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Endocrine, Metabolic and Morphologic Alterations of Adipose Tissue during Critical Illness

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Key terms: adipose tissue, critical illness, sepsis, macrophages, leptin, obesity

Abstract

Objective: Observational studies report lower mortality in obese than in lean critically ill patients, an association referred to as the “obesity paradox”. This may suggest a possible protective role for adipose tissue during severe illness.

Data sources: Relevant publications were identified based on searches in PubMed and on secondary searches of their bibliographies.

Data synthesis: The endocrine functions of adipose tissue might play a role in the adaptation to critical illness. In the acute phase of illness, the anti-inflammatory adiponectin is reduced, while pro-inflammatory cytokine expression in adipose tissue is upregulated. In the prolonged phase of critical illness, both adiponectin and anti-inflammatory cytokine production are increasing. Studies on the pro-inflammatory adipokine leptin during critical illness are inconsistent, possibly due to confounders such as gender, BMI, and feeding. Morphologically, adipose tissue of critically ill patients reveals an increased number of newly differentiated, smaller adipocytes. Accentuated macrophage accumulation showing a phenotypic switch to M2-type suggests an adaptive response to the micro-environment of severe illness. Functionally, adipose tissue of critically ill patients develops an increased ability to store glucose and triglycerides.

Conclusions: Endocrine, metabolic and morphologic properties of adipose tissue change during critical illness. These alterations may suggest a possible adaptive, protective role in optimizing chances of survival. More research is needed to understand the exact role of adipose tissue in lean versus obese critically ill patients, in order to understand how illness-associated alterations contribute to the obesity paradox.

Introduction

Several observational studies have shown a lower mortality in overweight and obese patients as compared with patients with a normal body mass index (BMI) (1-7). This association suggests a possible protective role for adipose tissue during critical illness. However, despite extensive evidence for an important role of adipose tissue in conditions such as obesity, type 2 diabetes and nonalcoholic fatty liver disease, the role of adipose tissue during critical illness remains poorly understood.

Whereas adipose tissue was traditionally considered to be an inert tissue, which merely stores excess energy and protects the body from low temperature and injury, it is now recognized as being highly dynamic and interactive, playing a central signaling role in the regulation of energy homeostasis, appetite, inflammation and insulin sensitivity. Adipose tissue is traditionally classified in white adipose tissue (WAT) and brown adipose tissue (BAT). The main function of WAT is energy storage, insulation and secretion of endocrine signals; the main function of BAT is the production of heat. In humans, BAT is mainly present in newborns, although recent research indicated that BAT also has physiological importance in adulthood (8). For this review we focus on morphological and functional alterations of white adipose tissue evoked by critical illness.

Morphology of adipose tissue

In health

Adipose tissue represents a loose connective tissue structured in lobules of adipocytes, held in place by fibrous septa and surrounded by a rich capillary and innervation network. In humans, adipose tissue is dispersed throughout the body with large depots located subcutaneously around the thighs, buttocks and abdomen, and viscerally around the omentum, intestines and kidneys. Mature white adipocytes comprise 30 to 70% percent of adipose tissue. The remaining portion consists of the stroma-vascular fraction, containing adipose precursor cells or pre-adipocytes, mesenchymal stem cells, macrophages, blood cells, small blood vessels, and nerve tissue (Figure 1). White adipocytes are spherical, and can vary enormously in size with a diameter ranging from 20 µm to more than 200 µm. Lipids within these adipocytes are organized in a large unilocular droplet, containing mainly triglycerides (up to 95%), and a small portion of diacylglycerols, unesterified fatty acids, phospholipids, and cholesterol. The lipid droplet in mature adipocytes occupies the majority of the cell volume,

stretching the nucleus and the cytoplasm to a small edge around the droplet. Although the adipose depot can increase from 20% of total body weight in lean individuals to more than 50% in morbidly obese individuals, the number of adipocytes appears to remain fairly constant in lean and obese individuals, once adulthood is reached (9). In contrast, the adipocyte turn-over is highly dynamic, with approximately 10% of the cells renewed annually (9;10). New adipocytes are derived from mesenchymal stem cells. A complex network of transcription factors in which the nuclear receptor PPARγ plays an indispensable role, induce the determination of stem cells to pre-adipocytes and further differentiation into mature adipocytes which are able to store triglycerides and secrete hormones (11).

