Advances in the Mechanistic Research of Metabolic Syndrome and Stroke-Associated Pneumonia

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Introduction. Stroke-associated pneumonia (SAP) is a major cause of morbidity and mortality in stroke patients, ranking as the third leading cause of death. Emerging evidence suggests that metabolic syndrome (MetS) significantly contributes to the development and progression of SAP, acting through multiple pathways that exacerbate inflammation and adversely affect patient outcomes. This review delves into the intricate relationship between MetS and SAP, exploring potential mechanisms underlying this association based on current research findings. Insulin resistance and obesity, prevalent in stroke patients, are implicated in the exacerbation of chronic inflammation by promoting the secretion of pro-inflammatory cytokines, such as TNF-α. Furthermore, hypertension, a hallmark of MetS, can exacerbate pulmonary infections by over-activating the sympathetic nervous system. This activation triggers the renin-angiotensin-aldosterone system (RAAS), leading to the production of the pro-inflammatory mediator Ang II and the subsequent release of pro-inflammatory cytokines. Moreover, chronic inflammation, driven by the effects of pro-inflammatory cytokines and chronic stress responses, can perpetuate metabolic disturbances, creating a vicious cycle that further exacerbates the disease process. This review underscores the importance of addressing both metabolic dysregulation and other contributing factors to SAP, such as dysphagia, for effective clinical management of stroke patients. By targeting these interconnected pathways, clinicians can potentially break the vicious cycle, leading to improved outcomes for stroke patients.

Keywords. Stroke-associated pneumonia;Metabolic syndrome;Stroke;Pulmonary infection

INTRODUCTION

In recent years, mortality rates among stroke patients have significantly increased, with stroke-associated pneumonia (SAP) emerging as a leading cause of death. Studies have shown that stroke patients who develop SAP have a six-fold higher 30-day mortality rate compared to those who do not develop SAP[1], with SAP accounting for approximately 10.1% to 37.3% of stroke-related deaths [2].SAP is defined as pneumonia that develops newly within seven days of hospital admission in stroke patients. The incidence of SAP is substantial, ranging from 7% to 38%[3], and is significantly associated with poor patient outcomes, prolonged hospital stays, and increased healthcare costs[4]. The development of SAP is influenced by numerous factors, with aspiration due to dysphagia and post-stroke immune suppression emerging as primary contributors [5]. Moreover, recent research, both domestically and internationally, suggests that metabolic syndrome, a cluster of metabolic abnormalities, can also contribute to the development of SAP in stroke patients. This syndrome, characterized by metabolic disturbances, exacerbates inflammation and can ultimately lead to more severe consequences[6, 7].

1. Overview of Metabolic Syndrome

Metabolic syndrome (MetS), also known as Syndrome X, is not a single disease but rather a complex metabolic disorder characterized by a cluster of metabolic abnormalities [8]. The World Health Organization defines MetS as a pathological condition characterized by a constellation of metabolic disturbances, including abdominal obesity, insulin resistance, and hypertension, among other features[9]. Metabolic syndrome (MetS) disrupts metabolic homeostasis in the body, leading to severe complications such as diabetes, fatty liver disease, and cancer[10]. This metabolic dysfunction is strongly associated with the development and exacerbation of stroke-associated pneumonia (SAP)[11-13]. Clinically, the primary treatment for SAP involves antibiotic therapy, often supplemented by chest physiotherapy techniques for expectoration, nutritional support, and traditional Chinese medicine[3] .

However, despite these efforts, the treatment efficacy remains limited, and SAP mortality rates have not shown significant improvement. Given the significant role of metabolic disturbances in the development and progression of SAP[11], a thorough understanding of the relationship between MetS and SAP is crucial for clinicians. Such an understanding could lead to the development of targeted therapies and potentially improve outcomes for patients with SAP. This review summarizes recent advances in research on the relationship between MetS and SAP, including their underlying mechanisms, with the aim of providing a reference for clinical practice and research into relevant pathological mechanisms.

