gene expression for RBP4 in the adipose tissue, but not in the liver of insulin-resistant mice, whereas the application of RBP4 to other mice led to insulin resistance [87]. Another study demonstrated down-regulation of the insulin-responsive glucose-transporter GLUT4 in adipocytes in obesity, resulting in increased secretion of RBP4 by a yet unknown regulatory mechanism [88]. RBP4 has been identified as a marker of insulin resistance in individuals with various clinical presentations, but not yet manifested diabetes mellitus. The strong correlation to insulin resistance in case of obesity, impaired glucose tolerance, type 2 diabetes and even in lean subjects seems to be more specific than the correlation of other adipocytokines like leptin and adiponectin to insulin resistance [89].

As a consequence of its main derivation from the liver, RBP4 serum levels are reduced in case of chronic and acute liver diseases or dysfunction [86, 90]. But also renal function seems to be important for the RBP4 metabolism with increasing levels in case of impaired renal function [91].

In critical disease RBP4 serum levels have been found decreased compared to healthy controls, independent of the origin of critical illness [64, 92]. During the course of disease, serum levels normalized with resolving critical illness [64]. Langouche and colleagues hypothesized that reduced synthesis or increased removal might be the reason for the decreased serum levels. In sepsis, capillary leakage has been considered as a possible mechanism for reducing the levels of adipocytokines in general [64]. As shown in another study the decrease in serum concentrations of RBP4 is independent of the origin of critical illness. There was no difference between concentrations in septic and non-septic patients requiring intensive care medicine, so capillary leakage as a well-known problem in sepsis seems not to be the main reason [92]. Instead, a strong correlation between liver and kidney function and serum RBP4 concentrations was found, reflecting the above mentioned relation of RBP4 to liver and kidney function observed in not critically ill patients [92]. As RBP4 levels were inversely correlated with markers of inflammation, RBP4 seems potentially to be a member of the negative acute-phase reactants described by Richie et al. [93], what might be another explanation for decreased levels in critical disease [92]. At present, no association between RBP4 and other adipokines like adiponectin and resistin has been reported, suggesting that the adipose tissue does not contribute to a great extent to serum RBP4 concentrations in critical disease [92].

Recently, despite a missing association of RBP4 with preexisting diabetes mellitus or obesity, a study reported a correlation with C-peptide levels, reflecting endogenous insulin production, and with insulin resistance (HOMA index) [92]. The hypothesis of RBP4 interaction in glucose metabolism is supported by a recent finding, that during intensive insulin therapy the raise of RBP4 levels in the course of critical illness is blunted [64].

Importantly, high serum concentrations of RBP4 at admission to the ICU have been identified as a positive predictor of ICU-survival [92]. Maybe this is due to the fact that higher RBP4 levels just represent preserved liver function and are not pathogenetically involved in the course of critical disease, as liver function itself is clearly linked to survival rates in critical disease [94]. Further studies are needed to definitely clarify the regulatory pathways of RBP4, its role in the pathogenesis of critical illness, and its significance as a potential novel biomarker for ICU patients.

9. Visfatin

Initially known as Pre-B-cell colony-enhancing factor (PBEF) this recently described adipocytokine was found in high concentrations in visceral fat, therefore renamed visfatin [95]. The third name for this eclectic protein is Nampt (nicotinamide phosphoribosyltransferase) [96]. Interestingly, visfatin has a unique structure without homology to other known proteins [96]. The number of names already indicates the divers properties exerted by this protein.

As Nampt, this protein acts intracellular as the rate-limiting part of the NAD (nicotinamide adenine dinucleotide) production in mice [97]. NAD is an essential cofactor in numerous fundamental intracellular processes [98]. Moreover Kitani et al. proposed a role for PBEF in cell cycle regulation because of its varying intracellular distribution due to the growth phase of the cell [99].

As characteristic for adipocytokines visfatin is involved in the glucose metabolism. By binding to the insulin-receptor it shows insulin-mimetic effects in mice and cultured cells [100]. In question of reproducibility of these effects of visfatin, this publication had to be retracted recently [101], but Xie et al. demonstrated an insulin-like effect of visfatin on cultured osteoblasts [102]. Furthermore, other authors reported a correlation between visfatin serum levels and obesity, diabetes mellitus, and visceral fat mass [103-105]. Therefore, visfatin seems to be involved in a number of metabolic processes, but the definite role remains to be clarified.

