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Potential Role of Adipose Tissue and its Hormones in Burns and Critically Ill Patients

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Abstract
Obesity has become a world-wide pandemic and is considered a major risk factor for various diseases. Despite this, recent intriguing clinical observations have been made suggesting that being overweight has some advantages. Overweight and some obese patients were reported to have significantly lower all-cause mortality, described as the 'obesity paradox'. This phenomenon resulted in increased research aimed at investigating the influence of adipose tissue on outcomes of various clinical states including critical illness. In this review, we summarise research findings on the effect burn injury and trauma-related critical illness have on adipose tissue and discuss potential mechanisms by which adipose tissue influences outcomes in burn and other critically ill patients. Burn injury and critical illness influence adipose tissue functionally and morphologically, with circulating levels of fat derived hormones, adipokines, altered in patients following injury and/or critical illness. As adipokines regulate a variety of processes including inflammation and metabolism, this disruption in the adipokine axis may explain the obesity paradox phenomenon observed in critically ill patients. We conclude that further research on the influence of individual adipokines on prognosis in burn and critically ill patients and the mechanisms involved is required to increase understanding of their therapeutic potential.

Highlights

- The Obesity Paradox has been reported in critically ill populations.
- Burn injury and critical illness affect adipose tissue morphologically and functionally.
- Adipokines exert anti- and pro-inflammatory effects influencing patient outcomes.
- Current scar reduction treatments utilising adipose tissue potentially mediate their effects through release of adipokines.

Keywords
Burns, Thermal Injury, Adipose Tissue, Fat, Hormones, Adipokines

Abbreviations

APACHE	Acute Physiological Assessment and Chronic Health Evaluation
CRP	C-Reactive Protein
FFA	Free Fatty Acids
HMG-CoA	Hydroxymethyl Glutaryl Coenzyme A
IL	Interleukin
RCT	Randomised Controlled Trial
SAPS	Simplified Acute Physiology Score
SOFA	Sequential Organ Failure Assessment

Introduction

Obesity is a complex multifactorial condition that affects over a third of the world's population [1]. With increasing prevalence of overweight and obese individuals [2, 3], obesity is being described as a global pandemic [4] as obesity greatly impacts the individual's health status and quality of life[5, 6] being a major risk factor for various pathologies including cancer, cardiovascular disease, diabetes and osteoarthritis [7].

In this context a recent and intriguing observation is that all-cause mortality is reported to be significantly lower in overweight and some obese patients [8]. This phenomenon, where outcomes are paradoxically better in overweight and obese patients compared to normal weight individuals, is described as the 'obesity paradox' and is the subject of increasing interest in scientific and medical communities [9-12]. The underlying mechanisms behind this phenomenon remain poorly understood and this is particularly the case in critically ill populations where the data on the obesity paradox are limited.

This review aims to summarise the observations suggesting the presence of the obesity paradox in critically ill patients, including burns and to discuss potential mechanisms that may explain the difference in outcomes between normal weight, overweight and obese patients, focusing primarily on hormones secreted by adipose tissue (adipokines).

Adipose Tissue in Burns and Critical Illness

Adipose tissue is one of the largest organs in the human body. Importantly, it is no longer deemed an inert tissue that serves the roles of thermal/mechanical insulation protecting internal organs from external stimuli (such as cold and shock) or as an energy storage modality. Since the discovery in 1994 of leptin, an adipokine or adipose-derived hormone capable of controlling body energy balance [13], adipose tissue is now recognised as endocrine organ able to influence metabolism and inflammatory status. As a result extensive research has been carried out investigating potential roles of adipokines in various clinical conditions including autoimmune and inflammatory disorders and connective tissue diseases [14], metabolic disorders [15, 16], cardiovascular and neurovascular diseases [17], and cancer [18, 19].