2. MetS Induction and Exacerbation of SAP

2.1 Insulin Resistance Induces and Exacerbates SAP

Insulin resistance is a prominent risk factor and a key pathological characteristic of MetS. Severe insulin resistance can lead to the development of diabetes, a condition that further contributes to the development and exacerbation of SAP in the context of stroke. Notably, statistics from 2019 indicate that approximately 23.5% of stroke patients in China have diabetes[14], with nearly 80% exhibiting abnormal blood sugar metabolism[15]. A retrospective study in the United States, analyzing 4.2 million patients with acute ischemic stroke in 2020, found that diabetes was a significant risk factor for developing SAP in stroke patients (AOR: 1.29, 95% CI: 1.03-1.61, P=0.0288) [11]. In a multi-factor analysis of clinical data from 1435 patients, Sui et al.[16] demonstrated that stroke patients with diabetes were 1.612 times more likely to develop pneumonia than those without diabetes, reinforcing the association between diabetes and the development of SAP in stroke patients [17]. Additionally, evidence suggests that even in stroke patients without diabetes, hyperglycemia arising from insulin resistance can increase the incidence of both SAP and urinary tract infections[18]. These findings underscore the direct link between the development of SAP and abnormal blood sugar metabolism resulting from insulin resistance.

A growing body of research corroborates that insulin resistance not only elevates the risk of SAP in stroke patients but also intensifies inflammatory responses, leading to an exacerbation of pulmonary infection[19-25]. The increased susceptibility to pneumonia observed during periods of hyperglycemia in stroke patients may be linked to impaired immune function. This can be attributed to the fact that in insulin-resistant patients, abnormal glucose metabolism leads to increased tissue breakdown, including protein and fat, resulting in elevated levels of glucose and free fatty acids (FFA). Chronic hyperglycemia, in turn, accelerates the formation of advanced glycation end products (AGEs)[19]. The accumulation of excess FFA and AGEs impairs neutrophil function, leading to reduced activity and the stimulation of inflammatory mediators and reactive oxygen species (ROS) production, ultimately increasing the risk of SAP[20]. In healthy individuals, ROS is tightly regulated through a dynamic cycle between reduced and oxidized states, mediated by glutathione[21]. However, under hyperglycemic conditions, NADPH, an essential cofactor for glutathione regeneration, is significantly depleted during the polyol pathway of glucose metabolism. This depletion leads to a reduction in glutathione concentration[22], disrupting the delicate balance of ROS regulation. Studies have demonstrated that diabetic patients experience a deficiency in glutathione precursors, such as cysteine and glycine[23], alongside a reduction in the activity of γ-glutamyl cysteine synthetase, the rate-limiting enzyme for glutathione synthesis[24]. This combination ultimately leads to impaired glutathione consumption and biosynthesis, resulting in enhanced oxidative stress and an increase in M1 macrophages. The activation of macrophages leads to the secretion of various inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), contributing to a chronic inflammatory state and exacerbating pulmonary infection. High concentrations of ROS in the body can also accompany ischemia-reperfusion injury, contributing to systemic inflammation[25]. These findings highlight the importance of vigilance for the development of SAP in stroke patients exhibiting insulin resistance or diabetes. Additionally, for SAP patients who have already developed an infection,

metabolic treatment targeting their hyperglycemia may offer potential benefits in mitigating pulmonary infection.

However, a clinical study reported a higher incidence of infection in diabetic patients receiving insulin therapy compared to those not receiving insulin therapy, despite no observed increase in mortality risk[26]. This discrepancy may be explained by differences in disease severity. Patients receiving regular insulin injections may present with more severe illness, prompting earlier and more rigorous monitoring for infection complications. This heightened surveillance could lead to an increased likelihood of detecting infections, potentially contributing to a higher observed incidence rate. Conversely, the lack of increased mortality risk suggests the effectiveness of insulin resistance therapy in mitigating inflammation and reducing mortality rates in SAP patients. Further investigation is warranted to clarify the association between insulin resistance therapy and infection development. Continued research is crucial for a more comprehensive understanding of the complex interplay between insulin, MetS, and SAP.

