

Review

Physiological Activities of Adiponectin Provide Therapeutic Opportunities in Sepsis

Thomas Grewal¹, Christa Buechler^{2,*}

¹School of Pharmacy, Faculty of Medicine and Health, University of Sydney, Sydney, NSW 2006, Australia

²Department of Internal Medicine I, University Hospital Regensburg, 93053 Regensburg, Germany

*Correspondence: christa.buechler@klinik.uni-regensburg.de (Christa Buechler)

Academic Editor: Graham Pawelec

Submitted: 14 August 2024 Revised: 22 October 2024 Accepted: 8 November 2024 Published: 17 June 2025

Abstract

Sepsis represents a life-threatening organ dysfunction due to a compromised host response caused by bacterial and viral infections. Although progress has been made to unravel the underlying pathophysiology, sepsis remains a very serious condition. Adiponectin is an adipokine with multiple beneficial activities relevant to glucose and lipid metabolism whose serum levels are low in obesity and metabolic diseases. In addition, several immunoregulatory activities of adiponectin have been described and circulating adiponectin levels have been positively associated with inflammation in autoimmune diseases such as rheumatoid arthritis and type 1 diabetes. Although an understanding of physiological consequences is still limited, blood adiponectin levels are also elevated in chronic kidney disease and liver cirrhosis, possibly due to impaired biliary and renal excretion. Natriuretic peptides, which increase adiponectin synthesis in adipocytes and are induced in autoimmune diseases and cirrhosis and decreased in obesity, appear to contribute to altered systemic adiponectin levels. In patients with sepsis, data on circulating adiponectin levels are not concordant, probably due to the large diversity in cohorts analyzed, often including patients with a higher risk for severe sepsis due to chronic metabolic disease or other comorbidities. This review article summarizes the main physiological activities of adiponectin and describes its role in inflammation and experimental sepsis. Adiponectin levels obtained in observational studies from serum or plasma of patients with critical illness are discussed. From this analysis, we conclude that circulating adiponectin levels are reduced in sepsis and septic shock, suggesting the potential of adiponectin receptor agonists as an option for sepsis therapy.

Keywords: adiponectin; bacterial infection; inflammation; SARS-CoV-2; obesity; sepsis

1. Introduction

Sepsis is a very serious health condition characterized by organ dysfunction that is predominantly (~90%) caused by bacterial and/or viral infections [1]. Hindering progress in disease management and therapy, early diagnosis of sepsis remains a major challenge and specific diagnostic and prognostic biomarkers are still lacking for daily clinical practice [2,3].

Along these lines, the high blood levels of pro- as well as anti-inflammatory cytokines and chemokines commonly found in sepsis patients implicated their potential for diagnosis and therapy. However, early approaches to treat sepsis using agents targeting hyperinflammation failed and despite the success of anti-inflammatory therapies such as cytokine blockers for severe coronavirus disease 2019 (COVID-19), sepsis-specific treatments are currently lacking [4–6]. Yet, it has become clear that novel immunomodulatory sepsis therapies need to address hyperinflammation, but also the immunosuppressive phase of sepsis [4]. In addition, monitoring the very complex sepsis patient response and stratification of patients for disease severity and immune characteristics may become an option for appropriate and patient-specific therapies [4]. The development and diagnostic value of specific biomarkers is highlighted

by several examples. For instance, despite the heterogeneity of COVID-19 symptoms [7], SARS-CoV-2 induces an innate immune reaction involving neutrophils, monocytes and macrophages, which subsequently prime an adaptive immune response in lymphocytes. Infection is cleared in almost 80% of cases but in patients developing sepsis upon SARS-CoV-2 infection, an exaggerated production of inflammatory cytokines such as interleukin-6 (IL-6) contributes to tissue injury and organ failure [8]. Here the identification of molecules that can help predict disease outcome and benefit the evaluation of disease pathophysiology could classify novel drug targets. In the case of infections with methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci, other challenges in sepsis therapy become apparent. As the identification and characterization of bacteria responsible for the infection commonly takes several days, antibiotics are initially given by chance. Hence, biomarkers for early detection of the bacterial strain causing the infection or the identification of antimicrobial resistances that can trigger sepsis are of utmost importance but have yet to be established [9,10].

We have recently addressed the relationship between adiponectin, a multifunctional adipokine almost exclusively produced by adipocytes, in patient cohorts of se-



vere diseases, identifying opportunities for the prognosis and management of sepsis [11,12]. In this review, we summarize the multiple pro- and anti-inflammatory activities of adiponectin and their effects in sepsis models and aim to provide an association of adiponectin levels with sepsis severity and outcome.

2. Adiponectin Function and Systemic Levels

2.1 Adiponectin

Adiponectin is produced by adipocytes from white and brown adipose tissues [13,14]. Circulating levels of adiponectin are much higher than other common adipocyte-derived adipokines such as leptin and exist as low molecular weight (LMW) trimer, medium molecular weight (MMW) hexamer and high molecular weight (HMW) multimer complexes [15–17]. Among the circulating adiponectin isomers, LMW and HMW make up the majority of adiponectin, while MMW hexamers are found in lower concentrations [15–17]. In addition, globular adiponectin, a proteolytic cleavage product of adiponectin (17 kDa), may circulate at very low levels in the blood [18,19].

Adiponectin conveys its diverse biological activities through the binding to the Adiponectin receptor 1 (AdipoR1) and AdipoR2 at the surface of target cells, leading to the activation of different signaling pathways [20, 21]. Downstream of AdipoR1 and AdipoR2, the signaling pathways regulated by adiponectin still have to be fully resolved, but adiponectin binding to AdipoR1 activates adenosine monophosphate-activated protein kinase, the fuel-sensing enzyme conserved in all mammalian cells. Further benefiting energy homeostasis, AdipoR2 activation increases the activity of the transcription factor peroxisome-proliferator activated receptor (PPAR) α , which stimulates hepatic fatty acid degradation (beta-oxidation) and simultaneously inhibits fatty acid synthesis [22]. For further reading on adiponectin-induced signaling pathways and their biological outcomes in healthy and pathophysiological settings, we refer the reader to excellent reviews on this topic [21,23–25].

2.2 Systemic Adiponectin Levels

Given the strong association of alterations in adipokine secretion with metabolic disease, a substantial number of studies have investigated the influence of gender, age, body mass, metabolic and other chronic diseases and their pharmacological treatments with plasma levels of adipokines, including adiponectin. Along these lines, females were found to exhibit higher circulating adiponectin levels than males. Furthermore, females displayed a higher proportion and absolute amount of HMW adiponectin, and demonstrated a robust inverse correlation between body fat measures and the proportion of HMW species [26].

As listed below, there is a common trend that systemic adiponectin levels are reduced in obesity, metabolic

disease and cardiovascular disease [24,27,28]. Patients with type 2 diabetes, hypertension and non-alcoholic fatty liver disease also revealed low blood adiponectin levels [21,24,27,29,30]. These reduced systemic adiponectin levels [24,27,28] are generally associated with low-grade systemic inflammation and elevated C-reactive protein (CRP) levels, the most commonly used clinical inflammation marker [31], implicating an interconnection of inflammation and adipokine production, secretion and plasma levels. In support of this, pro-inflammatory cytokines such as tumour necrosis factor (TNF) suppressed adiponectin synthesis in adipocytes to contribute to low circulating adiponectin levels [32]. Vice versa, low serum adiponectin concentrations in turn exacerbated metabolic dysfunction and inflammation, suggesting a positive feedback loop that enables adiponectin to self-reinforce hypoadiponectinemia [33].

Based on the various protective activities of adiponectin in metabolic and cardiovascular complications, drugs that selectively activate adiponectin receptor signaling have been developed. This includes AdipoRon, an orally active agonist for AdipoR1 and AdipoR2 that protects from diabetes, kidney injury and cardiac hypertrophy in several animal models [34]. In a murine model of systemic sclerosis, AdipoRon acted in an anti-inflammatory and anti-fibrotic manner in three fundamental pathomechanisms underlying the clinical manifestations of systemic sclerosis, (i) the activation of fibroblasts, (ii) the transdifferentiation of adipocytes to myofibroblasts, and (iii) T-helper cell polarisation to the Th2/Th17 type [35]. In spinal cord injury and neuroinflammation of mice, enhanced adenosine triphosphate-binding cassette transporter A1-dependent lipid efflux mediated the anti-inflammatory activity of AdipoRon [36].

These multiple beneficial metabolic effects of adiponectin listed above may also contribute to protecting against inflammatory-driven oncogenic malignancies. However, these discoveries may not apply to liver cancers as serum adiponectin concentrations of patients with hepatocellular carcinoma (HCC) were increased [37]. Notably, with circulating adiponectin levels being elevated in severe liver dysfunction and cholestasis, this suggests that higher adiponectin amounts in HCC are caused by an underlying liver disease. The source of higher adiponectin concentrations in liver disease is still unclear and as abundant amounts of adiponectin in urine and bile implicate renal as well as biliary excretion [38], an impaired hepatic uptake and biliary excretion of adiponectin may contribute to elevated levels in HCC.

Circulating adiponectin levels were also elevated in chronic kidney disease [39], leading to studies assessing the diagnostic value of urinary adiponectin in patients with renal dysfunction. Urinary adiponectin amounts were elevated in diabetic patients compared to normal weight and obese controls and may be used as a biomarker to assess the risk for diabetic nephropathy [40].