During critical illness

A remarkable clinical observation is that within a few days to weeks and despite feeding, critically ill patients suffer from severe muscle wasting, whereas fat stores appear preserved or even increased (12-17). We recently demonstrated profound alterations in morphology of adipose tissue during critical illness (Figure 1). In a rabbit model of prolonged illness, we demonstrated a decrease in median adipocyte cell size with time, whereas the total weight of the isolated fat pad did not change, together pointing to an increase in adipocyte cell number (18). This observation was confirmed in adipose tissue biopsies of critically ill patients (18). Furthermore, the preadipocyte marker Pref-1 and the adipogenic trigger PPARγ were markedly over-expressed in adipose tissue biopsies of critically ill patients (18;19). It appears that during critical illness, the differentiation of new small adipocytes is stimulated in subcutaneous as many as in visceral adipose tissue. Interestingly, smaller adipocytes are considered to be more lipid storage apt and insulin sensitive than large lipid-loaded adipocytes (20;21).

Another remarkable change in adipose tissue morphology observed during critical illness was the presence of numerous macrophages in biopsies obtained from critically ill patients and from critically ill rabbits (18). Intriguingly, it is well described that macrophages adapt to the micro-environment through functional reprogramming. In this sense, two distinctive macrophage phenotypes have been identified as the extremes of an activation continuum: the classically activated macrophage (M1), and the alternatively activated macrophage (M2) (22;23). M1 macrophages are mainly activated by interferon-γ and have an enhanced pro-inflammatory cytokine and excessive nitric oxide production. M2

macrophages are activated predominantly by IL-4 and IL-13, they secrete high levels of the anti-inflammatory IL-10 and arginase (24;25). In a subsequent study, we could identify the characteristics of the infiltrating macrophages: in both *in vivo* adipose tissue biopsies from surviving critically ill patients and in postmortem biopsies from nonsurviving critically ill patients, macrophages displayed M2-type characteristics (19). In our study, the circulating levels of the M2 activators IL-4 and Il-13 were low, but the nuclear receptor PPARγ was markedly increased, constituting a possible trigger for M2 polarization of the macrophages (19). In addition, experimental human inflammation leads to the increased gene expression of chemotactic factors MCP-1 and CXCL10, suggesting that macrophages do not migrate randomly to adipose tissue but are attracted to it by chemotactic factors (26).

Why critical illness is associated with increased infiltration and a phenotypical switch of macrophages is not clear yet. There is a variety of M2 macrophage features such as increased phagocytic activity, tissue healing and remodeling, tumor progression, and promotion of insulin sensitivity (22;27-30). Amid M2 phenotypic characteristics, inflammation dampening and insulin sensitizing properties might play a thought-provoking protective role during critical illness.

Adipose tissue as a storage organ

In health

Adipose tissue is the largest energy storage organ of the body. The stored triglycerides are primarily provided by dietary lipids as chylomicrons (assembled in the intestines) and to a lesser extent by very low density lipoproteins (VLDL) (generated in the liver) (31). Lipoprotein lipase, located in the capillaries, releases free fatty acids from these circulating particles, which are subsequently taken up by the adipocyte through specific fatty acid transporters and then reesterified into triglycerides. A small portion of the stored triglycerides is synthesized *de novo* in the adipocyte from circulating carbohydrates through lipogenesis (32). In times of positive energy balance or feeding, adipose tissue stores triglycerides, while during a negative energy balance or fasting, the stored triglycerides are hydrolyzed into glycerol and fatty acids, which leave the adipocyte to provide metabolic fuel for organs in need of energy (31).