Despite increasing interest in adipose tissues' role in clinical pathologies, its role in the context of critical illness including burns and trauma remains to be fully elucidated. With thousands of critically ill patients admitted to intensive care units every year [20] some interesting observations have been made. Patients requiring prolonged critical care were reported to lose lean body mass while adipose tissue mass remained preserved or even increased [21, 22]. Furthermore, although morbid obesity (BMI ≥ 40 kg/m^2) is an independent risk factor for mortality in critically ill patients [23], improved survival rates were observed among overweight (BMI 25-30 kg/m^2) and obese (BMI 30-40 kg/m^2) patients compared to normal BMI patients during critical illness [23-26]. These paradoxical findings have stimulated research in to the interplay between critical illness and adipose tissue and their influence on patient outcomes. Moreover the profound

inflammatory and metabolic response to burn and trauma related critical illness suggest a potential involvement for adipose tissue and adipokines.

Critical illness following injury is a multifactorial heterogeneous disorder characterised by an overwhelming pro-inflammatory response accompanied by a compensatory anti-inflammatory reaction and subsequent immunosuppression [27, 28].This classical paradigm also applies to severe forms of critical illness such as burns, the pathology of which we have described previously [29, 30]. The human response to burn injury includes a so-called 'genomic storm'[31], consistent with simultaneous increased systemic inflammation, innate immune activation and anti-inflammatory response [32, 33], as well as suppression of adaptive immunity[31]. In addition, burn patients and others with severe critical illness suffer from a prolonged hypermetabolic, hypercatabolic response [33, 34].

The metabolic response following thermal injury is characterised as a two phase response: the 'ebb' phase within 48 hours where metabolism, cardiac output and oxygen consumption are reduced, followed by the 'flow' phase at approximately 120 hours post-injury where these parameters increase and plateau [35]. This metabolic response includes: peripheral lipolysis and free fatty acid (FFA) [36] oxidation leading to an acute, global and complex increase in FFA levels[37]; systemic induction of endoplasmic reticulum (ER) stress and unfolded protein response [38]; up to 6-fold increase in breakdown rates of skeletal muscle protein[39]; elevation in resting energy expenditure up to 140%[40] that can be prolonged [33].

Burns and other severe critical illnesses have been reported to influence adipose tissue morphologically and functionally. Saraf *et al* reported the impact of severe burn injury on subcutaneous white adipose tissue in children and observed significantly reduced adipocyte size, increased collagen deposition and cell mitochondria content, increased immune cells such macrophages, as well as increased inflammatory cytokine production [41]. These morphological changes suggest "browning" of subcutaneous adipose tissue following thermal injury, a finding which was confirmed biochemically and functionally. Sidossis *et al* reported significantly increased mitochondrial density and mitochondrial respiratory capacity, as well as an 80-fold increase in the expression of uncoupling protein 1 (UCP1), a molecule abundantly observed in brown adipose tissue depots [42], in burn patients compared to healthy controls [43]. In addition, Patsouris *et al* reported similar findings including significantly increased mitochondrial mass and adipose tissue browning markers in burn patients [44]. This could be a compensatory mechanism since brown adipose tissue is known to induce thermogenesis, modulate energy expenditure and exert local tissue effects such as stimulating angiogenesis and influencing macrophage polarization [45]. Similar morphological and metabolic activity alterations of adipose tissue have been reported in critically ill patients[46, 47]. A functional aspect of adipose tissue is its endocrine role through the production of adipokines and these may mediate many of the effects seen in burns and critical illness.

Overview of Adipokines and their Biological Effects

There are approximately 600 identified hormones secreted by adipose tissue [48], providing a rich source of potential novel biomarkers and therapeutic targets for the management of various pathologies. In this review, we will focus on Adiponectin, Ghrelin, Leptin, Resistin and Visfatin as the best characterised adipokines.