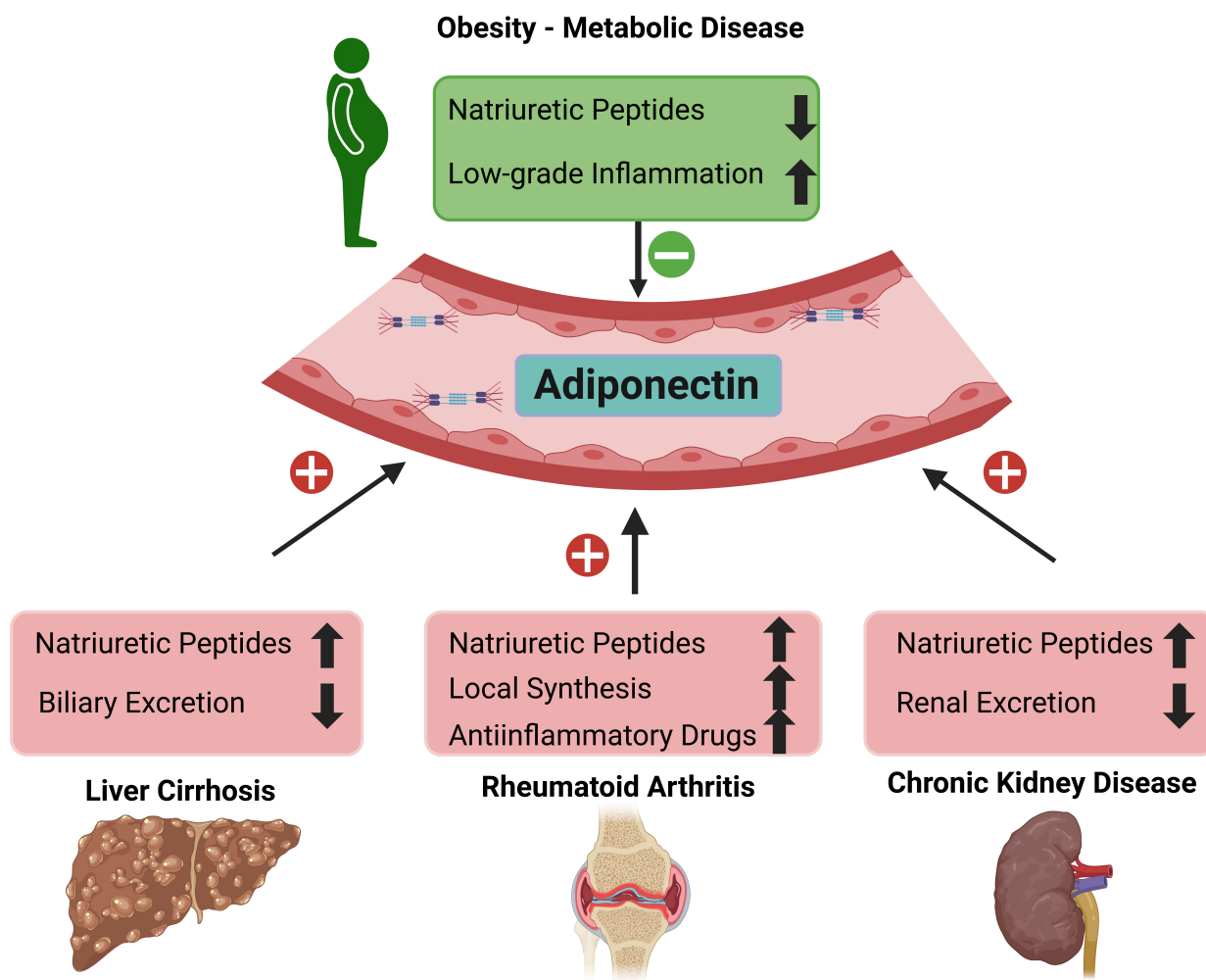


Fig. 1. Systemic adiponectin levels in relation to different diseases. Liver cirrhosis, chronic kidney and autoimmune diseases such as rheumatoid arthritis are related to high systemic adiponectin levels. In contrast, obesity and associated metabolic diseases are characterized by low amounts of systemic adiponectin levels. Factors which are increased in the respective diseases ↑ and those which are reduced ↓ are indicated. These conditions are related to increased (⊕) or decreased (⊖) adiponectin levels in blood. Created in BioRender.com (Created in <https://BioRender.com>).

Several other studies detected high systemic adiponectin levels in patients with autoimmune diseases such as type 1 diabetes and rheumatoid arthritis [41,42] (Fig. 1). Monoclonal antibodies against MMW adiponectin showed therapeutic potential and improved symptoms in a collagen-induced arthritis mouse model, indicating that specific adiponectin isoforms mediate deleterious effects in this autoimmune disease [43]. Notably, total and HMW adiponectin levels were positively related to all-cause mortality across several clinical studies and only a few studies reported an inverse relationship [44,45]. Brain natriuretic peptides (BNP) and atrial NP (ANP) increased adiponectin expression and secretion of primary human adipocytes [46] and the association of adiponectin with mortality rate was confounded after considering these paracrine/hormone factors [45]. NP hormones derived from the heart serve a variety of purposes and are indicators of vascular remodeling following ventricular or atrial wall

stretching. Additionally, some evidence supports inflammation to increase NP production [47]. While serum NP levels are elevated in liver cirrhosis [48], chronic kidney disease [49] and autoimmune diseases [47,50], reduced NP levels have been linked to obesity [51,52], non-alcoholic fatty liver disease [48], and insulin resistance [53] (Fig. 1). Therefore, it is reasonable to assume that NP plays a critical role in the regulation of serum adiponectin levels.

Other causes of high serum adiponectin levels in autoimmune diseases include drugs such as anti-IL receptor antibodies or glucocorticoids, which are associated with increased adiponectin levels [54] (Fig. 1). In rheumatoid arthritis patients, elevated serum levels of adiponectin are a result of higher local adiponectin synthesis in articular adipocytes and synovial membrane explants [54] (Fig. 1).

Taken together, efforts to utilize circulating adiponectin levels as a diagnostic and/or prognostic tool in sepsis has to consider various confounding fac-

tors such as gender and metabolic diseases as well as medications and underlying diseases.

2.3 Pro- and Anti-Inflammatory Roles of Adiponectin

The majority of studies investigating pro- and anti-inflammatory effects of adiponectin focussed on the analysis of monocytes/macrophages or myeloid cell lines, such as THP-1, U937 or RAW264.7. Full-length and globular adiponectin were shown to induce IL-10 expression in lipopolysaccharide (LPS)-activated Kupffer cells and reduce their pro-inflammatory response [55]. Incubation of THP-1 foam cells for 24 h with human adiponectin derived from HEK293 cells suppressed TNF and CC chemokine ligand 2 (CCL2) mRNA expression [56]. Adiponectin preincubation for 24 h, to mimic the mode of action of circulating adiponectin prior to an inflammatory response, lowered the pro-inflammatory effect of LPS in porcine macrophages, and was accompanied by IL-6 downregulation, while IL-10 expression increased [57]. LMW adiponectin produced in insect cells also exerted anti-inflammatory activities in LPS-incubated THP-1 cells [58]. HMW adiponectin preincubation conveyed potent anti-inflammatory activities in macrophages and suppressed *IL-1 β* gene expression in LPS-stimulated RAW264.7 macrophages [59]. Study strongly suggests that these anti-inflammatory effects of adiponectin are mediated by AdipoR1 and AdipoR2 [60]. Another study showed reduced expression of AdipoR1 and AdipoR2 in M1 macrophages compared to their expression levels in M2 cells [61], indicating a more prominent role for AdipoR1 and AdipoR2 in anti-inflammatory activities in M2 macrophages.

Further evidence for the anti-inflammatory roles of globular adiponectin, which circulates only in lower amounts compared to the other three adiponectin isoforms [18,19], for macrophages exist. Globular adiponectin was found to reduce production of inflammatory cytokines [41] and inhibited LPS-induced inflammasome activation in macrophages by induction of autophagy [62]. Globular adiponectin also reduced *TNF* expression and induced *IL-10* expression in rat Kupffer cells exposed to LPS [55]. Furthermore, globular adiponectin impaired C-reactive protein (CRP) synthesis in human aortic endothelial cells and rodent hepatocytes [63], consistent with an inverse correlation between systemic adiponectin and CRP levels in patients with coronary artery disease [64].

M1 and M2 polarization states of macrophages critically influence pro- and anti-inflammatory conditions. While M1 macrophages are mostly responsible for pro-inflammatory responses, M2 macrophages are generally considered to facilitate anti-inflammatory activities. These differential pro- and anti-inflammatory responses of M1 and M2 macrophages are also reflected in their response to adiponectin exposure. For instance, after the classical generation of activated M1 macrophages upon incubation with LPS and interferon- γ , these cells showed a pro-

inflammatory response when challenged with full-length adiponectin. On the other hand, M2 macrophages obtained by IL-4 or IL-10 stimulation produced higher levels of IL-10 when incubated with adiponectin [61].

Yet, despite the anti-inflammatory responses triggered by globular adiponectin described above, others reported activation of the transcription factor nuclear-factor kappa B (NF-kappaB) by globular adiponectin in myeloid cell lines [65,66]. Globular adiponectin also increased N-formylmethionyl-leucyl-phenylalanine-induced production of reactive oxygen species by human phagocytes [18] and TNF and IL-6 expression in macrophages and THP-1 cells [67]. Interestingly, in the latter studies, pre-incubation of THP-1 cells with globular adiponectin inhibited its ability to promote TNF or IL-6 secretion upon re-stimulation. It was proposed that chronic abundance of globular adiponectin may desensitize monocytes and macrophages for further activation by adiponectin (Fig. 2). Markedly, pre-incubation with globular adiponectin rendered THP-1 cells also incapable of mediating the pro-inflammatory effects of LPS [67].

In line with these observations, in the obese, low adiponectin levels may prime macrophages to an exacerbated response to inflammatory metabolites [24,33]. It should be noted that the studies listed above [65–67] used 5–10 $\mu\text{g/mL}$ globular adiponectin in their experimental setup. Although these amounts are equivalent to total adiponectin levels found in the circulation, these concentrations are much higher than physiological concentrations of globular adiponectin [18,19]. However, as macrophages express elastase, which can cleave full-length adiponectin, the levels of globular adiponectin may indeed be a lot higher in the microenvironment of these cells compared to values obtained for globular adiponectin amounts in the circulation [68]. Future research will have to address the potentially different systemic and local adiponectin levels and their impact on individual cells in tissue microenvironments.

In addition to globular adiponectin (see above), HMW adiponectin has also been reported to modulate inflammatory activities via NF-kappaB activation. HMW adiponectin was found to increase NF-kappaB activity as well as CCL2, CCL20, CXCL8 and IL-6 levels in monocytes/macrophages. Preincubation with native adiponectin (forming HMW, MMW and LMW complexes) reduced the activation of NF-kappaB by TNF and LPS [42,66]. In non-stimulated primary monocytes, overnight exposure with HMW, but not LMW adiponectin induced IL-6 expression [58]. On the other hand, adiponectin unable to form HMW isoforms failed to exert pro-inflammatory effects in U937 monocytes. Yet, in this study, globular adiponectin increased NF-kappaB activity, which correlated with increased mRNA and protein levels of inflammation marker genes [66].

From the studies on the role of adiponectin in macrophage activation and production of inflammatory

Monocytes/Macrophages

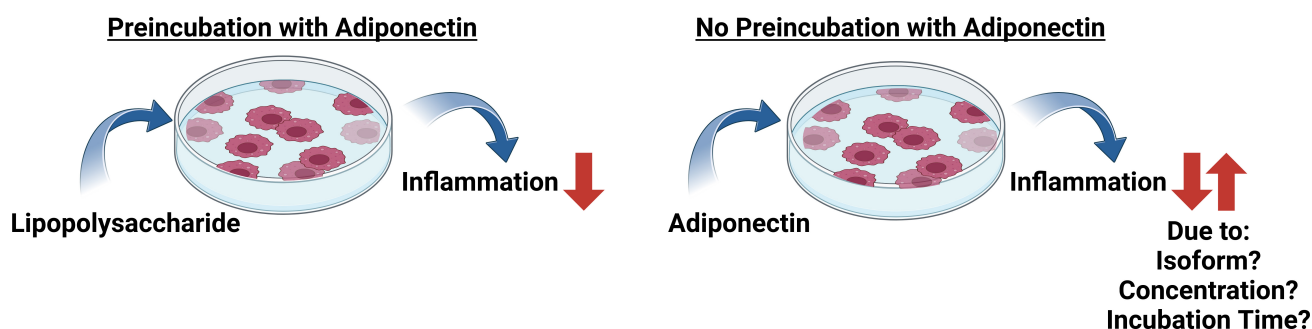


Fig. 2. *In vitro* effects of adiponectin exposure on the inflammatory response of monocytes/macrophages. Preincubation of monocytes/macrophages with adiponectin lowers the pro-inflammatory effects of lipopolysaccharide treatment. On the other hand, the cultivation of cells with adiponectin in the absence of lipopolysaccharide is capable of conferring pro- as well as anti-inflammatory responses. It should be noted that different experimental conditions (e.g., incubation times, activation procedures, adiponectin concentrations and isoform utilization) and cell models used in the various studies also need to be considered (see text for details). Created in <https://BioRender.com>.

cytokines and chemokines, it became apparent that it remained challenging to unravel opposite outcomes of adiponectin in inflammation, often possibly compounded by the different experimental models and conditions used (e.g., globular vs. full-length adiponectin; incubation periods) (Fig. 2). Overall, current models favour adiponectin-related effects to depend on the cellular activation status, the distinct signaling potential of the different adiponectin isoforms, their local concentrations and the receptor repertoire being expressed by the various cell types [69,70]. The time course of disease progression also needs to be considered (Fig. 2). For instance, in human endotoxemia, the initial increase in pro-inflammatory cytokines such as TNF was followed by the release of IL-6 and subsequently anti-inflammatory cytokines such as IL-10 [71]. Also, incubation periods chosen to expose cells with LPS as well as adiponectin may make a difference in experimental outcomes. Yet, despite the difficulties in aligning experimental settings, there is consensus that at least in macrophages, preincubation with adiponectin results in the downregulation of inflammatory cytokine production when cells are subsequently exposed to LPS (Fig. 2).