During critical illness

Only limited data is available regarding storage and release of lipids from adipose tissue during critical illness. Increased whole body lipolysis, measured by circulating glycerol, is consistently present in critical illness (33-35). However, whether the released lipids originate from adipose tissue or ectopic deposit sites such as liver and muscle is not clear. In addition, increased circulating glycerol during critical illness could be due to reduced glycerol uptake from the liver (36). In contrast, with the use of micro-dialysate samples of femoral adipose tissue, it was demonstrated that while adipose tissue can be a major source of serum glycerol during physiological conditions, it contributed little to the increased glycerol levels during experimental endotoxemia in healthy humans (37). In addition, we demonstrated that adipose tissue responds to critical illness by increasing its storage properties for circulating lipids (18). In adipose tissue biopsies of prolonged critically ill patients, the activity of lipoprotein lipase was increased, while hormone sensitive lipase (HSL), the enzyme responsible for the release of fatty acids from adipose tissue, remained low-normal (18).

The second metabolic storage pathway in adipose tissue is the uptake of glucose to store as triglycerides through the lipogenic pathway. For glucose transport into the cell, adipocytes mainly use the insulin-dependent glucose transporter GLUT4. In adipose tissue of prolonged critically ill patients, we demonstrated that the insulin-independent glucose transporters GLUT1 and GLUT3 were massively upregulated and associated with substantially increased glucose content (18). When glucose is metabolized into fatty acids, the glycolytic end product, pyruvate, is metabolized to fatty acid by the enzymes acetyl CoA carboxylase and fatty acid synthase. Remarkably, both lipogenic enzymes were elevated in adipose tissue of prolonged critically ill patients, which could be interpreted as an increasing glucose-storage capacity during illness (18). This increased glucose storage capacity appeared largely independent of circulating blood glucose levels or nutrient intake (18).

Taking into account the association between both hyperglycemia and dislipidemia and mortality of critical illness, the increase in key components of glucose and lipid uptake and storage in adipose tissue may present an adaptive and protective response to severe illness (33;38;39). In theory, an increased storage capacity in adipose tissue might help to lower detrimentally high circulating levels of glucose and lipids. Where more vital organs such as the liver and kidneys appear to suffer from high glucose levels (40;41), adipose tissue is prone to store this metabolite without vital consequences. Also, lowering of excess free fatty acid availability might reduce ectopic lipid deposition, which at least in liver and muscle has been related to insulin resistance (42).

Adipose tissue as an endocrine organ

In health

Besides its well-known storage role, adipose tissue also functions as the largest endocrine organ of the body. Not only adipocytes, but also endothelial cells, macrophages and pre-adipocytes secrete over 40 different autocrine, paracrine and endocrine factors such as hormones, cytokines, growth factors, complement factors, enzymes and matrix proteins (43). These secreted signaling factors or "adipokines", are involved in metabolism, inflammation and immunity, reproduction, vascular homeostasis and body weight regulation (44). As a complete summary of all known adipokines is beyond the scope of this review, we will focus on two adipokines, leptin and adiponectin, and the cytokines that have been studied extensively in relation to critical illness.

Leptin in critical illness

Leptin, a 16 kDa adipokine secreted by adipocytes, plays a critical role in determining food intake and energy expenditure (45;46). Circulating leptin concentrations are proportional to total body fat mass: levels are higher in obese individuals and are lowered when body fat mass is reduced by starvation or malnutrition (47). Through a homeostatic mechanism, high levels of leptin activate leptin receptors on specific neurons in the hypothalamus, which causes a reduction in food intake and an increase in peripheral energy expenditure while low leptin levels will evoke opposing effects (45;46). Leptin also has pro-inflammatory properties: it can modulate innate immune responses such as macrophage phagocytosis, T-helper cell differentiation and cytokine synthesis (48). Furthermore, leptin can stimulate proliferation and migration of endothelial cells, upregulation of endothelial NO production and ROS accumulation (49).