Adiponectin is released exclusively from white adipose tissue[49], and is the most abundant adipose-specific adipokine, with expression in subcutaneous fat being greater than visceral fat [50]. Adiponectin has anti-inflammatory effects [51]. Ghrelin is an orexigenic hormone that is an endogenous ligand to growth hormone and was initially thought to be produced mainly by the stomach [52], but has subsequently been identified in other tissues including adipose tissue [53]. Ghrelin signaling is associated with adiposity, changes in fat distribution and mobilisation, independent of growth hormone and dietary intake[54, 55]. Leptin is primarily secreted by subcutaneous white adipose tissue, the amount of leptin secreted into the circulation is proportional to adipose tissue mass and nutritional status[51]. Leptin exhibits structural similarities to cytokines [56] and is pro-inflammatory [57]. Resistin is also a pro-inflammatory adipokine expressed by adipocytes and other tissues including skeletal muscle [58, 59]. Visfatin, also called pre-B-cell colony enhancing factor, is primarily secreted by adipocytes in visceral white adipose tissue and exhibits pro-inflammatory effects [60].

Relevant to this review, adipokines have been reported to influence skin and adipose tissue. Adiponectin and ghrelin have been observed to exert anti-inflammatory and anti-fibrotic effects on skin [61-63] and were reported to enhance wound healing rates [64, 65]. Similarly, leptin has been observed to enhance human epidermal keratinocyte and epithelial cell proliferation, differentiation and migration, as well as promote angiogenesis within dermal connective tissues [66]. However, leptin was also found to be overexpressed in hypertrophic and keloid scars [67]. This could be due to increased pro-inflammatory cytokine release associated with leptin, as seen in inflammatory skin conditions [68]. Visfatin has been reported to enhance chemokine and antimicrobial peptide production in human keratinocytes [69, 70], as well as exhibit anti-fibrotic properties[71].

Adiponectin and leptin have been reported to induce browning of adipose tissue [72, 73] and adiponectin promotes adipogenesis as well as increasing lipid accumulation and insulin responsiveness of adipocytes [74]. In contrast, leptin inhibits insulin-dependent glucose uptake and lipogenesis and reverses insulin-induced lipolysis [75]. Ghrelin stimulates adipogenesis and glucose uptake, as well as inhibiting lipolysis, apoptosis and autophagy of adipocytes [76, 77]. Resistin and visfatin enhance pro-inflammatory cytokine expression in adipose tissue including TNF-α and IL-6 [78, 79]. Similarly, resistin and visfatin induce insulin resistance in adipocytes [79, 80]. The influence of these adipokines is not limited to skin and adipose tissue. The beneficial and detrimental effects of these adipokines on various cell types and tissues are summarized in Figure 1 and the reader is also referred to recent reviews for further detail [17, 81-88].

Figure 1. Effects of adipokines on various tissues and organs

Adipokine changes in burns and critically ill patients

Several studies have demonstrated acute reductions in circulating adiponectin levels in critical illness and/or injury including burns, sepsis and trauma [89-95]. In addition, an inverse association was reported between serum adiponectin levels and severity of illness as measured by C-Reactive Protein (CRP), Simplified Acute Physiology Score (SAPS) II and Sequential Organ Failure Assessment (SOFA) scores [91, 92, 95]. Similar findings were observed in patients with acute pancreatitis, where adiponectin levels in the blood were negatively associated with severity of disease and incidence of tissue necrosis [93]. Furthermore, adiponectin levels progressively increase with patient recovery [91, 94]. Although the above findings indicate that decreased serum adiponectin levels may lead to poor outcomes, other research has reported different findings. Circulating adiponectin levels in severely ill patients did not correlate with inflammatory markers including Interleukin (IL) -6, IL-10 and Tumour Necrosis Factor (TNF)-α [89, 96, 97] and clinical scores including Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score and SOFA [96, 98, 99]. Furthermore, higher blood adiponectin levels were associated with increased risk of mortality during critical illness[100-103].

Only two studies have investigated circulating ghrelin levels in critical illness. Wade *et al* reported significantly reduced ghrelin levels in severely burned patients correlating with metabolic/caloric needs. No other associations with other parameters such as injury severity and inflammatory status were observed [89]. Santacruz *et al* also observed significantly reduced plasma ghrelin levels in critically ill patients but saw no correlations with feeding status [104].