2.4 Adiponectin in Experimental Models

While numerous animal studies analysed the role of adiponectin in metabolic complications, data on its effect in animal models for infectious diseases and sepsis are rare [25,30,72,73].

Obese mice having low blood adiponectin levels as well as adiponectin null mice had an impaired clearance of *Listeria monocytogenes*, which was restored by supplementation with adiponectin [74]. Infection of murine adipocytes with *Listeria monocytogenes* causes a transient increase of CCL2 and this was followed by higher expression of adiponectin. Adiponectin deficiency abrogated

infection-mediated induction of CCL2, which is essential for macrophage recruitment and clearance of microbiota [75]. As *Listeria monocytogenes* is a pathogenic Gram-positive bacterium causing listeriosis that may result in septicemia [76], this could indicate high adiponectin levels to protect from the development of critical illness triggered by this bacterium. This hypothesis of adiponectin supplementation to act in an anti-inflammatory manner is supported by other findings. For instance, in a murine sepsis model caused by cecal ligation and puncture, repeated dosing of globular adiponectin (produced in *Escherichia coli*) prior to the sepsis-inducing procedure, normalized leukocyte/platelet adhesion in the cerebral microcirculation of normal diet-fed and diet-induced obese mice [24]. Also, in a rat model of abdominal sepsis, adiponectin treatment lowered the serum levels of TNF, soluble intercellular adhesion molecule 1, IL-6, and macrophage inhibitory factor, while IL-10 levels were elevated. Although the adiponectin isoform used for these experiments was not provided, these findings correlated with better survival compared to controls [77]. In line with these observations, adiponectin protected from severe lung injury in a rat sepsis model. In bronchoalveolar lavage neutrophil infiltration, levels of inflammatory cytokines and myeloperoxidase activity improved upon adiponectin therapy [78]. A substantial number of control animals, but not adiponectin-deficient mice survived cecal ligation and puncture. This was associated with a more severe renal and hepatic injury with higher infiltration of leukocytes in the adiponectin null animals [79].

Besides these findings from adiponectin supplementation studies and animal models lacking adiponectin, the determination of adiponectin levels supports a protective role for adiponectin in sepsis and inflammation. In an endotoxemia model and in cecal ligation and puncture, plasma adiponectin concentrations and its expression in epididy-

mal fat were decreased [79]. Notably, these findings might not be specific to the induction of sepsis, as similar results were obtained from sham-operated animals [79]. Reduced *adiponectin* mRNA expression in epididymal, perirenal and subcutaneous fat of mice challenged with LPS was also reported [80]. LPS injection to mimic murine sepsis caused a downregulation of *AdipoR1* expression in muscle and perirenal adipose tissue while *AdipoR2* levels were reduced in the liver, perirenal fat and subcutaneous fat. Interestingly, *AdipoR2* expression levels normalized within 24 h in all of these tissues. *AdipoR1* mRNA levels increased in muscle tissue and returned towards normal in perirenal fat, indicating an immediate transient response to LPS exposure, followed by normalization of mRNA expression [81]. Furthermore, AdipoR1 surface levels of lung leukocytes were also reduced when animals were challenged with chitin, yet lung inflammation nevertheless improved by exogenous adiponectin [82]. To date, a detailed knowledge on AdipoR1 and AdipoR2 expression patterns in different cells and tissues in human sepsis is still lacking. It is important to note that the levels of adiponectin receptors may be low in sepsis, which presents a challenge in the development of adiponectin receptor agonists for the treatment of sepsis.

Several studies addressed the therapeutic potential of adiponectin receptor agonists in animal and cell models for sepsis [83,84]. Notably, the 10-amino acid peptide analogue of adiponectin, ALY688, effectively reduced IL-6, CCL2, type 1 interferons and CXCL10 levels in a murine sublethal LPS endotoxemia model. ALY688 was found to increase transforming growth factor-beta expression in mice with and without LPS challenge [83], yet did not alter inflammatory cytokine and chemokine levels in control animals. An increase of circulating T-cell number was noticed in controls while T-cells decreased in endotoxemic mice. Neutrophil and monocyte counts were not modified by ALY688 treatment [83]. In addition, the globular adiponectin-derived peptide KS23 improved endotoxin-induced uveitis in Lewis rats. KS23 also decreased TNF and IL-6 levels in LPS-stimulated RAW264.7 cells by blocking nuclear translocation of NF-kappaB [84].

Taken together, all animal studies have reported protective effects of adiponectin and adiponectin receptor agonists in models of inflammation and sepsis. However, several other drugs that have shown anti-inflammatory effects in rodents have not been successful in patients with sepsis [85]. These observations could point at additional, yet to be identified beneficial activities mediated by adiponectin that other anti-inflammatories are lacking. It remains to be seen whether adiponectin-related approaches will be more successful.

2.5 Observational Studies in Human Sepsis

In addition to the various animal models and patient cohorts described in the previous sections, several stud-

ies determined serum/plasma adiponectin levels in patients with sepsis, yet results varied depending on the cohort analyzed [86]. Most reports were based on a limited number of sepsis patients and as outlined earlier (section 2.2), sepsis pathophysiology differs between genders, with male patients having a higher risk for critical illness and fatal outcomes [87,88]. Moreover, serum adiponectin levels of females are higher in comparison to males [25,69,73], but most observational studies did not account for gender differences. One gender-specific report found significantly lower plasma adiponectin levels only in female, but not male patients with systemic inflammatory response syndrome (SIRS)/sepsis compared to female controls. Infection of sepsis patients with either Gram-negative or Gram-positive bacteria exhibited negligible impacts on plasma adiponectin levels in both genders (Fig. 3) [12].

Differential outcomes from several other studies make an overall interpretation challenging. For instance, 41 mechanically ventilated patients with sepsis showed significantly higher adiponectin levels compared to 40 healthy controls ($10.9 \pm 6.1 \mu\text{g/mL}$ vs $6.0 \pm 2.9 \mu\text{g/mL}$, $p < 0.001$). In this study, adiponectin levels were not correlated with clinical markers of disease severity [89]. Positive correlations of adiponectin concentrations with CRP levels and negative associations with serum albumin levels were observed in a second study [90]. In this prospective study serum adiponectin levels of patients with sepsis were increased in comparison to controls. This study did not exclude patients with liver cirrhosis. Serum albumin levels of these patients were below 3.0 g/dL [90]. As the normal range for serum albumin levels is 3.5–5.0 g/dL [91], this suggests that patients with severe hepatic dysfunction may have contributed to the higher adiponectin levels observed. However, hypoalbuminemia may also develop in chronic inflammation [92] and the underlying pathophysiological conditions causing low serum albumin levels remain unclear. Koch and coworkers [93] described that critically ill patients and healthy controls had comparable systemic adiponectin concentrations. Despite these findings, the latter studies included sepsis patients with decompensated liver cirrhosis that are commonly characterized by strongly increased adiponectin levels [29,93]. It has yet to be determined if normal liver function can reveal lower adiponectin concentrations in sepsis compared to healthy controls. Opposing some of the findings described above, other reports showed that severely ill patients had low adiponectin levels in comparison to healthy controls, and recovery was related to normalization of systemic adiponectin amounts in one of these cohorts [94,95]. A prospective study of 21 patients with sepsis also reported normalisation of total as well as HMW adiponectin levels in sepsis patients who recovered from disease [96]. Sepsis patients were also shown to exhibit low adiponectin amounts compared to pre-septic patients, and a slight increase in plasma adiponectin concentrations during follow-up was related to higher mortal-

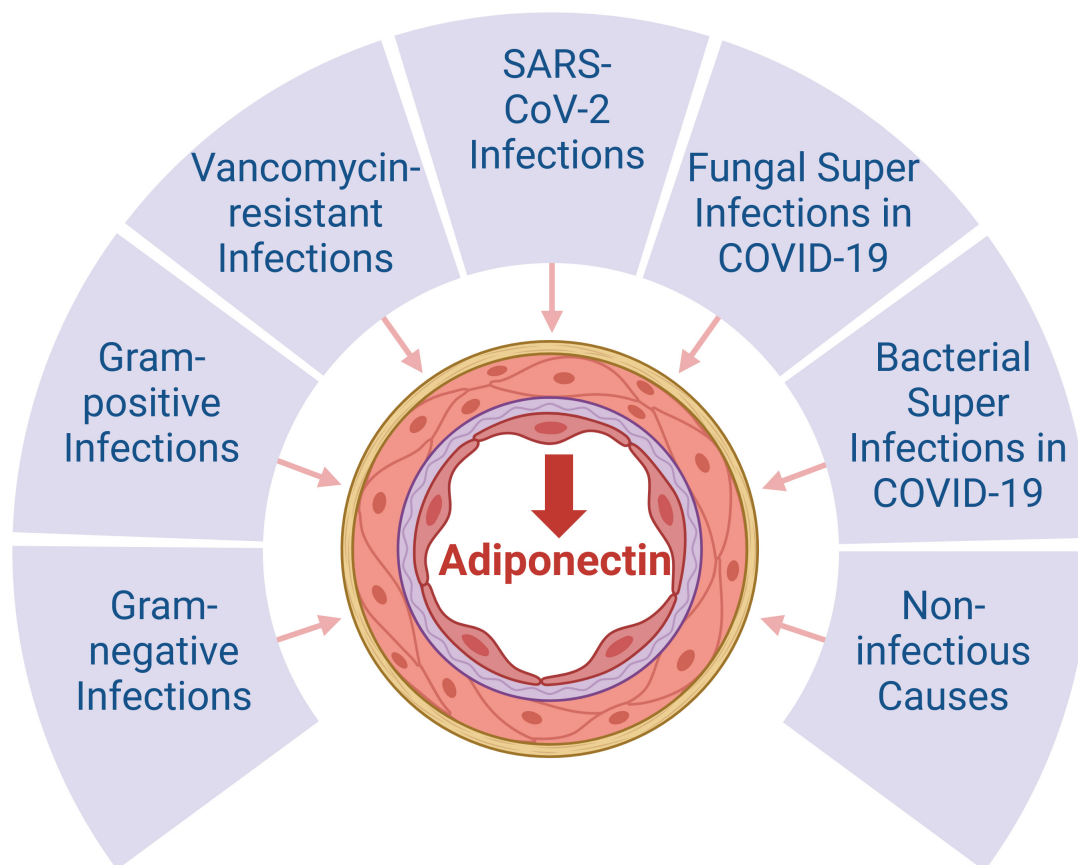


Fig. 3. Systemic adiponectin levels in patients with sepsis. There is consensus that systemic adiponectin concentrations are low in patients with sepsis ($\Downarrow$). With the exception of vancomycin-resistant infection, which may further reduce serum adiponectin levels, all other causes of sepsis exert comparable effects on adiponectin levels in blood. Created in <https://BioRender.com>.

ity [97]. However, in another cohort, severely ill patients with and without sepsis had similar adiponectin levels [94]. Hence, liver function and other yet to be identified factors seem to influence the levels of adiponectin in sepsis patients and a detailed correlation with other clinical parameters will be needed to possibly identify trends related to adiponectin levels in patients with sepsis.