In stressful conditions, leptin levels become disproportionate to fat mass. This sudden leptin increase during stress may be explained by the concomitant rise in glucocorticoids, as cortisol acutely increases leptin expression and secretion (50). Also elevated levels of endotoxin and certain cytokines result in a significant elevation of leptin (51-53).

In several studies of critically ill patients, high leptin levels upon admission to intensive care have been reported (54-57). These elevated leptin levels subsequently declined during the prolonged phase

of sepsis (54-58). Levels of leptin were also significantly elevated in animal models of acute sepsis (53;59-61). On the contrary, several other studies in critically ill patients described low to normal levels of leptin in the acute phase of illness, and normal to elevated levels in the prolonged phase of illness (62-67). Possibly, this discrepancy is related to differences in time of sampling. In a study on the time course of leptin throughout sepsis and systemic inflammation not the admission leptin levels, but rather the day-2 levels were elevated, and returned to normal levels after one week (67). A study in trauma patients demonstrated an initial decline in leptin in the first 6 hours after major surgery, followed by a culminating increase 6-24h after surgery, after which leptin levels again declined (68).

Confounders such as heterogeneous patient population, severity of the infection, gender, BMI and differences in feeding regimen, both pre-admission and during the stay in intensive care, may have affected circulating leptin levels. For example, fasting or a period of malnutrition prior to surgery was shown to be associated with lowered leptin levels, whereas the administration of parenteral feeding may increase leptin levels (62;69-71). In a controlled, randomized animal study on critically ill rabbits it was clearly demonstrated that the administration of parenteral feeding increased circulating leptin levels over several days, whereas fasting was associated with subnormal leptin levels (72).

Not only the current data regarding the time course of leptin secretion during critical illness appears controversial, also its association with survival remains debatable. Whereas several studies demonstrated higher leptin levels in surviving than in non-surviving ICU patients, others reported lower or unaltered levels in surviving patients (51;54;56;58;65;73;74). A recent study demonstrated an association between long term survival and the expression of the leptin receptor levels rather than with circulating leptin levels (58). Animal studies on the role of leptin during sepsis only add on to the contradiction. Leptin-deficient and leptin receptor-deficient mice exhibited increased mortality following intratrachial *K. pneumoniae* administration (48;75). This increased susceptibility of leptin-deficient mice was associated with impaired bacterial clearance and defective alveolar macrophage phagocytosis in vitro and could be counteracted by administering high doses of leptin (48). In contrast, in a study by Shapiro et al., leptin receptor-deficient mice were protected from sepsis-induced mortality and exogenous administration of leptin increased mortality (76).

In conclusion, although the prospect of leptin becoming a prognostic tool or a therapeutic target has been suggested (58;67;74), the available contradicting and mostly descriptive data indicate that

further studies are required, more specifically with the aim of identifying confounders and regulators during critical illness.

Adiponectin in critical illness

Adiponectin is a large (30 kDa) peptide, abundantly present in the circulation, and secreted mainly by adipocytes. Adiponectin is involved in lipid and glucose metabolism, vascular homeostasis and immune function. Adiponectin is an insulin-sensitizing hormone, stimulating insulin signaling, decreasing hepatic glucose production and increasing glucose uptake and fatty acid oxidation in skeletal muscle (77-79). Adiponectin also has anti-inflammatory and anti-atherogenic properties. It increases endothelial NO production, reduces T-lymphocyte recruitment, reduces macrophage growth and interferes with the function of macrophages by reducing their phagocytic activity and LPS-induced production of cytokines and chemokines (80-82).

Several studies have demonstrated reduced adiponectin levels in critically ill patients upon admission to intensive care (63;83-86). Hypoadiponectinemia has also been reported in rats with sepsis (87). Low levels of adiponectin in the acute phase of illness and sepsis could inferentially be due to cytokines such as TNF-α, IL-6, and PAI-1 for which an inhibiting effect on adiponectin secretion has been demonstrated (88). Animal work suggest that also hyperglycemia and high cortisol levels might modulate low adiponectin levels (89). Interestingly, adiponectin knockout mice suffer from substantially increased mortality after cecal ligation and puncture-induced sepsis or thioglyocollate-induced peritonitis, largely attributable to impaired immune and endothelial function (90). Treatment with adiponectin prior to the insult blunted these effects (90).

