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Research Insight Open Access

The Impact of GLP-1 Receptor Agonists on Weight Control in Patients with Diabetes and Comorbid Obesity

Jie Wang
Zhuji People's Hospital, Zhuji, 311800, Zhejiang, China
Corresponding email: 2308763906@qq.com

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Abstract This study explored the application significance of GLP-1 receptor agonists (GLP-1 RAs) in the population with diabetes mellitus complicated with obesity. This type of drug achieves the dual effects of lowering blood sugar and losing weight through multiple mechanisms such as inhibiting central appetite, delaying gastric emptying, and improving metabolic status. Clinical studies have shown that GLP-1 RAs can lead to significant weight loss related to dosage and medication duration, and is superior to traditional hypoglycemic drugs that are prone to cause weight gain in terms of waist circumference and BMI. However, after discontinuing the medication, some patients may experience varying degrees of weight gain, suggesting that long-term management and lifestyle intervention are still necessary. In practical applications, individualized medication selection should be made based on BMI, comorbidities and cardiovascular risks, and a low-dose starting and gradually increasing dosage approach should be adopted to reduce gastrointestinal adverse reactions. When used in combination with insulin or sulfonylurea drugs, attention should also be paid to dose adjustment and hypoglycemic monitoring. Under the premise of reasonable patient screening, standardized titration and follow-up monitoring, GLP-1 RAs has a relatively ideal risk-benefit ratio and is expected to continue to be an important treatment method in the comprehensive management of diabetes mellitus complicated with obesity.

Keywords GLP-1 receptor agonists (GLP-1 RAs); Diabetes mellitus complicated with obesity; Weight management / Weight loss; Glycemic control; Individualized treatment

1 Introduction

Diabetes, especially type 2 diabetes, along with obesity, is a global health problem. The increasing number of such patients has also led to the situation of "diabetes combined with obesity", exerting considerable pressure on individual health, the medical system and social resources (Yao et al., 2024). When diabetes and obesity coexist, metabolic problems in the body become more severe, the risk of cardiovascular diseases increases, and it also affects the quality of life. Therefore, weight control has become an important part of treatment. It can not only help control blood sugar, but also reduce metabolic and cardiovascular-related risks (Popoviciu et al., 2023; Liu and Shu, 2025).

Controlling blood sugar remains the core goal of diabetes treatment, but merely lowering blood sugar is difficult to solve a host of metabolic problems caused by diabetes combined with obesity. Appropriate weight loss not only helps improve blood sugar but also benefits blood pressure and blood lipid levels. However, due to factors such as physiology, habits and environment, most patients have difficulty maintaining an ideal weight all the time by merely controlling their diet and doing more exercise, and the overall effect is not very good (Popoviciu et al., 2023; Yao et al., 2024; Liu and Shu, 2025). Therefore, drugs that can both lower blood sugar and help lose weight have gradually become the focus of research and clinical attention.

This study will analyze the use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in the treatment of diabetes mellitus complicated with obesity. This type of medicine can not only lower blood sugar but also assist in weight loss. Compared with traditional hypoglycemic drugs, it has a lower possibility of causing weight gain, and some drugs can even help patients maintain a low weight for a long time. GLP-1 RAs can help patients lose weight by 5% to 15%, significantly reduce glycated hemoglobin levels (HbA1c), and also has a protective effect on organs such as the heart and kidneys. In the future, such drugs are expected to play a more important role in the comprehensive treatment of diabetes complicated with obesity, helping patients maintain a healthy state for a long time and reducing the burden brought by the disease.

2 Disease Foundation and Management Challenges

2.1 Obesity with insulin resistance and chronic inflammation

Obesity is a key factor causing insulin resistance and chronic low-grade inflammation, and insulin resistance and chronic low-grade inflammation are key causes of type 2 diabetes (Zatterale et al., 2020; Ahmed et al., 2021). When there is an excessive accumulation of adipose tissue (especially visceral fat), metabolism becomes more active, and inflammatory factors such as TNF-α and IL-6 are continuously released. These substances can interfere with the signal transmission of insulin and fail to function in the human body.

Chronic inflammation related to obesity can affect multiple organ systems and is closely associated with the occurrence of cardiovascular diseases, non-alcoholic fatty liver disease and chronic kidney disease. These pathological changes superimpose on each other, continuously promoting blood sugar imbalance and increasing the risk of diabetic complications It is suggested that during the treatment of diabetes, attention should be paid simultaneously to the regulation of body weight status and inflammation level (Zatterale et al., 2020; Kojta et al., 2020).