2.2 Obesity Induces and Exacerbates SAP

Obesity is a prominent feature of MetS and a well-established risk factor for stroke[27], with high prevalence among stroke patients. A cross-sectional study conducted in Brazil, involving 1255 first-time stroke patients across five cities, found that 64% were overweight (95% CI: 62-67) and 26% were obese (95% CI: 24-29)[28]. Obesity not only increases the risk of stroke[29] but also significantly contributes to the development and severity of SAP[30-32].

Obesity exacerbates pulmonary infection by secreting inflammatory mediators, thereby negatively impacting the prognosis of stroke patients[30-32]. Stressed adipocytes and adipose tissue macrophages within the adipose tissue of obese individuals release high levels of pro-inflammatory cytokines, such as TNF-α and IL-6. These cytokines induce cellular inflammation, contributing to a dysregulation of pro-inflammatory responses and an exacerbation of pulmonary infection[30]. Obesity can also impair the body’s immune response to respiratory infections by altering

cellular immune systems, leading to increased susceptibility to recurrent pulmonary infections. Research in animal models has shown that obese mice exhibit a significant decrease in regulatory T cell levels and an increase in cytotoxic CD8+ T cell levels during infection, leading to immune dysregulation[31]. Compared to lean mice, obese mice exhibit increased susceptibility to recurrent respiratory infections and are more susceptible to developing pulmonary infections[32]. Earlier studies have demonstrated that obese patients experience a decrease in the bactericidal capacity of polymorphonuclear leukocytes[33]. This phenomenon may be attributed to decreased activation of Toll-like receptor 4 (TLR4) on the cell membrane[34], with TLR4 receptors expressed by the innate immune system. This further emphasizes the detrimental effect of obesity on the immune system. Clinical research has consistently shown that obesity increases the risk of vaccine failure, as well as infectious complications and hospitalizations[35-37], further reinforcing the detrimental effects of obesity on the immune system. These negative impacts not only complicate and perpetuate immune-mediated metabolic dysfunction and disease risks, contributing to exacerbated pulmonary infection, but also potentially increase the risk of other infectious and chronic diseases. Moreover, obese individuals may be more susceptible to respiratory infections or pneumonia due to anatomical and respiratory physiological changes associated with obesity, including reduced lung volume and decreased pulmonary ventilation due to excessive chest and abdominal fat. This mechanical abnormality may blunt respiratory mechanisms, induce respiratory infections, and potentially worsen associated respiratory system complications such as chronic obstructive pulmonary disease, asthma, hypoventilation syndrome, and obstructive sleep apnea, thereby increasing the individual's susceptibility to viral infections [38].

Therefore, understanding these interconnected mechanisms underscores the importance of close monitoring for pulmonary infections in stroke patients who are overweight or obese, given their heightened susceptibility. This suggests that weight management, including weight loss and improvement in BMI, may serve as crucial targets for the clinical management of SAP in patients who have already developed an

infection.

Obesity itself can exacerbate pulmonary infection through multiple mechanisms. The risk of infection may be further exacerbated when obesity coexists with certain associated complications, such as type 2 diabetes. Obesity and insulin resistance are two prominent features of MetS, and they can mutually promote and influence each other, creating a vicious cycle that exacerbates the overall metabolic dysfunction. When pancreatic islet function is normal, insulin resistance inevitably leads to hyperinsulinemia. Hyperinsulinemia leads to increased appetite and overeating, resulting in the increased uptake and utilization of energy by tissues, which is subsequently stored as fat, leading to obesity. Adipose tissue, in turn, influences insulin resistance through the overexpression of TNF-α[39]. TNF-α can induce serine phosphorylation of insulin receptor substrate-1 (IRS-1) in insulin-sensitive cells, subsequently phosphorylating the serine residues of the insulin receptor. This phosphorylation hinders the normal phosphorylation of insulin receptor tyrosine, inhibiting insulin signaling[40]. This ultimately leads to inadequate T cell responses to pathogens, delaying T cell-mediated inflammation resolution, while simultaneously exacerbating insulin resistance and β-cell damage[41]. This creates a vicious cycle of increased insulin resistance and obesity, further exacerbating pulmonary infection.