SARS-CoV-2 infection is a more recent cause of sepsis [98,99] and most studies observed lower serum adiponectin levels in COVID-19 patients compared to healthy controls, which further declined with disease severity [11,100–103] (Fig. 3). Yet, others reported similar adiponectin amounts in COVID-19 patients and controls [104–106]. These opposing findings might in part be explained by the diversity of COVID-19 severity and associated complications, which may impact on adiponectin levels. In particular, the infection of adipocytes and adipose-tissue-localised macrophages by SARS-CoV-2 induces inflammation in adipose tissues, which is associated with a reduction in adiponectin synthesis [107,108] (Fig. 3). While this implicates low serum adiponectin levels in patients infected with SARS-CoV-2, Spirina *et al.* [109] found higher adiponectin levels in 92 COVID patients experiencing pneumonia. Adiponectin levels were not elevated any

further in severe cases developing acute respiratory distress syndrome. Diabetes and arterial hypertension were also not associated with lower adiponectin levels in this cohort. Conversely, infection with SARS-CoV-2 resulted in a reduction of adiponectin levels solely in females [12].

The diversity in symptoms associated with COVID-19 differentially affecting plasma adiponectin levels is further reflected in SARS-CoV-2 infected patients with intestinal lesions, which showed strongly elevated adiponectin levels. On the other hand, this was not observed in SARS-CoV-2 patients with hepatitis [109].

Notably, glucocorticoid therapy was associated with lower adiponectin levels [109]. This is in accordance with downregulation of adiponectin in fat tissues of mice after glucocorticoid administration [110,111]. In patients with rheumatoid arthritis glucocorticoids were related to increased adiponectin levels [54] and the association of this medication with systemic adiponectin levels in sepsis needs further study. Overall, the diverse outcomes of adiponectin levels in SARS-CoV-2 infected patients, often influenced by a variety of comorbidities, indicate that COVID-19 sepsis is not generally associated with grossly altered serum adiponectin levels in comparison to sepsis because of other causes.

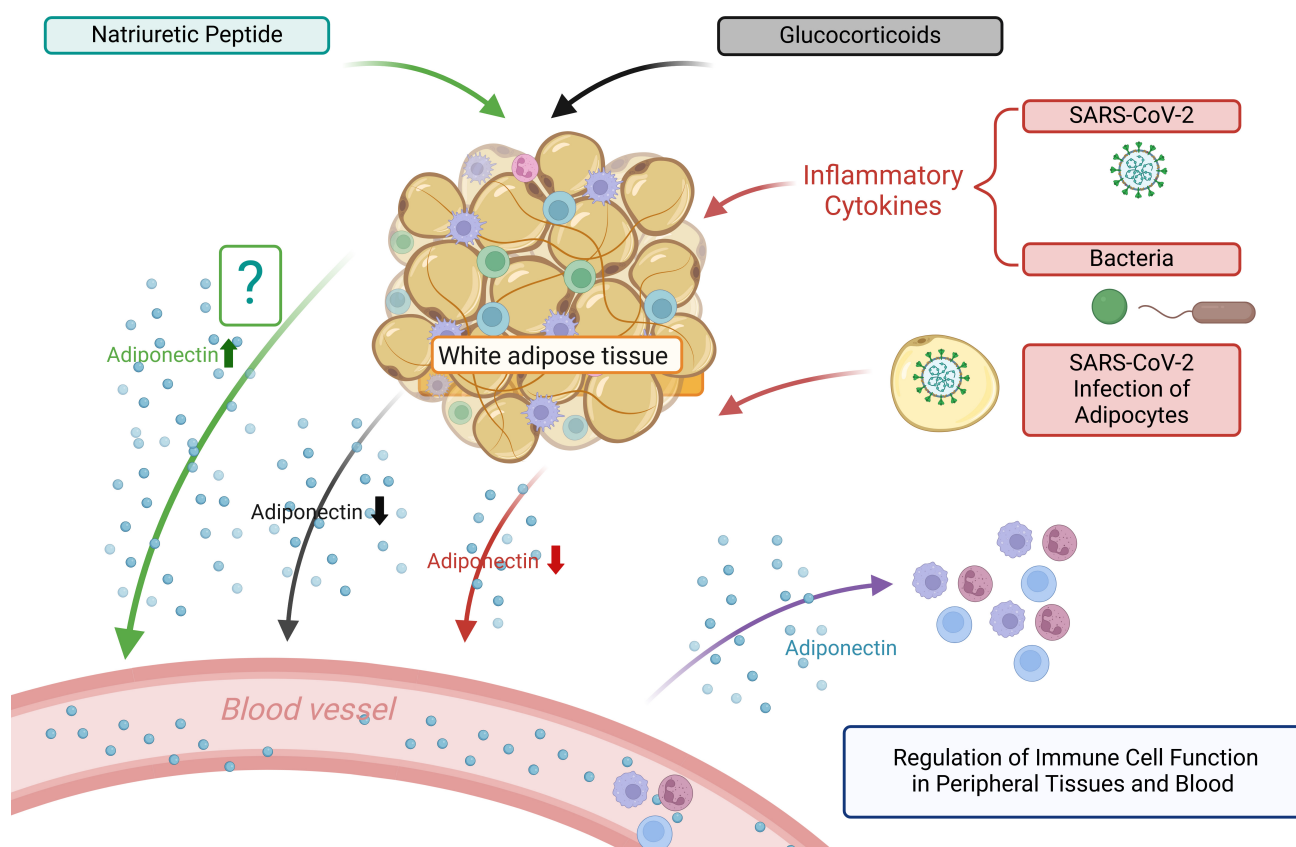


Fig. 4. Association of adiponectin and inflammation in sepsis. Infection with SARS-CoV-2 or bacteria increases systemic inflammation, and inflammatory cytokines lower adiponectin production of adipocytes. SARS-CoV-2 can infect adipocytes, which also contributes to reduce adiponectin production. It is yet unclear if high levels of natriuretic peptide increase adiponectin amounts in sepsis. Glucocorticoid therapy is likely to lower adiponectin levels, but the improvement in inflammation with this approach may also contribute to an increase in adiponectin levels. Low adiponectin in sepsis may affect the function of immune cells in the blood and peripheral tissues. Created in <https://BioRender.com>.

Moreover, patients with COVID-19 pneumonia and patients with bacterial community-acquired pneumonia, who were comparably ill, had similar adiponectin levels [112] (Fig. 3). These findings are in accordance with observations reported by others [100,113]. Nevertheless, it is pertinent to highlight that patients with COVID-19-related respiratory failure exhibited significantly lower plasma adiponectin levels compared to patients with respiratory failure unrelated to SARS-CoV-2 [101]. Thus, circulating adiponectin levels generally appear to decrease with severe disease, regardless of SARS-CoV-2 infection [98] (Fig. 3). However, adiponectin levels of patients with severe sepsis were not associated with a higher risk for acute respiratory distress syndrome [114].

Superinfection with bacteria occurs in approximately 25% of COVID-19 patients [115,116]. In non-hospitalized and hospitalized patients with COVID-19, 20% of cases had bacterial superinfections [117]. The meta-analysis revealed fungal and viral superinfections to occur in 8% and 4% of COVID-19 patients, respectively [117]. Superinfections were more prevalent in patients with severe COVID-

19 and associated with a more severe clinical course and poorer outcomes [117–119]. Despite bacterial infections generally worsening outcomes, the presence of bacterial superinfection did not result in a change in serum adiponectin levels with severe COVID-19 (Fig. 3). Conversely, in vancomycin-resistant enterococci bacteremia, a significant further reduction in serum adiponectin levels was observed [11]. Yet, these findings were obtained from a rather small cohort and need further confirmation (Fig. 3). Since the initial isolation of vancomycin-resistant enterococci in England in 1988, these bacteria have disseminated at an alarming rate, becoming the predominant cause of nosocomial infections worldwide. Over time, enterococci have acquired genes that render them resistant to a multitude of antibiotics, including vancomycin [120,121]. Low plasma adiponectin levels were also proposed to predict infections in patients with gastric surgeries [122]. The association of serum adiponectin concentrations with bacterial, viral and fungal infections is currently understudied, and further analysis is required.

The association of serum adiponectin levels and mortality in severely ill patients is a further unresolved issue. The adverse outcome was not related to altered adiponectin levels in two studies [11,109]. On the other hand, an association between higher plasma adiponectin concentrations and mortality was observed in patients with acute respiratory failure [123] and in patients with sepsis at the time of enrollment and at day 7 [90]. Another study found an association between low adiponectin levels in sepsis and mortality [124]. In a cohort of patients admitted to the intensive care unit, low adiponectin levels were found to predict overall survival [93]. Additionally, a gender-specific analysis identified a trend towards higher plasma adiponectin amounts in male non-survivors [12]. The relationship between serum adiponectin levels and survival is partly influenced by the inclusion of severely ill and less severely ill patients, with the latter cohort having higher adiponectin levels and better survival. However, most studies did not report a significant correlation between adiponectin levels and mortality [11,100,102].

The majority of studies have employed a single measurement of serum adiponectin levels at the time of hospital admission. Hillenbrand *et al.* [97] conducted a longitudinal analysis of adiponectin levels during the hospital stay, demonstrating a slight increase in adiponectin levels in non-survivors. Notably, in this cohort, the body mass index of survivors was 30 kg/m², which was higher than the BMI of non-survivors (25 kg/m²) [97]. A high BMI is a risk factor for severe COVID-19 and sepsis, but was also supposed to be protective in critical illness [125]. The fluctuations of adiponectin levels during sepsis may indicate a compensatory anti-inflammatory mechanism that counteracts the initial systemic inflammation, thereby facilitating the resolution of sepsis and promoting recovery. Conversely, an early pronounced response of adiponectin followed by a failure to sustain further increases could be indicative of a poor prognosis [126].

2.6 Potential Therapeutic Effects of Adiponectin in Sepsis

Sepsis is a state of an uncontrolled immune response [127,128]. Adiponectin has been shown to reduce inflammation in activated monocytes, increasing anti-inflammatory pathways and blocking pro-inflammatory effects [57,65,129]. In addition, adiponectin improves metabolic health, which may contribute to a better outcome [130]. Insulin response, hepatic steatosis and fibrosis are associated with low adiponectin levels [69]. A recent review summarised the increasing evidence pointing at multiple beneficial anti-inflammatory effects of adiponectin in the lung. Several lung cell types, including immune, epithelial and endothelial cells, express adiponectin receptors. While both pro-inflammatory and anti-inflammatory properties have been documented, the anti-inflammatory role of adiponectin has been predominantly noted in lung cells [131]. However, further analysis is required to define

the optimal timing of anti-inflammatory therapy in sepsis, as early blockade of inflammation may exacerbate disease severity [132]. Given the possibility that adiponectin receptors could be abundant in immune cells as well as peripheral cells such as pancreatic beta cells and hepatocytes, an adiponectin receptor agonist may improve sepsis severity and outcome.