2.2 The effect of lifestyle intervention is limited

Adjusting diet and increasing physical activity are the main methods for diabetic obese patients to control their weight. These methods can help with weight loss and improve blood sugar in the short term, but many patients have difficulty adhering to them in the long term, and the actual effect is often underestimated (Kheniser et al., 2021; Meir et al., 2025). During the process of losing weight, the body will have automatic responses, such as reduced energy consumption and feeling hungry more easily, which leads to easy weight rebound and affects the long-term effect (Aronne et al., 2021; Petroni et al., 2021).

Research has found that few people can maintain their weight loss effect in the long term merely by changing their lifestyle. Most patients' weight will gradually rebound and approach the pre-intervention level after reaching a certain stage of weight loss (Petroni et al., 2021; Meir et al., 2025). Weight regulation is influenced by multiple factors, including the body's own regulation, psychological state and the surrounding environment, etc. A single lifestyle intervention cannot meet the complex long-term management needs, so drug treatment or metabolic surgery is often regarded as an important supplement.

2.3 Some traditional hypoglycemic drugs may cause weight gain

Some traditional hypoglycemic drugs, such as insulin and sulfonylurea drugs, although they can lower blood sugar, may cause weight gain during the medication process. This has led to some patients, although their blood sugar levels have improved, having more severe obesity problems and the difficulty of treatment has also increased accordingly. The GRADE study indicates that treatment regimens such as insulin glargine and glimepiride can better control blood sugar, but they also lead to more significant weight gain and increase the risk of hypoglycemia, cardiovascular and kidney diseases (Wexler et al., 2025).

This therapeutic dilemma suggests that hypoglycemic strategies need to take into account the overall metabolic benefits and emphasize individualized plans. New-generation hypoglycemic drugs such as GLP-1 receptor agonists and SGLT2 inhibitors have neutral or weight-reducing effects while controlling blood sugar, which are more in line with the treatment needs of patients with diabetes complicated with obesity. Therefore, they have gradually been included in relevant guidelines and are recommended as preferred plans.

3 Overview and Clinical Localization of Three Types of GLP-1 RAs

3.1 Insulin therapy based on enterotropin

glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a class of hypoglycemic drugs whose main function is to regulate insulin secretion, and their mode of action is similar to the physiological effect of natural GLP-1 in the body after eating. When blood sugar levels rise, such drugs can promote insulin secretion and inhibit the release of glucagon, thereby helping to control blood sugar levels. Because its effect is glycemic-dependent, the risk of hypoglycemia is relatively low when used alone.

Besides lowering blood sugar, GLP-1 RAs can also slow down stomach emptying and make people feel fuller by acting on the central nervous system, which helps control blood sugar and manage weight (Maple-Brown et al., 2022). The glucose-dependent hypoglycemic characteristics of GLP-1 RAs have obvious advantages in the treatment of type 2 diabetes (T2D), and can effectively reduce hyperglycemic levels without increasing the frequency of hypoglycemia. Its good safety and regulatory ability for multiple metabolic links have gradually made it an important component of the current diabetes drug treatment system (Hamed et al., 2024).

3.2 Preferred regimens for overweight or obese T2D patients

For overweight or obese patients with type 2 diabetes, GLP-1 RAs is clinically important. Such drugs can usually reduce body weight and glycated hemoglobin (HbA1c) simultaneously (Hamed et al., 2024; Yao et al., 2024). Many clinical studies have shown that its weight loss effect is generally better than that of most traditional hypoglycemic drugs. Because GLP-1 RAs can manage both blood glucose and body weight simultaneously, it helps improve overall metabolism and reduce the risk of related complications (Wen et al., 2025).

In current clinical practice guidelines, GLP-1 RAs is gradually recommended for the population with diabetes mellitus complicated with obesity, especially for patients requiring weight intervention or cardiovascular risk management (Wen et al., 2025). Some preparations are administered once a week. The administration frequency is low and the operation is simple, which is conducive to improving treatment compliance and supporting long-term standardized treatment (Maple-Brown et al., 2022).

3.3 Combined treatment strategy

In clinical treatment, in order to improve metabolic status, GLP-1 RAs is often used in combination with other hypoglycemic drugs, among which metformin and SGLT2 inhibitors are the most common (Anderson, 2020; Gourdy et al., 2023). Metformin is a basic drug for treating type 2 diabetes, with stable effects and good safety. When used in combination with GLP-1 RAs, it can lead to better blood sugar control, contribute to weight loss, and the risk of hypoglycemia does not increase significantly (Maple-Brown et al., 2022).