Initially PBEF was discovered by Samal et al. (1994) as a mediator of maturation of B-cells precursors, secreted by activated lymphocytes in bone marrow stromal cells. Its gene was found mainly transcribed in human bone marrow, liver tissue, and muscle [106]. Even though the characteristic signal peptide required for extracellular secretion of mature protein is missing, PBEF shows other properties which allow allocation of it to the class of cytokines [106]. PBEF has been found as an inhibitor of apoptosis of neutrophils in experimental inflammation and clinical sepsis by Jia et al. [107]. The excess of neutrophils in sepsis accounts for inflammatory tissue damage, e.g. for respiratory distress syndromes as often observed in sepsis [108]. The prolonged survival of neutrophils in sepsis due to inhibition of apoptosis mediated by PBEF even amplifies these destructive effects [107]. Furthermore increased PBEF was found in swollen or infected human fetal membranes indicating cytokine functions [109]. It exerts chemotactic activity and up-regulates the serum levels of other pro-inflammatory cytokines [110]. Garcia and Vinasco demonstrated a crucial role for PBEF in acute lung injury (ALI), which is usually caused by sepsis [111]. In these critical ill patients they found elevated concentrations of PBEF in bronchoalveolar lavage and serum. They identified two single nucleotide polymorphisms in the PBEF promoter, which seems to enhance the susceptibility for the development of ALI in septic patients.

Although the role of PBEF as a cytokine is incompletely understood today, this protein seems to have a magnitude of properties contributing to the complex mechanisms accounting for the course of critical disease. Not at least this is underlined by the fact that PBEF is highly conserved through evolution as it could be identified in bacteria [112], invertebrate sponges [113], fishes [114], chickens and mammals [115].

10. Adipsin

When adipsin was initially identified in 1983, this was the first evidence for the potential role of adipose tissue in regulation of immune system biology [116]. Spiegelman and

colleagues discovered adipsin mRNA in cultured mouse adipocyte cell lines [117]. Just a short time after its identification the similarity between the novel serin protease adipsin in mice and human complement factor D was shown [118]. Factor D is a serin protease accounting for the activation of the alternative pathway of complement activation. It constitutes the initial obligatory, rate-limiting catalytic activity of this activation by cleaving complement factor B when B is complexed with an activated form of complement component C3 [119]. The complement system is the key in innate immunity with important properties in enhancing adaptive immunity and in the clearance of bacteria and apoptotic cells [120]. In dissimilarity to mouse adipsin, which is only expressed by adipose tissue, human complement factor D it mainly derived from macrophages and monocytes [121]. So the potential involvement of this adipocytokine in critical disease seems obvious. Adipsin-deficiency abolishes alternative-pathway dependent complement activation, in case of infection with *Neisseria meningitidis* leading to an increased susceptibility for invasive meningococcal disease [122, 123].

Adipsin also seems to play an important role in energy balance as it has been found to be decreased in fat from genetically obese and diabetic mice in comparison to normal lean mice and also in serum levels of varying animal models in obesity [124, 125]. Its serum concentrations decline during infusion of glucose which results in a hyperglycemic and hyperinsulinemic state [124]. Interestingly, the serum adipsin concentrations are reduced in case of genetically and chemical induced obesity, whereas in the state of adiposity resulting from pure overfeeding there is no change leading to the conclusion that adipsin could be a marker for distinguishing between obesity caused by metabolic disorders or caused just by overfeeding [124].

11. Conclusion

Overall, adipocytokines in critical illness seem to fulfill various functions which are at present not satisfyingly understood. The interaction of metabolic and inflammatory mediators has been found of prognostic impact in these patients. More and more functions of adipocytokines and their interaction in insulin resistance, obesity and immune reactions have been unraveled by an increasing number of clinical and animal studies. Nevertheless, further future research is crucial to understand the complex effects of adipocytokines and their role as a link between inflammation and metabolism in critical disease.

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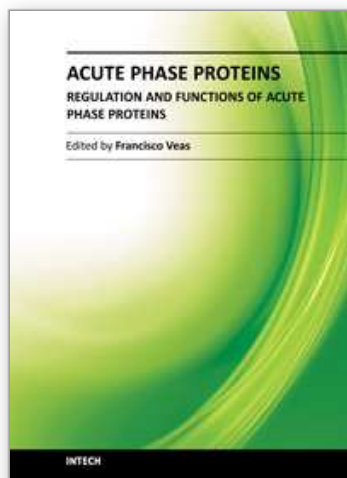
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