3. Conclusion

The current data indicate that systemic adiponectin levels are reduced in patients with sepsis. Experimental models have demonstrated that adiponectin exerts a protective effect against sepsis, and preliminary data suggest a protective role in Gram-positive bacterial infection [70,73,75,79]. The *in vitro* effects of adiponectin on monocytes/macrophages include both pro- and anti-inflammatory effects and are best explained by a model proposing that adiponectin activates these cells, rendering them resistant to further inflammatory stimuli. Another question to be addressed in future studies is the underlying mechanisms causing low adiponectin levels in sepsis. Inflammatory cytokines induced by viral and bacterial infections in sepsis cause reduced adiponectin synthesis in fat tissue. In addition, SARS-CoV-2 can infect adipocytes, thereby also lowering adiponectin expression (Fig. 4). NP levels in sepsis are commonly high [133] and should contribute to an increase of adiponectin production (Fig. 4). However, BNP resistance due to the lowering of BNP receptors and their concomitant desensitization has been described in heart failure [134,135]. BNP levels in sepsis are more than 8-fold higher than in controls [136,137] and increase about 5-fold in patients with liver cirrhosis [48], but whether BNP resistance specifically emerges in sepsis is unknown. Glucocorticoids such as prednisolone and dexamethasone are common therapies for these severely ill patients [138], which may also decrease serum adiponectin amounts (Fig. 4). In conclusion, the effects of adiponectin in sepsis and the pathways that contribute to low adiponectin levels in severe disease are incompletely understood. Current data suggest that adiponectin receptor agonists may have multiple beneficial effects in critically ill patients, but clinical trials have yet to be initiated.

Author Contributions

CB and TG performed literature search and wrote the first draft of this review article. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

- [1] Ling L, Mui OY, Laupland KB, Lefrant JY, Roberts JA, Gopalan PD, *et al.* Scoping review on diagnostic criteria and investigative approach in sepsis of unknown origin in critically ill patients. *Journal of Intensive Care*. 2022; 10: 44. <https://doi.org/10.1186/s40560-022-00633-4>.
- [2] Konjety P, Chakole VG. Beyond the Horizon: A Comprehensive Review of Contemporary Strategies in Sepsis Management Encompassing Predictors, Diagnostic Tools, and Therapeutic Advances. *Cureus*. 2024; 16: e64249. <https://doi.org/10.7759/cureus.64249>.
- [3] Zhu J, Dong Y, Liao P, Yin X, He J, Guo L. Prognostic value of hemoglobin in patients with sepsis: A systematic review and meta-analysis. *Heart & Lung: the Journal of Critical Care*. 2024; 64: 93–99. <https://doi.org/10.1016/j.hrtlng.2023.12.001>.
- [4] Marques A, Torre C, Pinto R, Sepodes B, Rocha J. Treatment Advances in Sepsis and Septic Shock: Modulating Pro- and Anti-Inflammatory Mechanisms. *Journal of Clinical Medicine*. 2023; 12: 2892. <https://doi.org/10.3390/jcm12082892>.
- [5] Chander S, Kumari R, Wang HY, Mohammed YN, Parkash O, Lohana S, *et al.* Effect of low vs. high vancomycin trough level on the clinical outcomes of adult patients with sepsis or gram-positive bacterial infections: a systematic review and meta-analysis. *BMC Infectious Diseases*. 2024; 24: 1114. <https://doi.org/10.1186/s12879-024-09927-4>.
- [6] Murray B, Athale J, Balk RA, Behal ML, Brown JE, Chanas T, *et al.* Major Publications in the Critical Care Pharmacotherapy Literature: 2023. *Critical Care Explorations*. 2024; 6: e1162. <https://doi.org/10.1097/CCE.0000000000001162>.
- [7] Khot WY, Nadkar MY. The 2019 Novel Coronavirus Outbreak - A Global Threat. *The Journal of the Association of Physicians of India*. 2020; 68: 67–71.
- [8] Kabir MA, Ahmed R, Chowdhury R, Iqbal SMA, Paulmurugan R, Demirci U, *et al.* Management of COVID-19: current status and future prospects. *Microbes and Infection*. 2021; 23: 104832. <https://doi.org/10.1016/j.micinf.2021.104832>.
- [9] He RR, Yue GL, Dong ML, Wang JQ, Cheng C. Sepsis Biomarkers: Advancements and Clinical Applications-A Narrative Review. *International Journal of Molecular Sciences*. 2024; 25: 9010. <https://doi.org/10.3390/ijms25169010>.
- [10] Umemura Y, Ogura H, Takuma K, Fujishima S, Abe T, Kushi-moto S, *et al.* Current spectrum of causative pathogens in sepsis: A prospective nationwide cohort study in Japan. *International Journal of Infectious Diseases: IJID: Official Publication of the International Society for Infectious Diseases*. 2021; 103: 343–351. <https://doi.org/10.1016/j.ijid.2020.11.168>.
- [11] Pavel V, R  th U, Schmid S, Krautbauer S, Keller D, Amend P, *et al.* Serum Adiponectin Predicts COVID-19 Severity. *Biomedicine*. 2024; 12: 1043. <https://doi.org/10.3390/biomedicines12051043>.
- [12] Mester P, R  th U, Schmid S, M  ller M, Buechler C, Pavel V. Exploring the Relationship between Plasma Adiponectin, Gender, and Underlying Diseases in Severe Illness. *Biomedicine*. 2023; 11: 3287. <https://doi.org/10.3390/biomedicines11123287>.
- [13] Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, *et al.* Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochemical and Biophysical Research Communications*. 1999; 257: 79–83. <https://doi.org/10.1006/bbrc.1999.0255>.
- [14] Iacobellis G, Di Gioia C, Petramala L, Chiappetta C, Serra V, Zinamosca L, *et al.* Brown fat expresses adiponectin in humans. *International Journal of Endocrinology*. 2013; 2013: 126751. <https://doi.org/10.1155/2013/126751>.
- [15] Iwata M, Hara K, Kamura Y, Honoki H, Fujisaka S, Ishiki M, *et al.* Ratio of low molecular weight serum adiponectin to the total adiponectin value is associated with type 2 diabetes through its relation to increasing insulin resistance. *PloS One*. 2018; 13: e0192609. <https://doi.org/10.1371/journal.pone.0192609>.
- [16] Pajvani UB, Hawkins M, Combs TP, Rajala MW, Doebber T, Berger JP, *et al.* Complex distribution, not absolute amount of adiponectin, correlates with thiazolidinedione-mediated improvement in insulin sensitivity. *The Journal of Biological Chemistry*. 2004; 279: 12152–12162. <https://doi.org/10.1074/jbc.M311113200>.
- [17] Schober F, Neumeier M, Weigert J, Wurm S, Wanninger J, Sch  ffler A, *et al.* Low molecular weight adiponectin negatively correlates with the waist circumference and monocytic IL-6 release. *Biochemical and Biophysical Research Communications*. 2007; 361: 968–973. <https://doi.org/10.1016/j.bbrc.2007.07.106>.
- [18] Chedid P, Hurtado-Nedelec M, Marion-Gaber B, Bournier O, Hayem G, Gougerot-Pocidalo MA, *et al.* Adiponectin and its globular fragment differentially modulate the oxidative burst of primary human phagocytes. *The American Journal of Pathology*. 2012; 180: 682–692. <https://doi.org/10.1016/j.ajpath.2011.10.013>.
- [19] Choi HM, Doss HM, Kim KS. Multifaceted Physiological Roles of Adiponectin in Inflammation and Diseases. *International Journal of Molecular Sciences*. 2020; 21: 1219. <https://doi.org/10.3390/ijms21041219>.
- [20] Rubina KA, Semina EV, Kalinina NI, Sysoeva VY, Balatskiy AV, Tkachuk VA. Revisiting the multiple roles of T-cadherin in health and disease. *European Journal of Cell Biology*. 2021; 100: 151183. <https://doi.org/10.1016/j.ejcb.2021.151183>.
- [21] Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. *Endocrine Reviews*. 2005; 26: 439–451. <https://doi.org/10.1210/er.2005-0005>.
- [22] Herzig S, Shaw RJ. AMPK: guardian of metabolism and mitochondrial homeostasis. *Nature Reviews. Molecular Cell Biology*. 2018; 19: 121–135. <https://doi.org/10.1038/nrm.2017.95>.
- [23] Ruan H, Dong LQ. Adiponectin signaling and function in insulin target tissues. *Journal of Molecular Cell Biology*. 2016; 8: 101–109. <https://doi.org/10.1093/jmcb/mjw014>.
- [24] Wang ZV, Scherer PE. Adiponectin, the past two decades. *Journal of Molecular Cell Biology*. 2016; 8: 93–100. <https://doi.org/10.1093/jmcb/mjw011>.
- [25] Turer AT, Scherer PE. Adiponectin: mechanistic insights and clinical implications. *Diabetologia*. 2012; 55: 2319–2326. <https://doi.org/10.1007/s00125-012-2598-x>.
- [26] Peake PW, Kriketos AD, Campbell LV, Shen Y, Charlesworth JA. The metabolism of isoforms of human adiponectin: studies in human subjects and in experimental animals. *European Journal of Endocrinology*. 2005; 153: 409–417. <https://doi.org/10.1530/eje.1.01978>.
- [27] Rabe K, Lehrke M, Parhofer KG, Broedl UC. Adipokines and insulin resistance. *Molecular Medicine (Cambridge, Mass.)*. 2008; 14: 741–751. <https://doi.org/10.2119/2008-00058.Rabe>.
- [28] Rasouli N, Kern PA. Adipocytokines and the metabolic complications of obesity. *The Journal of Clinical Endocrinology and Metabolism*. 2008; 93: S64–S73. <https://doi.org/10.1210/jc.2008-1613>.