When GLP-1 RAs is used in combination with SGLT2 inhibitors, their modes of action complement each other, and a better superimposed effect can be produced in terms of weight control, blood pressure reduction and cardiovascular protection (Anderson, 2020). The study by Gourdy et al. (2023) pointed out that this combination regimen is helpful for patients with type 2 diabetes who have a higher risk of cardiovascular or kidney disease, or whose metabolic response is not good after monotherapy. Therefore, choosing an appropriate combination medication regimen based on the specific condition of the patient is a key approach to enhancing the therapeutic effect.

4 Weight Loss Mechanism

4.1 Enhance satiety and reduce food intake

The weight loss effect of GLP-1 receptor agonists (GLP-1 RAs) is mainly related to the area of the brain that controls diet. When drugs pass through the bloodstream and stimulate the nerves in the brain, they activate specific receptors in the hypothalamus and brainstem that control the feelings of hunger and fullness. By altering neural signals, patients are more likely to feel full, have a reduced appetite and a decreased total food intake (Figure 1) (Bednarz et al., 2022; O Olukorode et al., 2024; Moiz et al., 2025). More in-depth research has found that such drugs can also affect the brain's reward system, making patients less likely to crave high-calorie foods and reducing the behavior of eating out of craving. This is very helpful for long-term weight control in patients with diabetes and obesity (Zhao et al., 2021; Fadel et al., 2025; Ilias et al., 2025; West et al., 2025).

Different GLP-1 RAs can significantly inhibit appetite (Zhao et al., 2021; Moiz et al., 2025; Fadel et al., 2025). This effect is not only due to the slower gastric emptying, but more importantly, it directly affects the pathways in the brain that control diet. Patients usually feel fuller and less hungry when taking the medicine, which is consistent with the weight loss observed in clinical trials and actual use (Bednarz et al., 2022; O Olukorode et al., 2024; Ilias et al., 2025; West et al., 2025).

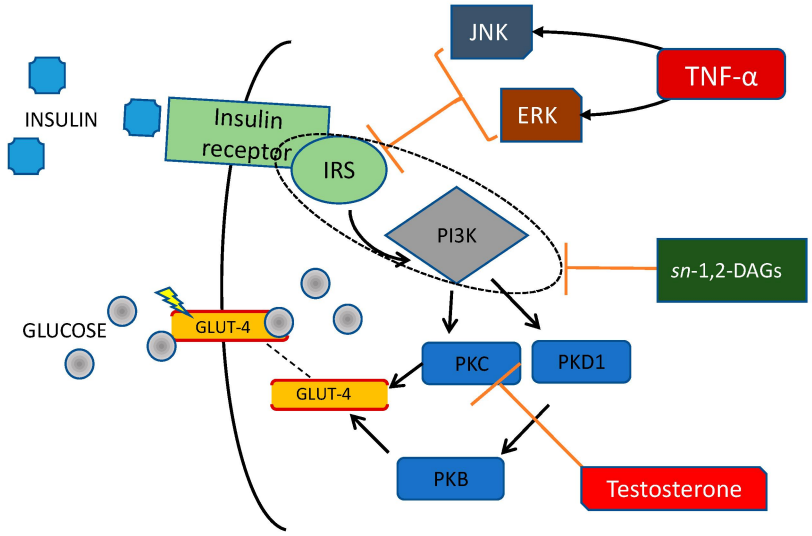

Figure 1 Alterations in the insulin receptor pathway, resulting from the activity of pro-inflammatory cytokines and androgens (Adopted from Bednarz et al., 2022)

Image caption: Tumour necrosis factor α (TNF-α) affects insulin signaling by phosphorylation of serine in insulin receptor substrate-1 (IRS-1) through activation of several serine kinases, including c-Jun-NH2-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK). It inhibits insulin-induced tyrosine phosphorylation of IRS-1 and downregulates phosphoinositide 3-kinase (PI3K) activity; Decreased adiponectin concentration results in increased membrane sn-1,2-diacylglycerols (sn-1,2-DAGs) activity. It leads to impaired kinases activity and decreased insulin signaling; Testosterone induces insulin resistance in cells by affecting insulin-stimulated phosphorylation of protein kinase C (PKC); All these mechanisms contribute to decreased glucose transporter type 4 (GLUT-4) expression and decreased glucose transport into cells (Adopted from Bednarz et al., 2022)

4.2 Slow down gastric emptying and improve post-meal conditions

GLP-1 RAs can also help with weight loss by influencing gastric activity. Mainly, it slows down the speed at which food enters the small intestine from the stomach, prolongs post-meal satiety, slows down glucose absorption, and makes post-meal blood glucose changes more stable (Zhao et al., 2021; Bednarz et al., 2022; Fadel et al., 2025). Generally, short-acting GLP-1 RAs inhibits gastric emptying more significantly and controls postprandial blood glucose better. Long-acting drugs are more often used to regulate fasting blood glucose and maintain overall blood glucose stability (Moiz et al., 2025).