From these reports, one might theorize that adiponectin treatment during critical illness would improve outcome, by improving the inflammatory response, increasing insulin sensitivity and reducing vasopressor needs (91). However, Walkey *et al.* demonstrated higher admission adiponectin levels in non-surviving patients with acute respiratory failure, compared to surviving patients (86). Additionally, Venkatesh et al described a positive, albeit weak correlation between sickness severity and plasma adiponectin at day 3 of illness (84). Furthermore, as in healthy humans, plasma adiponectin showed a positive correlation with plasma cortisol levels and with a higher insulin demand (84;92;93). Thus, higher admission adiponectin levels that were observed in more severely ill patients, might just be a reflection of the severity of their illness.

When patients do not recover immediately and enter a sustained phase of critical illness, adiponectin tends to normalize (63;83;85;86). This biphasic pattern of circulating adiponectin, could explain the conflicting results regarding outcome. Possibly, low adiponectin levels during the acute phase may allow a pro-inflammatory response whereas a rise in adiponectin during the prolonged phase of illness could mediate the late anti-inflammatory phase (94). It is possible that patients with higher adiponectin levels upon admission to intensive care suffer from higher mortality because they are not able to lower the anti-inflammatory adiponectin in an acute pro-inflammatory state.

The lack of data clearly indicate that, although adiponectin holds promise as a prognostic marker and therapeutic target, more study on the pathophysiology of adiponectin in relation to severe illness is needed.

Cytokines from adipose tissue and critical illness

Increasing evidence has emerged over the last couple of years indicating that adipose tissue is involved in inflammation and innate immunity (95;96). Chronic inflammation in adipose tissue and residing macrophages play an important role in the development of obesity-related insulin resistance (30;97). Adipocytes produce numerous pro-inflammatory, anti-inflammatory and immune-modulating proteins, belonging to the cytokine, chemokine, complement and growth factor families (96). Although extensive literature is available on circulating levels of different cytokines during critical illness, information on the role of adipose tissue in secreting or expressing such cytokines during critical illness remains scarce.

In humans, cardiac surgery has shown to induce a strong elevation in gene expression of IL-6, monocyte chemoattractant protein-1 (MCP-1) and TNF-α in adipose tissue (98). Also in adipose tissue of LPS injected mice, large increases in TNF-α, MCP-1 and IL-6 mRNA levels were evident (99;100). Experimental endotoxemia in healthy humans induced gene expression of pro-inflammatory cytokines IL-6, MCP-1 and TNF-α in gluteal adipose tissue aspirates (26). Remarkably, also the expression of the chemotactic CXCL10 and EMR1-F4/80 was upregulated, pointing to an increased macrophage recruitment (26).

In a study on prolonged critically ill patients, adipose tissue biopsies expressed low levels of TNF-α and high levels of the anti-inflammatory cytokine IL-10 (19). Furthermore, subcutaneous and visceral adipose tissue biopsies from prolonged critically ill patients displayed a large increase in macrophage

staining (18;19). This staining corresponded with elevated gene expression of "alternatively activated" M2 macrophage markers, such a as arginase-1 and CD163. In contrast with the classic activated M1 macrophages, M2 macrophages have local anti-inflammatory and insulin sensitizing features (19).

Taken together, in acute illness adipose tissue produces predominantly pro-inflammatory cytokines and chemotactic factors, thereby stimulating differentiation and attraction of macrophages, whereas in the prolonged phase, the accumulated adipose tissue macrophages are switched to an anti-inflammatory, insulin sensitizing macrophage profile. The trigger causing the switch of M1 to M2 type macrophages might involve increased levels of IL-4, IL-13 and IL-10, glucocorticoids, and macrophage colony-stimulating factor (GM-CSF), and necessarily depends upon activation of the nuclear receptor PPARγ (24;97).