- [29] Buechler C, Haberl EM, Rein-Fischboeck L, Aslanidis C. Adipokines in Liver Cirrhosis. *International Journal of Molecular Sciences*. 2017; 18: 1392. <https://doi.org/10.3390/ijms18071392>.
- [30] Ouchi N, Kihara S, Funahashi T, Matsuzawa Y, Walsh K. Obesity, adiponectin and vascular inflammatory disease. *Current Opinion in Lipidology*. 2003; 14: 561–566. <https://doi.org/10.1097/00041433-200312000-00003>.
- [31] Brignardello J, Morales P, Diaz E, Romero J, Brunser O, Goteland M. Pilot study: alterations of intestinal microbiota in obese humans are not associated with colonic inflammation or disturbances of barrier function. *Alimentary Pharmacology & Therapeutics*. 2010; 32: 1307–1314. <https://doi.org/10.1111/j.1365-2036.2010.04475.x>.
- [32] Nguyen MTA, Satoh H, Favelyukis S, Babendure JL, Imamura T, Sbodio JJ, *et al.* JNK and tumor necrosis factor- α mediate free fatty acid-induced insulin resistance in 3T3-L1 adipocytes. *The Journal of Biological Chemistry*. 2005; 280: 35361–35371. <https://doi.org/10.1074/jbc.M504611200>.
- [33] Fantuzzi G. Adiponectin and inflammation: consensus and controversy. *The Journal of Allergy and Clinical Immunology*. 2008; 121: 326–330. <https://doi.org/10.1016/j.jaci.2007.10.018>.
- [34] Bhat IA, Kabeer SW, Reza MI, Mir RH, Dar MO. AdipoRon: A Novel Insulin Sensitizer in Various Complications and the Underlying Mechanisms: A Review. *Current Molecular Pharmacology*. 2020; 13: 94–107. <https://doi.org/10.2174/1874467212666191022102800>.
- [35] Yamashita T, Lakota K, Taniguchi T, Yoshizaki A, Sato S, Hong W, *et al.* An orally-active adiponectin receptor agonist mitigates cutaneous fibrosis, inflammation and microvascular pathology in a murine model of systemic sclerosis. *Scientific Reports*. 2018; 8: 11843. <https://doi.org/10.1038/s41598-018-29901-w>.
- [36] Zhou Q, Xiang H, Li A, Lin W, Huang Z, Guo J, *et al.* Activating Adiponectin Signaling with Exogenous AdipoRon Reduces Myelin Lipid Accumulation and Suppresses Macrophage Recruitment after Spinal Cord Injury. *Journal of Neurotrauma*. 2019; 36: 903–918. <https://doi.org/10.1089/neu.2018.5783>.
- [37] Chen MJ, Yeh YT, Lee KT, Tsai CJ, Lee HH, Wang SN. The promoting effect of adiponectin in hepatocellular carcinoma. *Journal of Surgical Oncology*. 2012; 106: 181–187. <https://doi.org/10.1002/jso.23059>.
- [38] Tews HC, Elger T, Grewal T, Weidlich S, Vitali F, Buechler C. Fecal and Urinary Adipokines as Disease Biomarkers. *Biomedicines*. 2023; 11: 1186. <https://doi.org/10.3390/biomedicines11041186>.
- [39] Heidari M, Nasri P, Nasri H. Adiponectin and chronic kidney disease; a review on recent findings. *Journal of Nephro pharmacology*. 2015; 4: 63–68.
- [40] Yamamoto M, Fujimoto Y, Hayashi S, Hashida S. A study of high-, middle- and low-molecular weight adiponectin in urine as a surrogate marker for early diabetic nephropathy using ultra-sensitive immune complex transfer enzyme immunoassay. *Annals of Clinical Biochemistry*. 2018; 55: 525–534. <https://doi.org/10.1177/0004563217748681>.
- [41] Luo L, Liu M. Adiponectin: friend or foe in obesity and inflammation. *Medical Review* (2021). 2022; 2: 349–362. <https://doi.org/10.1515/mr-2022-0002>.
- [42] Abke S, Neumeier M, Weigert J, Wehrwein G, Eggenhofer E, Schäffler A, *et al.* Adiponectin-induced secretion of interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1, CCL2) and interleukin-8 (IL-8, CXCL8) is impaired in monocytes from patients with type I diabetes. *Cardiovascular Diabetology*. 2006; 5: 17. <https://doi.org/10.1186/1475-2840-5-17>.
- [43] Lee YA, Hahm DH, Kim JY, Sur B, Lee HM, Ryu CJ, *et al.* Potential therapeutic antibodies targeting specific adiponectin isoforms in rheumatoid arthritis. *Arthritis Research & Therapy*. 2018; 20: 245. <https://doi.org/10.1186/s13075-018-1736-3>.
- [44] Menzaghi C, Trischitta V. The Adiponectin Paradox for All-Cause and Cardiovascular Mortality. *Diabetes*. 2018 67: 12–22. <https://doi.org/10.2337/dbi17-0016>.
- [45] Scarale MG, Fontana A, Trischitta V, Copetti M, Menzaghi C. Circulating adiponectin levels are paradoxically associated with mortality rate. A systematic review and meta-analysis. *The Journal of Clinical Endocrinology and Metabolism*. 2019; 104: 1357–1368. <https://doi.org/10.1210/je.2018-01501>.
- [46] Tsukamoto O, Fujita M, Kato M, Yamazaki S, Asano Y, Ogai A, *et al.* Natriuretic peptides enhance the production of adiponectin in human adipocytes and in patients with chronic heart failure. *Journal of the American College of Cardiology*. 2009; 53: 2070–2077. <https://doi.org/10.1016/j.jacc.2009.02.038>.
- [47] Dimitroulas T, Giannakoulas G, Karvounis H, Garyfallos A, Settas L, Kitis G. B-type natriuretic peptide in rheumatic diseases: a cardiac biomarker or a sophisticated acute phase reactant? *Autoimmunity Reviews*. 2012; 11: 837–843. <https://doi.org/10.1016/j.autrev.2012.02.018>.
- [48] Metwaly A, Khalik AA, Nasr FM, Sabry AI, Gouda MF, Hassan M. Brain Natriuretic Peptide in Liver Cirrhosis and Fatty Liver: Correlation with Cardiac Performance. *Electronic Physician*. 2016; 8: 1984–1993. <https://doi.org/10.19082/1984>.
- [49] Ogawa N, Komura H, Kuwasako K, Kitamura K, Kato J. Plasma levels of natriuretic peptides and development of chronic kidney disease. *BMC Nephrology*. 2015; 16: 171. <https://doi.org/10.1186/s12882-015-0163-9>.
- [50] McKenna K, Smith D, Sherlock M, Moore K, O'Brien E, Tormey W, *et al.* Elevated plasma concentrations of atrial and brain natriuretic peptide in type 1 diabetic subjects. *Irish Journal of Medical Science*. 2005; 174: 53–57. <https://doi.org/10.1007/BF03169149>.
- [51] Koizumi M, Watanabe H, Kaneko Y, Iino K, Ishida M, Kosaka T, *et al.* Impact of obesity on plasma B-type natriuretic peptide levels in Japanese community-based subjects. *Heart and Vessels*. 2012; 27: 287–294. <https://doi.org/10.1007/s00380-011-0143-3>.
- [52] Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PWF, *et al.* Impact of obesity on plasma natriuretic peptide levels. *Circulation*. 2004; 109: 594–600. <https://doi.org/10.1161/01.CIR.0000112582.16683.EA>.
- [53] Echouffo-Tcheugui JB, Zhang S, McEvoy JW, Juraschek SP, Fang M, Ndumele CE, *et al.* Insulin Resistance and N-Terminal Pro-B-Type Natriuretic Peptide Among Healthy Adults. *JAMA Cardiology*. 2023; 8: 989–995. <https://doi.org/10.1001/jamacardio.2023.2758>.
- [54] Brezovec N, Perdan-Pirkmajer K, Čučnik S, Sodin-Šemrl S, Varga J, Lakota K. Adiponectin Deregulation in Systemic Autoimmune Rheumatic Diseases. *International Journal of Molecular Sciences*. 2021; 22: 4095. <https://doi.org/10.3390/ijms22084095>.
- [55] Mandal P, Park PH, McMullen MR, Pratt BT, Nagy LE. The anti-inflammatory effects of adiponectin are mediated via a heme oxygenase-1-dependent pathway in rat Kupffer cells. *Hepatology* (Baltimore, Md.). 2010; 51: 1420–1429. <https://doi.org/10.1002/hep.23427>.
- [56] Tian L, Luo N, Zhu X, Chung BH, Garvey WT, Fu Y. Adiponectin-AdipoR1/2-APPL1 signaling axis suppresses human foam cell formation: differential ability of AdipoR1 and AdipoR2 to regulate inflammatory cytokine responses. *Atherosclerosis*. 2012; 221: 66–75. <https://doi.org/10.1016/j.atherosclerosis.2011.12.014>.
- [57] Wulster-Radcliffe MC, Ajuwon KM, Wang J, Christian JA, Spurlock ME. Adiponectin differentially regulates cytokines in porcine macrophages. *Biochemical and Biophysical Research Communications*. 2004; 316: 924–929. <https://doi.org/10.1016/>

j.bbrc.2004.02.130.