Slower gastric emptying can prolong the feeling of fullness and reduce snack and calorie intake between meals (Hamed et al., 2024; Ilias et al., 2025), but this is only an auxiliary effect. The main weight loss effect still comes from the brain's control of appetite (Zhao et al., 2021; Bednarz et al., 2022; Fadel et al., 2025). In addition, changes in gastric activity may increase the risk of gastrointestinal discomfort. Therefore, it is best to conduct an assessment before performing certain medical procedures or examinations (Urva et al., 2023; Nadeem et al., 2024).

4.3 Regulate glucagon and improve insulin resistance

In addition to influencing eating and gastric activity, GLP-1 RAs is also involved in the body's metabolic regulation, helping to control weight and blood sugar. The research by O Olukorode et al. (2024) and Bednarze et al. (2024) mentioned that when blood sugar is high, it can prompt pancreatic β cells to secrete more insulin and prevent α cells from secreting excessive glucagon, thereby improving fasting and postprandial blood sugar. When glucagon levels decrease, the process of glucose production in the liver is inhibited, which is more pronounced in patients with type 2 diabetes (Hamed et al., 2024; Moiz et al., 2025; Fadel et al., 2025).

Studies also suggest that GLP-1 RAs can enhance insulin sensitivity and reduce various chronic inflammatory indicators, such as C-reactive protein and interleukin-6, which are often elevated in obese and type 2 diabetic populations (Yao et al., 2024; Ren et al., 2025). Related metabolic improvements contribute to reducing visceral fat accumulation, optimizing lipid profiling and enhancing overall cardiometabolic health (Moiz et al., 2025;

Fadel et al., 2025; Ilias et al., 2025). Enables GLP-1 RAs to form synergistic effects at the levels of central regulation, gastrointestinal motility regulation and metabolic regulation, supporting its application advantages in weight management and long-term prognosis improvement in diabetes mellitus complicated with obesity.

5 Clinical Evidence: Impact on Weight Control

5.1 Relationship between weight loss and dosage as well as treatment duration

Many clinical studies have shown that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) can significantly reduce the weight of patients with diabetes complicated with obesity. The more obvious the weight loss effect is usually associated with a larger dosage and a longer treatment duration (Figure 2) (Liu et al., 2023; Hamed et al., 2024). When using drugs for a long time, the weight loss effect of high-dose drugs such as semaglutide and ciceptide is more prominent. After more than one year of treatment, the average body weight decreased by approximately 13.9% and 17.8% respectively compared to the beginning (Xie et al., 2024; Moiz et al., 2025). Other studies have also observed similar situations, especially in patients who were initially overweight or had a longer medication duration, with more significant effects (Wong et al., 2025).

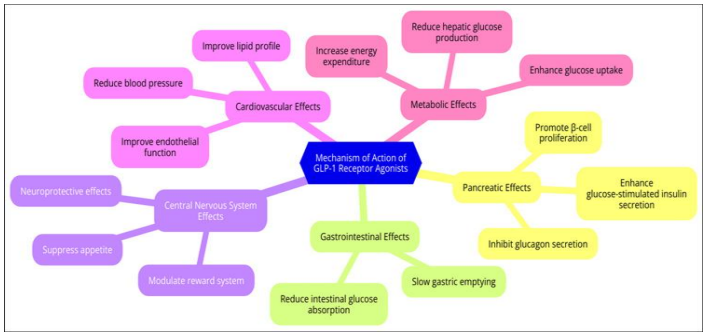

Figure 2 Mechanism of action of GLP-1-RAs (Adopted from Hamed et al., 2024)

The weight loss brought by GLP-1 RAs is not only significant in value, but mostly exceeds the 5% weight loss standard required for metabolic and cardiovascular benefits, and its practical application is clear (Yao et al., 2024). Although many GLP-1 drugs can help with weight loss, on the whole, the effects of drugs such as semaglutide and tipalatide may be better than those of illaglutide and exenatide (Liu et al., 2023; Zhang et al., 2025). Overall, this type of drug has good tolerance, and the main side effect is gastrointestinal discomfort (Iqbal et al., 2022; Wong et al., 2025).

5.2 Advantages over traditional hypoglycemic regimens

Compared with traditional hypoglycemic methods, GLP-1 RAs has obvious advantages in controlling body weight and improving body shape (Yao et al., 2024). Meta-analysis and direct comparative studies have found that such drugs can significantly reduce body weight, waist circumference, and body mass index (BMI) associated with cardiometabolic risk (Xie et al., 2024). Studies have shown that the average waist circumference can be reduced by 4 to 17 centimeters. The higher the initial BMI or the longer the treatment duration, the more obvious the improvement (Liu et al., 2023; Wong et al., 2025).