The association of BMI and mortality in critically ill patients

In the general population, obesity, defined according to the World Health Organization as a body mass index > 30 kg/m^2, is associated with increased risk for morbidity, mortality and health care costs (101;102). Metabolic changes associated with obesity lead to deleterious conditions and diseases, among which dyslipidemia, atherosclerosis, arterial hypertension, diabetes, cardiac ischemic disease and fatty liver disease. Coinciding with its increasing prevalence in the general population, the number of obese patients in the intensive care unit has steadily increased over the years. In contrast with the above mentioned association with mortality in the general population, a high number of studies have described an inverse relationship among higher BMI and mortality in critically ill patients.

Three meta-analyses combining in total 25 different studies on BMI and outcome of the critically ill patient were recently published (103-105). Although largely heterogeneous and working with different obesity definitions, the studies included in the meta-analyses altogether are highly suggestive of a lower mortality risk in overweight (BMI 25-29.9 kg/m^2) and obese (BMI 30-39.9 kg/m^2) patients, whereas underweight (BMI<18.5 kg/m^2) patients appear to suffer from increased risk of mortality. Morbidly obese patients however do suffer from longer duration of mechanical ventilation and longer ICU length of stay (106). In more detail, the association between BMI and mortality in critically ill patients appears to follow a J-shaped curve (Figure 2). Remarkably, a comparable relationship between mortality and weight percentiles was found in the pediatric ICU (107).

Possible explanations for the obesity paradox in the ICU

Because of the feared risks and complications, obese patients might simply be admitted to the ICU earlier, while their condition is in fact less severe. Alternatively, underweight patients may suffer from chronic wasting caused by underlying pathologies. Nevertheless, trauma and surgical patients are less likely to suffer from such serious premorbid catabolic conditions and in these very patient populations a reduced mortality in overweight and/or mild obese patients could be detected (2;108-110).

It is possible that overweight and obese individuals have a lower mortality rate during critical illness, only because they have a larger amount of nutritional reserves. Indeed, mortality is also reduced in obese patients suffering from chronic wasting conditions such as congestive heart failure (111), renal disease (112;113), advanced malignancies and HIV/AIDS (114). Furthermore, from starvation research, it has become clear that obese individuals lose proteins much slower than lean individuals (115). This might protect the obese patient from the severe hypercatabolism present in critical illness, which generally evokes a profound decrease of lean body mass. On the other hand, the excessive adipose tissue in overweight and obese patients may play a metabolic role through enhanced triglycerides and glucose storage, which could be protective during critical illness (18).

Alternatively, one can speculate that excess adipose tissue might also act protectively as a source of beneficial adipokines. Obese, non-critically ill individuals generally display high leptin levels and low adiponectin levels. This adipokine profile is related to the amount of adipose tissue, and bariatric surgery with concomitant weight reduction will over time restore leptin and adiponectin levels (116). Normally, this adipokine profile is associated with increased insulin resistance (117;118). However, during critical illness, leptin has been shown to modulate innate immune responses, which might point to a protective role in the acute critically ill setting. In addition, low admission adiponectin levels were linked to better survival, possibly by allowing a pro-inflammatory response during the initial phase of illness (85). So in contrast with the chronic detrimental consequences of high leptin and low adiponectin levels, obese patients might benefit from their endocrine profile during the acute stress phase of critical illness.

Cytokines produced in the adipose tissue might be of importance as obese individuals often suffer from chronic adipose tissue inflammation with higher circulating TNF-α levels (30;97). However, a study performed by Collier *et al.* indicated that visceral body fat distribution in obese patients was not

associated with increased inflammatory profiles or clinical outcomes after trauma (119). The initial blood leukocyte inflammatory response to blunt trauma did not differ significantly between patients from different BMI categories (109). It is possible that the impact of severe injury or illness on acute inflammation overwhelms the metabolic disturbances and subclinical inflammation associated with obesity.