- [58] Neumeier M, Weigert J, Schäffler A, Wehrwein G, Müller-Ladner U, Schölmerich J, *et al.* Different effects of adiponectin isoforms in human monocytic cells. *Journal of Leukocyte Biology*. 2006; 79: 803–808. <https://doi.org/10.1189/jlb.0905521>.
- [59] Tanioka T, Iwamoto S, Nakano Y. Suppression of Lipopolysaccharide-Induced IL-1 β Gene Expression by High-Molecular-Weight Adiponectin in RAW264.7 Macrophages. *Biological & Pharmaceutical Bulletin*. 2023; 46: 1498–1505. <https://doi.org/10.1248/bpb.b23-00213>.
- [60] Ohashi K, Parker JL, Ouchi N, Higuchi A, Vita JA, Gokce N, *et al.* Adiponectin promotes macrophage polarization toward an anti-inflammatory phenotype. *The Journal of Biological Chemistry*. 2010; 285: 6153–6160. <https://doi.org/10.1074/jbc.M109.088708>.
- [61] van Stijn CMW, Kim J, Lusis AJ, Barish GD, Tangirala RK. Macrophage polarization phenotype regulates adiponectin receptor expression and adiponectin anti-inflammatory response. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology*. 2015; 29: 636–649. <https://doi.org/10.1096/fj.14-253831>.
- [62] Kim MJ, Kim EH, Pun NT, Chang JH, Kim JA, Jeong JH, *et al.* Globular Adiponectin Inhibits Lipopolysaccharide-Primed Inflammasomes Activation in Macrophages via Autophagy Induction: The Critical Role of AMPK Signaling. *International Journal of Molecular Sciences*. 2017; 18: 1275. <https://doi.org/10.3390/ijms18061275>.
- [63] Devaraj S, Torok N, Dasu MR, Samols D, Jialal I. Adiponectin decreases C-reactive protein synthesis and secretion from endothelial cells: evidence for an adipose tissue-vascular loop. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2008; 28: 1368–1374. <https://doi.org/10.1161/ATVBAHA.108.163303>.
- [64] Ouchi N, Kihara S, Funahashi T, Nakamura T, Nishida M, Kumada M, *et al.* Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. *Circulation*. 2003; 107: 671–674. <https://doi.org/10.1161/01.cir.0000055188.83694.b3>.
- [65] Jin X, Wang Y. Mechanisms of Adiponectin in Regulation of Proinflammatory Cytokine Production and Migration in Macrophages. *Journal of Inflammation Research*. 2021; 14: 981–993. <https://doi.org/10.2147/JIR.S292137>.
- [66] Haugen F, Drevon CA. Activation of nuclear factor-kappaB by high molecular weight and globular adiponectin. *Endocrinology*. 2007; 148: 5478–5486. <https://doi.org/10.1210/en.2007-0370>.
- [67] Tsatsanis C, Zacharioudaki V, Androulidaki A, Dermizaki E, Charalampopoulos I, Minas V, *et al.* Adiponectin induces TNF-alpha and IL-6 in macrophages and promotes tolerance to itself and other pro-inflammatory stimuli. *Biochemical and Biophysical Research Communications*. 2005; 335: 1254–1263. <https://doi.org/10.1016/j.bbrc.2005.07.197>.
- [68] Waki H, Yamauchi T, Kamon J, Kita S, Ito Y, Hada Y, *et al.* Generation of globular fragment of adiponectin by leukocyte elastase secreted by monocytic cell line THP-1. *Endocrinology*. 2005; 146: 790–796. <https://doi.org/10.1210/en.2004-1096>.
- [69] Buechler C, Wanninger J, Neumeier M. Adiponectin, a key adipokine in obesity related liver diseases. *World Journal of Gastroenterology*. 2011; 17: 2801–2811. <https://doi.org/10.3748/wjg.v17.i23.2801>.
- [70] Fantuzzi G. Adiponectin in inflammatory and immune-mediated diseases. *Cytokine*. 2013; 64: 1–10. <https://doi.org/10.1016/j.cyt.2013.06.317>.
- [71] Andreasen AS, Krabbe KS, Krogh-Madsen R, Taudorf S, Pedersen BK, Møller K. Human endotoxemia as a model of systemic inflammation. *Current Medicinal Chemistry*. 2008; 15: 1697–1705. <https://doi.org/10.2174/092986708784872393>.
- [72] Goldstein BJ, Scalia RG, Ma XL. Protective vascular and myocardial effects of adiponectin. *Nature Clinical Practice. Cardiovascular Medicine*. 2009; 6: 27–35. <https://doi.org/10.1038/ncpcardio1398>.
- [73] Ouchi N, Walsh K. Adiponectin as an anti-inflammatory factor. *Clinica Chimica Acta; International Journal of Clinical Chemistry*. 2007; 380: 24–30. <https://doi.org/10.1016/j.cca.2007.01.026>.
- [74] Masamoto Y, Arai S, Sato T, Yoshimi A, Kubota N, Takamoto I, *et al.* Adiponectin Enhances Antibacterial Activity of Hematopoietic Cells by Suppressing Bone Marrow Inflammation. *Immunity*. 2016; 44: 1422–1433. <https://doi.org/10.1016/j.immuni.2016.05.010>.
- [75] Sashinami H, Nakane A. Adiponectin is required for enhancement of CCL2 expression in adipose tissue during *Listeria monocytogenes* infection. *Cytokine*. 2010; 50: 170–174. <https://doi.org/10.1016/j.cyto.2009.12.005>.
- [76] Schaefer K, Austhof E, Boyd K, Armstrong A, Hoffman S, Pogreba-Brown K. Septicemia Due to *Listeria monocytogenes* Infection: A Systematic Review and Meta-Analysis. *Foodborne Pathogens and Disease*. 2022; 19: 104–114. <https://doi.org/10.1089/fpd.2021.0046>.
- [77] Salman B, Yılmaz TU, Tezcaner T, Demir EO, Paşaoğlu OT. Exogenous recombinant adiponectin improves survival in experimental abdominal sepsis. *Balkan Medical Journal*. 2014; 31: 244–248. <https://doi.org/10.5152/balkanmedj.2014.13202>.
- [78] Xu L, Bao HG, Si YN, Han L, Zhang R, Cai MM, *et al.* Effects of adiponectin on acute lung injury in cecal ligation and puncture-induced sepsis rats. *The Journal of Surgical Research*. 2013; 183: 752–759. <https://doi.org/10.1016/j.jss.2013.01.055>.
- [79] van Meurs M, Castro P, Shapiro NI, Lu S, Yano M, Maeda N, *et al.* Adiponectin diminishes organ-specific microvascular endothelial cell activation associated with sepsis. *Shock (Augusta, Ga.)*. 2012; 37: 392–398. <https://doi.org/10.1097/SHK.0b013e318248225e>.
- [80] Leuwer M, Welters I, Marx G, Rushton A, Bao H, Hunter L, *et al.* Endotoxaemia leads to major increases in inflammatory adipokine gene expression in white adipose tissue of mice. *Pflügers Archiv: European Journal of Physiology*. 2009; 457: 731–741. <https://doi.org/10.1007/s00424-008-0564-8>.
- [81] Hall A, Leuwer M, Trayhurn P, Welters ID. Lipopolysaccharide induces a downregulation of adiponectin receptors in-vitro and in-vivo. *PeerJ*. 2015; 3: e1428. <https://doi.org/10.7717/peerj.1428>.
- [82] Amarsaikhan N, Stolz DJ, Wilcox A, Sands EM, Tsoggerel A, Gravely H, *et al.* Reciprocal Inhibition of Adiponectin and Innate Lung Immune Responses to Chitin and *Aspergillus fumigatus*. *Frontiers in Immunology*. 2019; 10: 1057. <https://doi.org/10.3389/fimmu.2019.01057>.
- [83] Lone AH, Tang J, Pignalosa A, Hsu HH, Abdul-Sater AA, Sweeney G. A novel blood-based bioassay to monitor adiponectin signaling. *International Immunopharmacology*. 2024; 132: 111890. <https://doi.org/10.1016/j.intimp.2024.111890>.
- [84] Shi X, Zhu S, Jin H, Fang J, Xing X, Wang Y, *et al.* The Anti-Inflammatory Effect of KS23, A Novel Peptide Derived From Globular Adiponectin, on Endotoxin-Induced Uveitis in Rats. *Frontiers in Pharmacology*. 2021; 11: 585446. <https://doi.org/10.3389/fphar.2020.585446>.
- [85] Buechler C, Pohl R, Aslanidis C. Pro-Resolving Molecules-New Approaches to Treat Sepsis? *International Journal of Molecular Sciences*. 2017; 18: 476. <https://doi.org/10.3390/ijms18030476>.
- [86] Loosen SH, Koch A, Tacke F, Roderburg C, Luedde T. The Role of Adipokines as Circulating Biomarkers in Critical Illness and Sepsis. *International Journal of Molecular Sciences*. 2019; 20: 4820. <https://doi.org/10.3390/ijms20194820>.
- [87] Failla KR, Connelly CD. Systematic Review of Gender Differ-

- ences in Sepsis Management and Outcomes. *Journal of Nursing Scholarship: an Official Publication of Sigma Theta Tau International Honor Society of Nursing*. 2017; 49: 312–324. <https://doi.org/10.1111/jnu.12295>.
- [88] Lakbar I, Einav S, Lalevée N, Martin-Loeches I, Pastene B, Leone M. Interactions between Gender and Sepsis-Implications for the Future. *Microorganisms*. 2023; 11: 746. <https://doi.org/10.3390/microorganisms11030746>.
- [89] Vassiliadi DA, Tzanela M, Kotanidou A, Orfanos SE, Nikitas N, Armaganidis A, *et al.* Serial changes in adiponectin and resistin in critically ill patients with sepsis: associations with sepsis phase, severity, and circulating cytokine levels. *Journal of Critical Care*. 2012; 27: 400–409. <https://doi.org/10.1016/j.jcrc.2012.04.007>.
- [90] Karampela I, Kandri E, Antonakos G, Vogiatzakis E, Christodoulatos GS, Nikolaidou A, *et al.* Kinetics of circulating fetuin-A may predict mortality independently from adiponectin, high molecular weight adiponectin and prognostic factors in critically ill patients with sepsis: A prospective study. *Journal of Critical Care*. 2017; 41: 78–85. <https://doi.org/10.1016/j.jcrc.2017.05.004>.
- [91] Walayat S, Martin D, Patel J, Ahmed U, N Asghar M, Pai AU, *et al.* Role of albumin in cirrhosis: from a hospitalist's perspective. *Journal of Community Hospital Internal Medicine Perspectives*. 2017; 7: 8–14. <https://doi.org/10.1080/20009666.2017.1302704>.
- [92] Wiedermann CJ. Hypoalbuminemia as Surrogate and Culprit of Infections. *International Journal of Molecular Sciences*. 2021; 22: 4496. <https://doi.org/10.3390/ijms22094496>.
- [93] Koch A, Sanson E, Voigt S, Helm A, Trautwein C, Tacke F. Serum adiponectin upon admission to the intensive care unit may predict mortality in critically ill patients. *Journal of Critical Care*. 2011; 26: 166–174. <https://doi.org/10.1016/j.jcrc.2010.07.015>.
- [94] Langouche L, Vander Perre S, Frystyk J, Flyvbjerg A, Hansen TK, Van den Berghe G. Adiponectin, retinol-binding protein 4, and leptin in protracted critical illness of pulmonary origin. *Critical Care (London, England)*. 2009; 13: R112. <https://doi.org/10.1186/cc7956>.
- [95] Venkatesh B, Hickman I, Nisbet J, Cohen J, Prins J. Changes in serum adiponectin concentrations in critical illness: a preliminary investigation. *Critical Care (London, England)*. 2009; 13: R105. <https://doi.org/10.1186/cc7941>.
- [96] Welters ID, Bing C, Ding C, Leuwer M, Hall AM. Circulating anti-inflammatory adipokines High Molecular Weight Adiponectin and Zinc- α 2-glycoprotein (ZAG) are inhibited in early sepsis, but increase with clinical recovery: a pilot study. *BMC Anesthesiology*. 2014; 14: 124. <https://doi.org/10.1186/1471-2253-14-124>.
- [97] Hillenbrand A, Xu P, Zhou S, Blatz A, Weiss M, Hafner S, *et al.* Circulating adipokine levels and prognostic value in septic patients. *Journal of Inflammation (London, England)*. 2016; 13: 30. <https://doi.org/10.1186/s12950-016-0138-z>.
- [98] Grewal T, Buechler C. Adipokines as Diagnostic and Prognostic Markers for the Severity of COVID-19. *Biomedicines*. 2023; 11: 1302. <https://doi.org/10.3390/biomedicines11051302>.
- [99] Grewal T, Nguyen MKL, Buechler C. Cholesterol and COVID-19-therapeutic opportunities at the host/virus interface during cell entry. *Life Science Alliance*. 2024; 7: e202302453. <https://doi.org/10.26508/lsa.202302453>.
- [100] Flikweert AW, Kobold ACM, van der Sar-van der Brugge S, Heeringa P, Rodenhuis-Zybert IA, Bijzet J, *et al.* Circulating adipokine levels and COVID-19 severity in hospitalized patients. *International Journal of Obesity (2005)*. 2023; 47: 126–137. <https://doi.org/10.1038/s41366-022-01246-5>.
- [101] Kearns SM, Ahern KW, Patrie JT, Horton WB, Harris TE, Kadl A. Reduced adiponectin levels in patients with COVID-19 acute respiratory failure: A case-control study. *Physiological Reports*. 2021; 9: e14843. <https://doi.org/10.14814/phy2.14843>.
- [102] Perrotta F, Scialò F, Mallardo M, Signoriello G, D'Agnano V, Bianco A, *et al.* Adiponectin, Leptin, and Resistin Are Dysregulated in Patients Infected by SARS-CoV-2. *International Journal of Molecular Sciences*. 2023; 24: 1131. <https://doi.org/10.3390/ijms24021131>.
- [103] Sulicka-Grodzicka J, Surdacki A, Surmiak M, Sanak M, Wizner B, Sydor W, *et al.* Chemerin as a Potential Marker of Resolution of Inflammation in COVID-19 Infection. *Biomedicines*. 2022; 10: 2462. <https://doi.org/10.3390/biomedicines10102462>.
- [104] Caterino M, Gelzo M, Sol S, Fedele R, Annunziata A, Calabrese C, *et al.* Dysregulation of lipid metabolism and pathological inflammation in patients with COVID-19. *Scientific Reports*. 2021; 11: 2941. <https://doi.org/10.1038/s41598-021-82426-7>.
- [105] Di Filippo L, De Lorenzo R, Sciorati C, Capobianco A, Lorè NI, Giustina A, *et al.* Adiponectin to leptin ratio reflects inflammatory burden and survival in COVID-19. *Diabetes & Metabolism*. 2021; 47: 101268. <https://doi.org/10.1016/j.diabet.2021.101268>.
- [106] Minuzzi LG, Seelaender M, Silva BSDA, Cunha EDBB, Deus MDC, Vasconcellos FTF, *et al.* COVID-19 Outcome Relates With Circulating BDNF, According to Patient Adiposity and Age. *Frontiers in Nutrition*. 2021; 8: 784429. <https://doi.org/10.3389/fnut.2021.784429>.
- [107] Al-Kuraishy HM, Al-Gareeb AI, Bungau SG, Radu AF, Batiha GES. The potential molecular implications of adiponectin in the evolution of SARS-CoV-2: Inbuilt tendency. *Journal of King Saud University. Science*. 2022; 34: 102347. <https://doi.org/10.1016/j.jksus.2022.102347>.
- [108] Reiterer M, Rajan M, Gómez-Banoy N, Lau JD, Gomez-Escobar LG, Ma L, *et al.* Hyperglycemia in acute COVID-19 is characterized by insulin resistance and adipose tissue infectivity by SARS-CoV-2. *Cell Metabolism*. 2021; 33: 2174–2188.e5. <https://doi.org/10.1016/j.cmet.2021.09.009>.
- [109] Spirina LV, Masunov VN, Dyakov DA, Akbasheva OE, Kebekbayeva AY, Shuvalov IY, *et al.* Sars-Cov2 Induced Biochemical Mechanisms in Liver Damage and Intestinal Lesions. *Indian Journal of Clinical Biochemistry: IJCB*. 2022; 38: 1–10. <https://doi.org/10.1007/s12291-022-01089-x>.
- [110] Luo L, Wang L, Luo Y, Romero E, Yang X, Liu M. Glucocorticoid/Adiponectin Axis Mediates Full Activation of Cold-Induced Beige Fat Thermogenesis. *Biomolecules*. 2021; 11: 1573. <https://doi.org/10.3390/biom11111573>.
- [111] Shi JH, Du WH, Liu XY, Fan YP, Hu XL, Zhou HY, *et al.* Glucocorticoids decrease serum adiponectin level and WAT adiponectin mRNA expression in rats. *Steroids*. 2010; 75: 853–858. <https://doi.org/10.1016/j.steroids.2010.05.001>.
- [112] Rysø CK, Dungu AM, Hegelund MH, Jensen AV, Sejdic A, Faurholt-Jepsen D, *et al.* Body composition, physical capacity, and immuno-metabolic profile in community-acquired pneumonia caused by COVID-19, influenza, and bacteria: a prospective cohort study. *International Journal of Obesity (2005)*. 2022; 46: 817–824. <https://doi.org/10.1038/s41366-021-01057-0>.
- [113] Blot M, David Masson, Nguyen M, Bourredjem A, LYMPHONIE Study Group, Binquet C, *et al.* Are adipokines the missing link between obesity, immune response, and outcomes in severe COVID-19? *International Journal of Obesity (2005)*. 2021; 45: 2126–2131. <https://doi.org/10.1038/s41366-021-00868-5>.
- [114] Palakshappa JA, Anderson BJ, Reilly JP, Shashaty MGS, Ueno R, Wu Q, *et al.* Low Plasma Levels of Adiponectin Do Not Explain Acute Respiratory Distress Syndrome Risk: a Prospective Cohort Study of Patients with Severe Sepsis. *Critical Care (London, England)*. 2016; 20: 71. <https://doi.org/10.1186/s13054-016-1484-3>.