The above advantages are simultaneously reflected in blood glucose control and lipid profile improvement, differentiating GLP-1 RAs from the hyperglycemic hypoglycemic regimen in terms of overall metabolic benefits (Hamed et al., 2024). When weight management becomes the focus of treatment, this type of drug is often regarded as one of the important treatment options for patients with type 2 diabetes mellitus complicated with obesity. Existing studies support its use as a component of basic treatment to simultaneously improve metabolic indicators and body type-related outcomes (Yao et al., 2024; Wong et al., 2025).

5.3 Issues of weight maintenance and rebound after drug withdrawal

Although GLP-1 drugs can help patients lose weight effectively during the treatment period, maintaining weight in the long term still faces challenges, especially after drug withdrawal. Several studies have shown that the weight of most patients will rebound to varying degrees after drug withdrawal, and the extent of rebound is

directly related to the extent of weight loss during treatment (Jensen et al., 2024). Take semaglutide or cticipatide as examples. Within one year of drug withdrawal, the patient's weight rebounded by approximately 75%, but was still lower than the pre-treatment level. This indicates that obesity is a chronic disease that requires long-term management (Berg et al., 2025; Budini et al., 2025).

In terms of intervention strategies, maintaining weight without rebound requires a combination of medication and lifestyle adjustments, such as increasing physical activity. Jensen (2024) pointed out that this comprehensive approach can slow down the rate of weight rebound after drug withdrawal, and the weight loss effect of GLP-1 RAs is more obvious in the initial stage. Long-term effects rely on continuous personalized management and support to reduce the risk of rebound (Berg et al., 2025; Budini et al., 2025). Therefore, when using GLP-1 RAs to manage body weight, a long-term follow-up plan needs to be formulated and practical and sustainable treatment goals should be set.

6 Practical Treatment Strategies

6.1 Patient selection

In clinical practice, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are more commonly used in overweight or obese patients with type 2 diabetes (T2D), especially those with significant weight concerns or those at high risk of cardiovascular disease with complications. Current guidelines and studies show that patients with a BMI of≥27 kg/m², especially those with concurrent hypertension, dyslipidemia or non-alcoholic fatty liver disease, have a better response to these drugs (Alfaris et al., 2024; Hamed et al., 2024). GLP-1 RAs is also applicable to patients with atherosclerotic cardiovascular disease or those at high risk of cardiovascular disease. Studies have confirmed that such drugs can reduce the risk of cardiovascular problems and contribute to the recovery of kidney function (Ussher and Drucker, 2023; Yao et al., 2024; Sheth et al., 2025).

Patient screening is mainly based on individualized assessment and requires a comprehensive judgment based on previous medication response, hypoglycemia risk, patient preference, as well as weight status and comorbidities information (Alfaris et al., 2024). Patients who experienced weight gain or still failed to reach the target blood glucose level after insulin or sulfonylurea treatment were often given priority in the consideration of GLP-1 RAs, which was associated with a higher risk of weight gain and hypoglycemia with traditional regimens (Hamed et al., 2024; Yao et al., 2024). Patients with obesity-related problems such as obstructive sleep apnea and fatty liver are more suitable for incorporating GLP-1 RAs into the overall management plan (Popoviciu et al., 2023; Sheth et al., 2025). The rationality of population selection directly affects the presentation of therapeutic effect and the control of medication risk.

6.2 Administration method

The treatment of GLP-1 RA usually adopts the dose-titration method, that is, starting with a low dose and gradually increasing the dose to improve patient tolerance and reduce gastrointestinal adverse reactions. Nausea, vomiting and diarrhea often occur in the early stage of treatment or when the dose is increased rapidly (Hamed et al., 2024). In clinical practice, it is generally started from the lowest recommended dose and the dose is gradually adjusted within 1 to 2 weeks to enable patients to gradually adapt to the drug effect, thereby reducing the risk of treatment interruption due to discomfort (Madsbad and Holst, 2025).

Gradually adjusting the dosage can help patients develop the habit of taking medicine on time for a long time. Tell the patient that if any symptoms occur, they should consult a doctor immediately. If the reaction is mild, there are corresponding solutions (Yao et al., 2024). Some patients may need a relatively long time to find the appropriate dosage during treatment, or adjust the dosage regularly to ensure correct medication. Formulating treatment plans based on the patient's condition can make the patient more willing to take medicine and help stabilize blood sugar and control weight (Alfaris et al., 2024).