Obese individuals generally have higher circulating levels of lipoproteins and lipids then lean individuals. This could theoretically be beneficial during critical illness, because during acute illness hypo-cholesterolemia has been associated with severity of illness, morbidity and mortality (120;121). Especially low levels of HDL and LDL cholesterol have been linked to worse outcome in critically ill patients (39;122). This might be due to the importance of these lipoproteins in neutralizing endotoxins. Higher circulating levels in obese patients might thus reflect a larger availability to scavenge circulating endotoxin. In addition, low HDL levels have been linked to the development of adrenal insufficiency in the intensive care unit (123), whereas obese individuals often present a hyperactive hypothalamo-pituitary-adrenal axis and increased cortisol activation in adipose tissue (124;125).

One might speculate that just having a larger total fat depot is associated with a lower ICU mortality, be it because of having a higher energy reservoir to protect against hypercatabolism, a larger storage depot for toxic metabolites, or an increased availability of adipokines. In our study on the storage properties of adipose tissue, we could indeed demonstrate that adipose tissue from either normal or overweight critically ill patients acted identical in response to the stress of illness (19). However, the study did not include sufficient obese or morbidly obese patients to be able to extrapolate this conclusion to the whole range of excess BMI. The J-shaped relationship of BMI and mortality in critically ill patients indicates that too much excess fat is no longer protective. In addition, some studies did demonstrate a higher mortality in obese patients (108;109;126), making it thus as yet unclear at what point a higher BMI switches from being protective to malignant.

In addition, a study by Paolini *et al* demonstrated that only abdominal obese patients suffered from a higher risk of death, which suggests that also adipose location might be an important factor in determining the relation between BMI and outcome (127). Indeed, while increased visceral adiposity is a strong predictor of type 2 diabetes and cardiovascular disease, subcutaneous adipose tissue is thought to offer improved glucose tolerance (128). This location dependent metabolic differences might be due to a differential developmental gene expression profile, or to diverse exposition to

paracrine and endocrine signals where visceral fat metabolites are particularly drained to the liver via the portal circulation (129;130). Noticeable, adipose tissue site-related diverse functioning appears completely overwhelmed by critical illness (18;19;63).

An important limitation in the current knowledge however is that cited studies only describe an association between better survival and obesity and thus do not prove a cause-and-effect relationship. Future studies on the relation between obesity and mortality in critically ill patients should preferably include more relevant information on the feeding status of the patients, clearly describe weight categories, admission severity of illness, and provide more elaborate information on weight and body composition. In addition, well-controlled animal studies are needed to clarify the mechanisms behind the obesity paradox.

Conclusions

Critically ill patients suffer from severe muscle wasting, whereas fat stores are preserved or even built up. A high number of studies have described a J-shaped relationship between BMI and mortality in critically ill patients. Altogether, these studies suggest a lower mortality in overweight and obese patients, whereas underweight patients appear to suffer from increased mortality. These observations indicate a possible important metabolic role for adipose tissue during critical illness.

Morphologically, adipose tissue of prolonged critically ill patients reveals an increase in newly differentiated, smaller adipocytes and an infiltration of M2 macrophages. Functionally, adipose tissue of critically ill patients increases its property to store glucose and triglycerides, thereby possibly reducing detrimental effects of high levels of these circulating metabolites.

The endocrine functions of adipose tissue might play a role in the adaptation to critical illness. In the acute phase of illness, the anti-inflammatory adiponectin is reduced, while pro-inflammatory cytokine expression in adipose tissue is upregulated. In the prolonged phase of critical illness, both adiponectin and anti-inflammatory cytokine production is increasing and accumulated macrophages switch to the anti-inflammatory, insulin-sensitizing M2 type. Studies on the pro-inflammatory leptin during critical illness are inconsistent possibly due to confounders such as gender, BMI and concomitant feeding.