1186/s13054-016-1244-2.

- [115] Bergmann F, Gabler C, Nussbaumer-Pröll A, Wölfl-Duchek M, Blaschke A, Radtke C, *et al.* Early Bacterial Coinfections in Patients Admitted to the ICU With COVID-19 or Influenza: A Retrospective Cohort Study. *Critical Care Explorations*. 2023; 5: e0895. <https://doi.org/10.1097/CCE.0000000000000895>.
- [116] Contou D, Claudinon A, Pajot O, Micaëlo M, Longuet Flan-dre P, Dubert M, *et al.* Bacterial and viral co-infections in pa-tients with severe SARS-CoV-2 pneumonia admitted to a French ICU. *Annals of Intensive Care*. 2020; 10: 119. <https://doi.org/10.1186/s13613-020-00736-x>.
- [117] Musuuzza JS, Watson L, Parmasad V, Putman-Buehler N, Chris-tensen L, Safdar N. Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: A systematic review and meta-analysis. *PloS One*. 2021; 16: e0251170. <https://doi.org/10.1371/journal.pone.0251170>.
- [118] Garcia-Vidal C, Sanjuan G, Moreno-García E, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, *et al.* Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. *Clinical Microbiology and Infection: the Official Publication of the European Society of Clinical Microbiology and Infectious Diseases*. 2021; 27: 83–88. <https://doi.org/10.1016/j.cmi.2020.07.041>.
- [119] Bazaid AS, Barnawi H, Qanash H, Alsaif G, Aldarhami A, Gattan H, *et al.* Bacterial Coinfection and Antibiotic Resistance Profiles among Hospitalised COVID-19 Patients. *Microorgan-isms*. 2022; 10: 495. <https://doi.org/10.3390/microorganisms10030495>.
- [120] Raza T, Ullah SR, Mehmood K, Andleeb S. Vancomycin re-sistant Enterococci: A brief review. *JPMA. the Journal of the Pakistan Medical Association*. 2018; 68: 768–772.
- [121] Zakaria ND, Hamzah HH, Salih IL, Balakrishnan V, Abdul Razak K. A Review of Detection Methods for Vancomycin-Resistant *Enterococci* (VRE) Genes: From Conventional Approaches to Potentially Electrochemical DNA Biosen-sors. *Biosensors*. 2023; 13: 294. <https://doi.org/10.3390/bios13020294>.
- [122] Yamamoto H, Maeda K, Uji Y, Tsuchihashi H, Mori T, Shimizu T, *et al.* Association between reduction of plasma adiponectin levels and risk of bacterial infection after gastric cancer surgery. *PloS One*. 2013; 8: e56129. <https://doi.org/10.1371/journal.po-ne.0056129>.
- [123] Walkey AJ, Rice TW, Konter J, Ouchi N, Shibata R, Walsh K, *et al.* Plasma adiponectin and mortality in critically ill subjects with acute respiratory failure. *Critical Care Medicine*. 2010; 38: 2329–2334. <https://doi.org/10.1097/CCM.0b013e3181fa0561>.
- [124] Wang H, Gao YX, Wu YN, Li C, Duan J. Association between plasma adiponectin levels and left ventricular systolic dysfunc-tion in sepsis patients. *Journal of Critical Care*. 2020; 60: 195–201. <https://doi.org/10.1016/j.jcrc.2020.06.020>.
- [125] Hornung F, Rogal J, Loskill P, Löffler B, Deinhardt-Emmer S. The Inflammatory Profile of Obesity and the Role on Pul-monary Bacterial and Viral Infections. *International Journal of Molecular Sciences*. 2021; 22: 3456. <https://doi.org/10.3390/ijms22073456>.
- [126] Karampela I, Christodoulatos GS, Dalamaga M. The Role of Adipose Tissue and Adipokines in Sepsis: Inflammatory and Metabolic Considerations, and the Obesity Paradox. *Current Obesity Reports*. 2019; 8: 434–457. <https://doi.org/10.1007/s13679-019-00360-2>.
- [127] Henriquez-Camacho C, Losa J. Biomarkers for sepsis. *BioMed Research International*. 2014; 2014: 547818. <https://doi.org/10.1155/2014/547818>.
- [128] Urbaschek B, Urbaschek R. The inflammatory response to en-dotoxins. *Bibliotheca Anatomica*. 1979; 74–104.
- [129] Luo Y, Liu M. Adiponectin: a versatile player of innate im-munity. *Journal of Molecular Cell Biology*. 2016; 8: 120–128. <https://doi.org/10.1093/jmcb/mjw012>.
- [130] Van Wyngene L, Vandewalle J, Libert C. Reprogramming of basic metabolic pathways in microbial sepsis: therapeutic tar-gets at last? *EMBO Molecular Medicine*. 2018; 10: e8712. <https://doi.org/10.15252/emmm.201708712>.
- [131] Lim JY, Templeton SP. Regulation of lung inflammation by adiponectin. *Frontiers in Immunology*. 2023; 14: 1244586. <http://doi.org/10.3389/fimmu.2023.1244586>.
- [132] Nedeva C, Menassa J, Puthalakath H. Sepsis: Inflammation Is a Necessary Evil. *Frontiers in Cell and Developmental Biology*. 2019; 7: 108. <https://doi.org/10.3389/fcell.2019.00108>.
- [133] Vallabhajosyula S, Wang Z, Murad MH, Vallabhajosyula S, Sundaragiri PR, Kashani K, *et al.* Natriuretic Peptides to Predict Short-Term Mortality in Patients With Sepsis: A Systematic Re-view and Meta-analysis. *Mayo Clinic Proceedings. Innovations, Quality & Outcomes*. 2020; 4: 50–64. <https://doi.org/10.1016/j.mayocpiqo.2019.10.008>.
- [134] Liu S, Ngo DTM, Chong CR, Amarasekera AT, Procter NEK, Licari G, *et al.* Suppression of neutrophil superoxide generation by BNP is attenuated in acute heart failure: a case for 'BNP resistance'. *European Journal of Heart Failure*. 2015; 17: 475–483. <https://doi.org/10.1002/ejhf.242>.
- [135] Tsutamoto T, Wada A, Maeda K, Hisanaga T, Maeda Y, Fukai D, *et al.* Attenuation of compensation of endogenous cardiac na-triuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. *Circulation*. 1997; 96: 509–516. <https://doi.org/10.1161/01.cir.96.2.509>.
- [136] Kandil E, Burack J, Sawas A, Bibawy H, Schwartzman A, Ze-nilman ME, *et al.* B-type natriuretic peptide: a biomarker for the diagnosis and risk stratification of patients with septic shock. *Archives of Surgery (Chicago, Ill.: 1960)*. 2008; 143: 242–246; discussion 246. <https://doi.org/10.1001/archsurg.2007.69>.
- [137] Yue L, Deng X, Yang M, Li X. Elevated B-type natriuretic pep-tide (BNP) and soluble thrombomodulin (sTM) indicates sever-ity and poor prognosis of sepsis. *Annals of Palliative Medicine*. 2021; 10: 5561–5567. <https://doi.org/10.21037/apm-21-1048>.
- [138] Rochwerf B, Oczkowski SJ, Siemieniuk RAC, Agoritsas T, Belley-Cote E, D'Aragnon F, *et al.* Corticosteroids in Sepsis: An Updated Systematic Review and Meta-Analysis. *Critical Care Medicine*. 2018; 46: 1411–1420. <https://doi.org/10.1097/CCM.0000000000003262>.