6.3 Joint processing and plan adjustment

When GLP-1 RAs is used in combination with insulin or sulfonylurea drugs, it is usually necessary to reduce the dosage of other hypoglycemic drugs. This approach is more effective and can also reduce the risk of

hypoglycemia. GLP-1 RAs only functions when blood sugar is high (glucose-dependent), so the risk of hypoglycemia is relatively low when used alone. However, when used in combination with insulin or sulfonylureas (drugs that stimulate insulin secretion), the risk of hypoglycemia may increase. Clinical guidelines recommend that when GLP-1 RAs is initially used, the dosage of sulfonylureas or insulin should be appropriately reduced, especially in patients with blood glucose close to the target value (Hamed et al., 2024).

After combined medication, the doctor or the patient themselves should measure blood sugar multiple times. At the same time, the doctor should teach the patient to identify hypoglycemic symptoms and coping methods. Some patients can gradually adjust the original medication regimen and reduce the total dosage of insulin after using GLP-1 RAs. This contributes to better weight loss and improved metabolic function (Yao et al., 2024). Patients who receive combined therapy should be followed up regularly, and their medication should be adjusted according to their individual conditions to ensure that blood sugar control, weight management and medication safety all meet the standards.

7 Safety and Conclusion

The most common side effect in the treatment with GLP-1 receptor agonists (GLP-1 RA) is gastrointestinal problems, which are specifically manifested as nausea, vomiting, diarrhea or constipation. These reactions usually occur at the beginning of taking medicine or when the dosage is large. If it is more serious, it may prevent the patient from continuing to take the medicine. Gradually increasing the dosage and frequently informing patients of precautions are the main ways to alleviate discomfort and enhance their tolerance. It is necessary to tell the patient that adjusting their diet can relieve these symptoms. If they feel uncomfortable and it doesn't get better, they should speak up immediately. It should also be noted that most gastrointestinal reactions will gradually improve as the duration of taking the medicine increases. By adopting a more proactive management approach, doctors can help patients adhere to their medication and enjoy more stable metabolic benefits.

Although GLP-1 RAs has a relatively low risk of hypoglycemia due to its glucose-dependent mechanism, the risk of hypoglycemia increases when used in combination with insulin or sulfonylurea drugs. At this point, closer blood glucose monitoring is required, and the dosage of other hypoglycemic drugs should be adjusted as the situation requires to reduce the occurrence of hypoglycemia. On the other hand, if gastrointestinal reactions persist for a long time, it may cause dehydration or electrolyte imbalance. Elderly people or those with poor kidney function need to pay more attention. Clinically, attention should be paid to dehydration manifestations such as reduced urine output and orthostatic hypotension, and electrolyte levels should be evaluated when necessary. It is also necessary to guide patients to ensure they drink plenty of water and identify in which situations they need to seek medical attention promptly.

Overall, the value of GLP-1 receptor agonists in the population with type 2 diabetes mellitus complicated with obesity is clear, and they can simultaneously improve blood glucose and body weight. Their potential benefits in cardiovascular and renal aspects also support their use in the long-term comprehensive management of high-risk populations. Although safety issues such as gastrointestinal discomfort need to be managed in a standardized manner, under the premise of reasonable patient screening, sequential dosage increase and good monitoring, the overall benefits of GLP-1 RAs are usually greater than the risks. With the continuous increase in research, GLP-1 RAs is likely to continue to be one of the important drugs for the management of metabolic diseases, helping to improve the outcomes of patients with diabetes and obesity.

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Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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Research Insight Open Access

Central Mechanisms of Inflammatory Cytokines in the Initiation and Progression of Metabolic Syndrome

Liqin Guo, Jiayi Wu
Biotechnology Research Center, Cuixi Academy of Biotechnology, Zhuji, 311800, Zhejiang, China
Corresponding author: jiayi.wu@cuixi.org

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Abstract This study explored the central-related mechanisms of inflammatory cytokines in the occurrence and development of metabolic syndrome, analyzed the way peripheral inflammatory signals enter the center, the inflammatory response in the hypothalamus, and the participation of glial cells. It also investigated the key central pathways through which inflammatory cytokines affect metabolic regulation and the specific process by which central inflammation promotes the progression of metabolic syndrome. Based on the relevant evidence from animal experiments, human studies and intervention studies, the core role of central inflammatory cytokines was clarified, and the therapeutic methods targeting the central inflammatory pathway and future research directions were prospected. This study aims to provide a basis for understanding the pathogenesis of metabolic syndrome and developing new therapeutic measures.