Leptin levels in the blood have been reported to be elevated in critical illness [105-108]. Furthermore, leptin was positively associated with pro-inflammatory status of severely ill patients, as measured by CRP, IL-6, sTNFR1 and TNF-α [106, 108-111]. Additionally, other studies have reported that serum-soluble leptin receptor (SLR) in patients correlated with inflammatory response and illness severity as measured by IL-6, lactate, procalcitonin and APACHE II score [112, 113]. Interestingly, elevated levels of leptin were observed in survivors of acute sepsis [105], while increased SLR levels in critically ill patients were associated with increased mortality [112]. However, other studies have reported different findings. Blood leptin levels in severely ill patients were similar or reduced compared to healthy volunteers [89, 94, 95, 109, 112, 114] and no associations were found between circulating leptin levels and inflammatory status, illness severity, or mortality in critical illness [94, 95, 107, 109, 111, 112, 114].

In contrast to the heterogeneity of results reported on the impact adiponectin, ghrelin and leptin on critical illness outcomes, the influence of resistin and visfatin on outcomes

of severely ill patients is consistent in the literature. Critically ill patients exhibit significantly elevated circulating levels of resistin [89, 95, 98, 99, 111, 115-120] and visfatin [111, 121-127]. Additionally, both resistin and visfatin significantly correlated with pro-inflammatory responses (including CRP, IL-6, IL-8 and TNF-α), and worse clinical severity scores (including APACHE II, Glasgow Coma score, multiple organ dysfunction score, SAPS II and SOFA)[89, 95, 98, 99, 111, 115-119, 121-127]. Furthermore, high resistin and visfatin levels in blood were associated with poor outcomes including mortality [116, 117, 122-126].

A systematic review examining the evidence for adipokines having an influence on critical care patients has been published recently [128]. It concludes that although strong observations were reported indicating the influence of adipokines on the prognosis of critical illness, additional larger studies that incorporate more diverse cohorts (such as age, gender, BMI, ethnic groups and different pathologies) is required to better understand the relationship between adipokines and critical illness. This is essential in order to validate the potential clinical value and utility of adipokines as diagnostic and/or prognostic biomarkers, as well their potential as therapeutic targets in critical illness including burn and trauma. Furthermore, studies to date have investigated the association of adipokines with critical illness in the acute setting only. This focus on the acute setting has further limited the translation of adipokines in clinical settings. Importantly, since medical care advancements have improved survival rates after critical trauma [129-131], greater emphasis is now placed on the prevention and treatment of potentially debilitating long-term sequelae experienced by survivors of severe illness including chronic critical illness [132-134], prolonged pathophysiological responses[33] and scarring [135].

Conclusions

Several studies have reported changes in the serum levels of specific adipokines and their role in the regulation of a range of biological responses to injury including inflammation, metabolic dysregulation and wound healing is emerging. However a robust characterisation of the impact of such changes in individual adipokines on patient outcomes, especially in burns patients, is lacking. Large clinical and scientific studies are required to establish the mechanisms by which adipose tissue may influence patient outcomes and translate the research into clinical practice to improve short and long-term outcomes of burn and critically ill patients.

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Highlights

- The Obesity Paradox has been reported in critically ill populations.
- Burn injury and critical illness affect adipose tissue morphologically and functionally.
- Adipokines exert anti- and pro-inflammatory effects influencing patient outcomes.
- Current validated medical treatments utilize adipose tissue and potentially adipokines.