Several of the changes in adipose tissue observed during critical illness could in theory be adaptive and protective. Hence, stimulation of the endocrine and storage properties of adipose tissue may hold therapeutic promise, which should be investigated.

Further research is needed to understand the exact functioning of adipose tissue in lean versus obese critically ill patients and its potential role in the observed obesity paradox.

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Figures

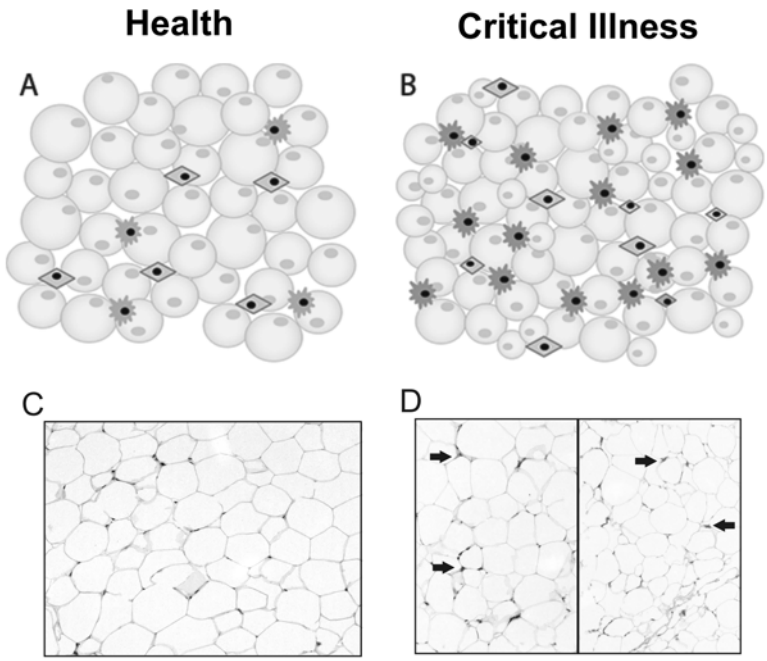

Figure 1: Overview of the morphological changes observed in adipose tissue during critical illness (18). (A-B) schematic overview of the observed changes: during critical illness adipocytes (round cells) become smaller and increase in number, macrophages (starlike shaped cells) increase in number and pre-adipocyte markers (diamond shaped cells) are elevated. (C-D) Microscopic representative adipose tissue images from a healthy volunteer and from 2 critically ill patients, stained for macrophages. The black arrows illustrate stained macrophages.

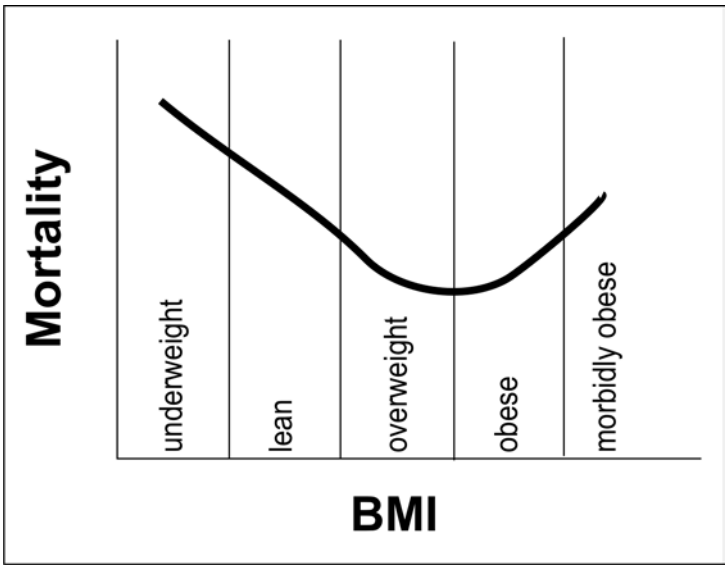

Figure 2: Schematic presentation of the association of mortality and BMI of critically ill patients.

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