In conclusion, insulin resistance and obesity mutually exert negative effects, accelerating and exacerbating inflammation. Therefore, effective management of metabolic disturbances may be a crucial strategy to prevent and mitigate inflammation in clinical SAP patients. By effectively targeting factors associated with insulin resistance and obesity, it may be possible to improve infection outcomes and severity in stroke patients, leading to improved outcomes for SAP patients.

2.3 Hypertension Exacerbates SAP

Hypertension is a prevalent comorbidity among stroke patients. A large-scale cohort study in the United States, encompassing over 500,000 patients with acute stroke, revealed that over 60% presented with hypertension[42]. A separate retrospective study found that 52% of stroke patients exhibited hypertension at the

time of hospital admission[43]. Hypertension not only increases the risk of stroke[44]and impacts long-term stroke risk[45]but also plays a significant role in the development and progression of SAP[13, 46-49].

In a study by Ishigami et al.[13] , hypertension was identified as a significant risk factor for the development of SAP following stroke (OR: 2.83, 95% CI: 1.14-7.05, P=0.025). Furthermore, their study indicated that hypertension significantly increased mortality rates in SAP patients (OR: 5.20, 95% CI: 1.01-26.8, P=0.049). This association may be linked to an overactivation of the sympathetic nervous system. In the early stages of acute ischemic stroke, elevated blood pressure is associated with sympathetic nervous system activation triggered by the stroke. In stroke patients with pre-existing hypertension, sympathetic nervous system activation may induce immune suppression, leading to a secondary state of immunosuppression that increases the risk of developing SAP. This observation has been confirmed in rodent models of cerebral ischemia[50, 51], however, further research is required to validate these findings in humans. Further research is warranted to investigate the relationship between sympathetic activity, immunosuppression, and SAP by assessing catecholamine levels and immune markers in patients.

Emerging evidence suggests that systemic hypertension is strongly associated with activation of the renin-angiotensin-aldosterone system (RAAS). Activation of the RAAS promotes a pro-inflammatory and pro-coagulant state, contributing to an overall pro-thrombotic environment . Angiotensin II (Ang II) is a key inflammatory mediator during the acute inflammatory phase and serves as a critical component of the RAAS . Ang II exacerbates inflammation and contributes to the development of SAP by activating the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells, which regulates leukocyte adhesion and migration. This, in turn, stimulates the synthesis of pro-inflammatory cytokines IL-6 and TNF-α . Furthermore, stroke patients with coexisting hypertension often exhibit reduced activity and levels of antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPX), and

catalase, leading to an increase in oxidative stress. This heightened oxidative stress further exacerbates inflammation, intensifies pulmonary infection, and ultimately contributes to increased mortality in stroke patients.

Studies have reported that angiotensin-converting enzyme inhibitors, by activating the arachidonic acid metabolic pathway, can increase the synthesis of thromboxane A2 and prostaglandin E2, which not only reduces hypertension but also enhances airway reactivity and strengthens the cough reflex, potentially mitigating dysphagia[52]. This suggests that angiotensin-converting enzyme inhibitors could be considered as a potential therapeutic strategy in the acute phase of stroke patients with hypertension, without contraindications, to potentially reduce the risk of developing SAP.

Therefore, the strong association between SAP and hypertension highlights that stroke patients with significant post-stroke blood pressure elevation are at high risk for developing SAP. Clinicians should carefully monitor these patients, closely manage their hypertension, and strive for early detection and treatment to improve their prognosis.