Potential Role of Adipose Tissue and its Hormones in Burns and Critically Ill Patients

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Abstract
Obesity has become a world-wide pandemic and is considered a major risk factor for various diseases. Despite this, recent intriguing clinical observations have been made suggesting that being overweight has some advantages. Overweight and some obese patients were reported to have significantly lower all-cause mortality, described as the 'obesity paradox'. This phenomenon resulted in increased research aimed at investigating the influence of adipose tissue on outcomes of various clinical states including critical illness. In this review, we summarise research findings on the effect burn injury and trauma-related critical illness have on adipose tissue and discuss potential mechanisms by which adipose tissue influences outcomes in burn and other critically ill patients. Burn injury and critical illness influence adipose tissue functionally and morphologically, with circulating levels of fat derived hormones, adipokines, altered in patients following injury and/or critical illness. As adipokines regulate a variety of processes including inflammation and metabolism, this disruption in the adipokine axis may explain the obesity paradox phenomenon observed in critically ill patients. We conclude that further research on the influence of individual adipokines on prognosis in burn and critically ill patients and the mechanisms involved is required to increase understanding of their therapeutic potential.

Highlights

- The Obesity Paradox has been reported in critically ill populations.
- Burn injury and critical illness affect adipose tissue morphologically and functionally.
- Adipokines exert anti- and pro-inflammatory effects influencing patient outcomes.
- Current scar reduction treatments utilising adipose tissue potentially mediate their effects through release of adipokines.

Keywords
Burns, Thermal Injury, Adipose Tissue, Fat, Hormones, Adipokines

Abbreviations

APACHE	Acute Physiological Assessment and Chronic Health Evaluation
CRP	C-Reactive Protein
FFA	Free Fatty Acids
HMG-CoA	Hydroxymethyl Glutaryl Coenzyme A
IL	Interleukin
RCT	Randomised Controlled Trial
SAPS	Simplified Acute Physiology Score
SOFA	Sequential Organ Failure Assessment

Introduction

Obesity is a complex multifactorial condition that affects over a third of the world's population [1]. With increasing prevalence of overweight and obese individuals [2, 3], obesity is being described as a global pandemic [4] as obesity greatly impacts the individual's health status and quality of life[5, 6] being a major risk factor for various pathologies including cancer, cardiovascular disease, diabetes and osteoarthritis [7].

In this context a recent and intriguing observation is that all-cause mortality is reported to be significantly lower in overweight and some obese patients [8]. This phenomenon, where outcomes are paradoxically better in overweight and obese patients compared to normal weight individuals, is described as the 'obesity paradox' and is the subject of increasing interest in scientific and medical communities [9-12]. The underlying mechanisms behind this phenomenon remain poorly understood and this is particularly the case in critically ill populations where the data on the obesity paradox are limited.

This review aims to summarise the observations suggesting the presence of the obesity paradox in critically ill patients, including burns and to discuss potential mechanisms that may explain the difference in outcomes between normal weight, overweight and obese patients, focusing primarily on hormones secreted by adipose tissue (adipokines).

Adipose Tissue in Burns and Critical Illness

Adipose tissue is one of the largest organs in the human body. Importantly, it is no longer deemed an inert tissue that serves the roles of thermal/mechanical insulation protecting internal organs from external stimuli (such as cold and shock) or as an energy storage modality. Since the discovery in 1994 of leptin, an adipokine or adipose-derived hormone capable of controlling body energy balance [13], adipose tissue is now recognised as endocrine organ able to influence metabolism and inflammatory status. As a result extensive research has been carried out investigating potential roles of adipokines in various clinical conditions including autoimmune and inflammatory disorders and connective tissue diseases [14], metabolic disorders [15, 16], cardiovascular and neurovascular diseases [17], and cancer [18, 19].

Despite increasing interest in adipose tissues' role in clinical pathologies, its role in the context of critical illness including burns and trauma remains to be fully elucidated. With thousands of critically ill patients admitted to intensive care units every year [20] some interesting observations have been made. Patients requiring prolonged critical care were reported to lose lean body mass while adipose tissue mass remained preserved or even increased [21, 22]. Furthermore, although morbid obesity (BMI ≥ 40 kg/m^2) is an independent risk factor for mortality in critically ill patients [23], improved survival rates were observed among overweight (BMI 25-30 kg/m^2) and obese (BMI 30-40 kg/m^2) patients compared to normal BMI patients during critical illness [23-26]. These paradoxical findings have stimulated research in to the interplay between critical illness and adipose tissue and their influence on patient outcomes. Moreover the profound

inflammatory and metabolic response to burn and trauma related critical illness suggest a potential involvement for adipose tissue and adipokines.