Keywords Metabolic syndrome; Inflammatory cytokines; Central inflammation; Hypothalamus; Insulin resistance

1 Introduction

Metabolic syndrome (MetS) is a disease characterized by multiple metabolic abnormalities, with its core manifestations being excessive abdominal fat, insulin resistance, dyslipidemia, hypertension and poor blood sugar regulation. These manifestations can serve as diagnostic criteria and will significantly increase the risk of type 2 diabetes, cardiovascular diseases and other conditions. In the past decade, sedentary lifestyle, overnutrition and genetic factors have led to a rapid increase in the prevalence of MetS, affecting a large number of adults and adolescents worldwide (Fahed et al., 2022; Islam et al., 2024), becoming a public health issue that requires high attention (Rossi et al., 2021).

The typical feature of MetS is chronic mild inflammation ("meta-inflammation"), which is different from acute inflammation (such as Fahed, etc.). This persistent inflammation is mainly caused by the dysfunction of adipose tissue. Adipose tissue secretes pro-inflammatory factors such as TNF-α and IL-6, attracting immune cells to aggregate and transform into a pro-inflammatory state, thereby aggravating systemic inflammation (Islam et al., 2024). This is key to the occurrence of MetS and related complications (Rossi et al., 2024).

This study will explore the core issue of the peripheral inflammatory mechanism of MetS: how the brain perceives and integrates peripheral inflammatory signals to regulate metabolic balance or trigger diseases. Pro-inflammatory factors can transmit signals to the central nervous system through pathways such as the blood-brain barrier, activating immune cells like microglia. The resulting central inflammation can disrupt the neural circuits in the hypothalamus that regulate appetite and blood sugar, creating a vicious cycle of metabolic disorders. Clarifying the core mechanism by which inflammatory factors regulate metabolism-related neural regulation is of great significance for formulating new treatment strategies and breaking the mutually reinforcing cycle between inflammation and metabolic diseases.

2 Overview of Inflammatory Cytokines

2.1 Key pro-inflammatory factors

Pro-inflammatory factors are important regulatory factors for the occurrence and development of metabolic syndrome, and they form chronic low-grade inflammation by promoting insulin resistance and metabolic

abnormalities. Among them, the roles of TNF-α, IL-6, IL-1β and MCP-1 are particularly crucial. TNF-α mainly originates from adipose tissue macrophages and interferes with insulin signaling by promoting the phosphorylation of serine, a substrate of insulin receptors, thereby inducing insulin resistance.

IL-6 is derived from adipocytes and immune cells. Its content in the blood is directly related to the degree of obesity, visceral fat accumulation, and insulin resistance (Rossi et al., 2021; Tylutka et al., 2023). IL-1β is produced by activating inflammosomes, which can amplify inflammatory responses and interfere with blood glucose stability. As a chemokine, MCP-1 promotes the aggregation of monocytes to adipose tissue, triggering persistent inflammation and tissue changes (Cao et al., 2025).

These factors not only act locally but also cause endothelial dysfunction, arteriosclerosis and metabolic disorders through systemic effects. The levels of TNF-α, IL-6, and IL-1β in patients such as MetS continued to increase, and their contents were positively correlated with the severity of metabolic abnormalities (Rossi et al., 2021; Tylutka et al., 2023). It can also activate pathways such as NF-κB and JNK, enhance the expression of inflammatory genes, and form a persistent inflammatory environment to accelerate disease progression (Cao et al., 2025).

2.2 Key anti-inflammatory factors

Unlike pro-inflammatory factors, anti-inflammatory factors such as IL-10 and TGF-β can maintain immune balance and inhibit metabolic inflammation. IL-10 is derived from regulatory T cells and M2 macrophages, and can inhibit the release of pro-inflammatory factors and promote the resolution of inflammation. TGF-β has anti-inflammatory effects by regulating the function of immune cells and is also involved in tissue repair. In healthy individuals, these two factors remain balanced to maintain normal fat and metabolism (Tylutka et al., 2023).

Obesity and metabolic disorders can disrupt this balance. Fat dilation and pro-inflammatory immune cell infiltration can reduce IL-10 and alter TGF-β signaling (Tylutka et al, 2023), and decreased anti-inflammatory ability can aggravate insulin resistance. It is evident that the dynamic balance of these two factors is the key to determining metabolic status and disease progression.

2.3 Characteristics of cytokine changes

Unlike acute inflammation which experiences a significant increase in a short period of time, METS-related inflammation is characterized by low levels of cytokines, chronic and continuous changes, insipidous inflammation, and a long-term mild increase in cytokines. This is because metabolic stress such as overnutrition and adipocyte enlargement continuously stimulates adipose tissue and immune cells to release inflammatory substances (Rossi et al., 2021; Ren et al., 2022), this mild inflammation can also disrupt insulin signaling and cause cardiovascular problems (Van De Vyver, 2023).