3. Pulmonary Infection Induces and Exacerbates Metabolic Disturbances

Metabolic abnormalities associated with MetS not only increase the incidence and severity of SAP, but inflammation resulting from SAP can also exacerbate metabolic disturbances, negatively impacting the prognosis of stroke patients[52, 53] 53-56]. This complex interplay can occur through several key pathways, which are described below:①Chronic stress: Pulmonary inflammation and immunosuppression lead to the release of high levels of catecholamines, counter-regulatory hormones, and inflammatory mediators into the bloodstream, further exacerbating metabolic disturbances such as increased catabolism, hyperglycemia, and insulin resistance [53].②Mitochondrial dysfunction: Pro-inflammatory cytokines can target mitochondria, reducing the activity of respiratory chain enzymes and decreasing mitochondrial oxygen consumption. This ultimately leads to decreased adenosine

triphosphate (ATP) levels, insufficient cellular energy metabolism, and the exacerbation of energy imbalance, ultimately causing tissue and cell damage[6].③Insulin resistance: Inflammation leads to an increase in the production of relevant cytokines and chemokines, activating immune cells, including monocytes and macrophages. This contributes to insulin resistance and induces stress-induced hyperglycemia, further exacerbating metabolic dysregulation [54].④Lipid metabolism abnormalities: During the inflammatory response, the synthesis of lipid mediators derived from polyunsaturated fatty acids (PUMAs), such as arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), increases, leading to dysregulation of lipid metabolism [55].⑤Uncontrolled catabolism: During inflammation, metabolic rate increases. Combined endocrine and inflammatory responses lead to the mobilization of energy stores, triggering lipolysis and the release of fatty acids. This also involves glycolysis, glycogenolysis, and hepatic gluconeogenesis [25], ultimately leading to uncontrolled catabolism and resistance to metabolic substances (e.g., insulin) [56].

In summary, comprehensive management of SAP in stroke patients should not only focus on addressing metabolic disturbances to prevent and improve SAP, but also include measures targeting other mechanisms of SAP development. This includes maintaining good oral hygiene to reduce bacterial colonization in sputum and minimize the occurrence of SAP. Early interventions such as enteral feeding to alleviate dysphagia, the cautious use of invasive respiratory procedures, and judicious use of acid-suppressing medications should be implemented. This comprehensive approach can help prevent the vicious cycle between SAP and metabolic disturbances, leading to improved outcomes for stroke patients.

4. Summary and Future Perspectives

Stroke disproportionately affects older adults, who often experience declines in physical function, cellular immunity, and humoral immunity, rendering them highly susceptible to pulmonary infections. These infections impede rehabilitation efforts,

negatively impact prognosis, and can even lead to mortality. Additionally, older adults often experience reduced metabolic function, leading to metabolic disturbances that contribute to the development of MetS. While MetS is a known factor influencing stroke pathogenesis, the complex interplay between MetS and SAP has been under-explored, necessitating a comprehensive review.This review summarizes the relationship between MetS and SAP, drawing upon the existing body of literature. It highlights that insulin resistance and obesity in stroke patients can exacerbate chronic inflammation by promoting the secretion of pro-inflammatory cytokines, including TNF-α, contributing to a pro-inflammatory milieu. Hypertension, through overactivation of the sympathetic nervous system and RAAS-mediated production of the inflammatory mediator Ang II, further contributes to inflammation and increases the risk of pulmonary infection. Moreover, inflammation can further mediate metabolic disturbances through mechanisms such as chronic stress responses and the actions of pro-inflammatory cytokines, forming a vicious cycle that ultimately affects stroke patient prognosis, prolongs hospital stays, and increases mortality.This review aims to clarify the underlying mechanistic relationship between SAP and MetS, emphasizing the importance of close monitoring and proactive management for stroke patients exhibiting MetS features such as insulin resistance, obesity, and hypertension. Early detection and intervention are crucial to prevent the development of SAP. In patients who have already developed SAP, metabolic modulation strategies and tailored treatment plans can improve abnormal metabolic presentations, including insulin resistance, obesity, and hypertension, ultimately improving outcomes for SAP.

Furthermore, this review provides insights for researchers to conduct high-quality clinical studies and fundamental research into relevant pathophysiological mechanisms. Future research endeavors could focus on developing animal or cellular models of SAP. Building upon these models, investigating the correlation between MetS metabolic abnormalities and SAP, and solidifying clinical findings will facilitate further exploration of the underlying mechanisms.

CONFLICT OF INTEREST STATEMENT

All authors declare that there are no conflicts of interest.

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