Critical illness following injury is a multifactorial heterogeneous disorder characterised by an overwhelming pro-inflammatory response accompanied by a compensatory anti-inflammatory reaction and subsequent immunosuppression [27, 28].This classical paradigm also applies to severe forms of critical illness such as burns, the pathology of which we have described previously [29, 30]. The human response to burn injury includes a so-called ‘genomic storm’[31], consistent with simultaneous increased systemic inflammation, innate immune activation and anti-inflammatory response [32, 33], as well as suppression of adaptive immunity[31]. In addition, burn patients and others with severe critical illness suffer from a prolonged hypermetabolic, hypercatabolic response [33, 34].

The metabolic response following thermal injury is characterised as a two phase response: the ‘ebb’ phase within 48 hours where metabolism, cardiac output and oxygen consumption are reduced, followed by the ‘flow’ phase at approximately 120 hours post-injury where these parameters increase and plateau [35]. This metabolic response includes: peripheral lipolysis and free fatty acid (FFA) [36] oxidation leading to an acute, global and complex increase in FFA levels[37]; systemic induction of endoplasmic reticulum (ER) stress and unfolded protein response [38]; up to 6-fold increase in breakdown rates of skeletal muscle protein[39]; elevation in resting energy expenditure up to 140%[40] that can be prolonged [33].

Burns and other severe critical illnesses have been reported to influence adipose tissue morphologically and functionally. Saraf *et al* reported the impact of severe burn injury on subcutaneous white adipose tissue in children and observed significantly reduced adipocyte size, increased collagen deposition and cell mitochondria content, increased immune cells such macrophages, as well as increased inflammatory cytokine production [41]. These morphological changes suggest “browning” of subcutaneous adipose tissue following thermal injury, a finding which was confirmed biochemically and functionally. Sidossis *et al* reported significantly increased mitochondrial density and mitochondrial respiratory capacity, as well as an 80-fold increase in the expression of uncoupling protein 1 (UCP1), a molecule abundantly observed in brown adipose tissue depots [42], in burn patients compared to healthy controls [43]. In addition, Patsouris *et al* reported similar findings including significantly increased mitochondrial mass and adipose tissue browning markers in burn patients [44]. This could be a compensatory mechanism since brown adipose tissue is known to induce thermogenesis, modulate energy expenditure and exert local tissue effects such as stimulating angiogenesis and influencing macrophage polarization [45]. Similar morphological and metabolic activity alterations of adipose tissue have been reported in critically ill patients[46, 47]. A functional aspect of adipose tissue is its endocrine role through the production of adipokines and these may mediate many of the effects seen in burns and critical illness.

Overview of Adipokines and their Biological Effects

There are approximately 600 identified hormones secreted by adipose tissue [48], providing a rich source of potential novel biomarkers and therapeutic targets for the management of various pathologies. In this review, we will focus on Adiponectin, Ghrelin, Leptin, Resistin and Visfatin as the best characterised adipokines.

Adiponectin is released exclusively from white adipose tissue[49], and is the most abundant adipose-specific adipokine, with expression in subcutaneous fat being greater than visceral fat [50]. Adiponectin has anti-inflammatory effects [51]. Ghrelin is an orexigenic hormone that is an endogenous ligand to growth hormone and was initially thought to be produced mainly by the stomach [52], but has subsequently been identified in other tissues including adipose tissue [53]. Ghrelin signaling is associated with adiposity, changes in fat distribution and mobilisation, independent of growth hormone and dietary intake[54, 55]. Leptin is primarily secreted by subcutaneous white adipose tissue, the amount of leptin secreted into the circulation is proportional to adipose tissue mass and nutritional status[51]. Leptin exhibits structural similarities to cytokines [56] and is pro-inflammatory [57]. Resistin is also a pro-inflammatory adipokine expressed by adipocytes and other tissues including skeletal muscle [58, 59]. Visfatin, also called pre-B-cell colony enhancing factor, is primarily secreted by adipocytes in visceral white adipose tissue and exhibits pro-inflammatory effects [60].

Relevant to this review, adipokines have been reported to influence skin and adipose tissue. Adiponectin and ghrelin have been observed to exert anti-inflammatory and anti-fibrotic effects on skin [61-63] and were reported to enhance wound healing rates [64, 65]. Similarly, leptin has been observed to enhance human epidermal keratinocyte and epithelial cell proliferation, differentiation and migration, as well as promote angiogenesis within dermal connective tissues [66]. However, leptin was also found to be overexpressed in hypertrophic and keloid scars [67]. This could be due to increased pro-inflammatory cytokine release associated with leptin, as seen in inflammatory skin conditions [68]. Visfatin has been reported to enhance chemokine and antimicrobial peptide production in human keratinocytes [69, 70], as well as exhibit anti-fibrotic properties[71].

Adiponectin and leptin have been reported to induce browning of adipose tissue [72, 73] and adiponectin promotes adipogenesis as well as increasing lipid accumulation and insulin responsiveness of adipocytes [74]. In contrast, leptin inhibits insulin-dependent glucose uptake and lipogenesis and reverses insulin-induced lipolysis [75]. Ghrelin stimulates adipogenesis and glucose uptake, as well as inhibiting lipolysis, apoptosis and autophagy of adipocytes [76, 77]. Resistin and visfatin enhance pro-inflammatory cytokine expression in adipose tissue including TNF-α and IL-6 [78, 79]. Similarly, resistin and visfatin induce insulin resistance in adipocytes [79, 80]. The influence of these adipokines is not limited to skin and adipose tissue. The beneficial and detrimental effects of these adipokines on various cell types and tissues are summarized in Figure 1 and the reader is also referred to recent reviews for further detail [17, 81-88].

Figure 1. Effects of adipokines on various tissues and organs

Adipokine changes in burns and critically ill patients

Several studies have demonstrated acute reductions in circulating adiponectin levels in critical illness and/or injury including burns, sepsis and trauma [89-95]. In addition, an inverse association was reported between serum adiponectin levels and severity of illness as measured by C-Reactive Protein (CRP), Simplified Acute Physiology Score (SAPS) II and Sequential Organ Failure Assessment (SOFA) scores [91, 92, 95]. Similar findings were observed in patients with acute pancreatitis, where adiponectin levels in the blood were negatively associated with severity of disease and incidence of tissue necrosis [93]. Furthermore, adiponectin levels progressively increase with patient recovery [91, 94]. Although the above findings indicate that decreased serum adiponectin levels may lead to poor outcomes, other research has reported different findings. Circulating adiponectin levels in severely ill patients did not correlate with inflammatory markers including Interleukin (IL) -6, IL-10 and Tumour Necrosis Factor (TNF)-α [89, 96, 97] and clinical scores including Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score and SOFA [96, 98, 99]. Furthermore, higher blood adiponectin levels were associated with increased risk of mortality during critical illness[100-103].

Only two studies have investigated circulating ghrelin levels in critical illness. Wade *et al* reported significantly reduced ghrelin levels in severely burned patients correlating with metabolic/caloric needs. No other associations with other parameters such as injury severity and inflammatory status were observed [89]. Santacruz *et al* also observed significantly reduced plasma ghrelin levels in critically ill patients but saw no correlations with feeding status [104].

Leptin levels in the blood have been reported to be elevated in critical illness [105-108]. Furthermore, leptin was positively associated with pro-inflammatory status of severely ill patients, as measured by CRP, IL-6, sTNFR1 and TNF-α [106, 108-111]. Additionally, other studies have reported that serum-soluble leptin receptor (SLR) in patients correlated with inflammatory response and illness severity as measured by IL-6, lactate, procalcitonin and APACHE II score [112, 113]. Interestingly, elevated levels of leptin were observed in survivors of acute sepsis [105], while increased SLR levels in critically ill patients were associated with increased mortality [112]. However, other studies have reported different findings. Blood leptin levels in severely ill patients were similar or reduced compared to healthy volunteers [89, 94, 95, 109, 112, 114] and no associations were found between circulating leptin levels and inflammatory status, illness severity, or mortality in critical illness [94, 95, 107, 109, 111, 112, 114].

In contrast to the heterogeneity of results reported on the impact adiponectin, ghrelin and leptin on critical illness outcomes, the influence of resistin and visfatin on outcomes

of severely ill patients is consistent in the literature. Critically ill patients exhibit significantly elevated circulating levels of resistin [89, 95, 98, 99, 111, 115-120] and visfatin [111, 121-127]. Additionally, both resistin and visfatin significantly correlated with pro-inflammatory responses (including CRP, IL-6, IL-8 and TNF-α), and worse clinical severity scores (including APACHE II, Glasgow Coma score, multiple organ dysfunction score, SAPS II and SOFA)[89, 95, 98, 99, 111, 115-119, 121-127]. Furthermore, high resistin and visfatin levels in blood were associated with poor outcomes including mortality [116, 117, 122-126].

A systematic review examining the evidence for adipokines having an influence on critical care patients has been published recently [128]. It concludes that although strong observations were reported indicating the influence of adipokines on the prognosis of critical illness, additional larger studies that incorporate more diverse cohorts (such as age, gender, BMI, ethnic groups and different pathologies) is required to better understand the relationship between adipokines and critical illness. This is essential in order to validate the potential clinical value and utility of adipokines as diagnostic and/or prognostic biomarkers, as well their potential as therapeutic targets in critical illness including burn and trauma. Furthermore, studies to date have investigated the association of adipokines with critical illness in the acute setting only. This focus on the acute setting has further limited the translation of adipokines in clinical settings. Importantly, since medical care advancements have improved survival rates after critical trauma [129-131], greater emphasis is now placed on the prevention and treatment of potentially debilitating long-term sequelae experienced by survivors of severe illness including chronic critical illness [132-134], prolonged pathophysiological responses[33] and scarring [135].

Conclusions

Several studies have reported changes in the serum levels of specific adipokines and their role in the regulation of a range of biological responses to injury including inflammation, metabolic dysregulation and wound healing is emerging. However a robust characterisation of the impact of such changes in individual adipokines on patient outcomes, especially in burns patients, is lacking. Large clinical and scientific studies are required to establish the mechanisms by which adipose tissue may influence patient outcomes and translate the research into clinical practice to improve short and long-term outcomes of burn and critically ill patients.

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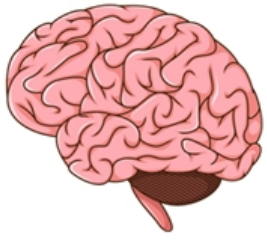
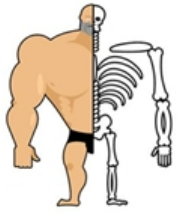
Cardiovascular System

- Influences myocardial and vascular inflammation, remodeling and fibrosis
- Affects myocardial metabolism and function
- Modulates atherosclerosis and thrombotic activity



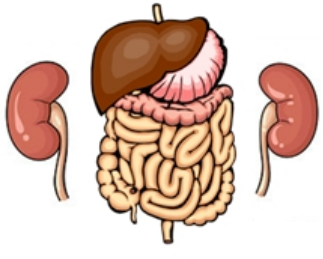
Nervous System

- Influences neuronal responsiveness
- Affects neuroendocrine mechanisms associated with feeding and energy expenditure
- Modulates neuro-inflammation



Musculoskeletal System

- Influences glucose uptake and insulin sensitivity
- Modulates protein and fatty acid metabolism
- Affects lipid deposition in muscle



Gastrointestinal and Renal System

- Modulates gastrointestinal and renal inflammation
- Influences cellular apoptosis
- Affects renal metabolism and function

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Declaration of interest

Declarations of interest: none.