Cytokine levels are not fixed and change with metabolic loads such as body weight, diet, and exercise (Koelman et al., 2019; Rossi et al., 2021). Measures to improve metabolism, such as weight loss and anti-inflammatory treatment, can reduce pro-inflammatory factors and enhance insulin sensitivity. When there is an excess of nutrition, inflammation and cytokine production will increase. This indicates that the environment and individual susceptibility jointly determine the inflammatory characteristics of MetS, and regulating cytokine balance may improve metabolism.

3 Sources of Peripheral Inflammation

3.1 Adipose tissue inflammation

Adipose tissue is the main source of chronic low-grade inflammation in metabolic syndrome. When there is overnutrition and obesity, the volume of fat cells increases, making them prone to metabolic stress, hypoxia and even death, which disrupts the homeostasis of adipose tissue. These changes prompt the massive aggregation and infiltration of immune cells, especially pro-inflammatory M1 macrophages, into adipose tissue. Infiltrating macrophages, T cells, etc. continuously release pro-inflammatory factors such as TNF-α, IL-6, and MCP-1, amplifying local inflammation and promoting systemic inflammation, which is closely related to insulin resistance and metabolic abnormalities (Reddy et al., 2019; Saito et al., 2021).

At the same time, the secretion of adipokines has changed. Pro-inflammatory factors such as leptin and chemokines have increased, while anti-inflammatory factors such as adiponectin have decreased, putting adipose tissue in a pro-inflammatory state. This imbalance can maintain local inflammation and also affect vascular endothelial function through the blood, promoting atherosclerosis. Moreover, the long-term activation of inflammatory pathways such as NF-κB and JNK in adipose tissue will inhibit insulin signaling and glucose uptake, forming a vicious cycle of inflammation and metabolic disorders and accelerating the occurrence of metabolic syndrome (Reddy et al., 2019; Saito et al., 2021).

3.2 Intestinal-related factors

The intestine is an important peripheral source of systemic inflammation caused by MetS. Under normal circumstances, the barrier formed by intestinal wall cells and tight junctions can prevent intestinal microbiota products from entering the bloodstream. However, poor diet, intestinal flora disorder, etc. can damage the barrier function, resulting in increased intestinal permeability (i.e., "leaky gut") (Ghosh et al., 2020; Di Vincenzo et al., 2023). At this time, bacterial components (such as lipopolysaccharide LPS) are prone to enter the bloodstream and cause endotoxemia. LPS binds to receptors such as TLR4 to release pro-inflammatory factors, amplifying systemic inflammation (Tilg et al., 2019; Mohammad and Thiemermann, 2021; Nozu and Okumura, 2022).

Damage to the intestinal barrier can also affect other organs. Inflammatory signals induced by LPS can activate inflammation in adipose tissue, liver and other areas, exacerbating insulin resistance (Nozu and Okumura, 2022). The gut microbiota participates in this process by regulating barrier integrity, and its imbalance will further aggravate inflammation (Tilg et al., 2019; Di Vincenzo et al., 2023), thus the gut-liver-fat axis is the key to connecting environmental factors, immune activation and systemic inflammation (Ghosh et al., 2020; Mohammad and Thiemermann, 2021).

3.3 Liver and skeletal muscle

The liver and skeletal muscle are key organs for energy metabolism and are highly sensitive to chronic inflammation and excessive lipids. In MetS, the excess free fatty acids released by inflammatory adipose tissue deposit in these two organs, causing fatty toxicity and activating inflammatory pathways (Meex et al., 2019; Da Silva Rosa et al., 2020). The liver will show an increase in pro-inflammatory factors and activation of kupffer cells. These inflammations will inhibit insulin signaling, increase hepatic glucose production, and aggravate systemic insulin resistance (Ghosh et al., 2020; Nozu and Okumura, 2022).

Skeletal muscle inflammation can lead to immune cell infiltration, continuous activation of signaling pathways such as PKC, JNK, and NF-κB, and pro-inflammatory factors (such as TNF-α and IL-1β) can interfere with insulin receptor signaling and reduce glucose uptake capacity (Meex et al., 2019; Da Silva Rosa et al., 2020). Furthermore, the interaction among the liver, skeletal muscle and adipose tissue enables the transmission of inflammatory signals between tissues, demonstrating the systemic nature of MetS inflammation-peripheral organs are both the source of inflammation and the target of inflammatory action (Ghosh et al., 2020; Nozu and Okumura, 2022).

4 The Triggering Process of Central Inflammation

4.1 Pathways for inflammatory signals to enter the brain

The brain protects the central nervous system with the blood-brain barrier (BBB), which is a structure that selectively blocks substances and cells from entering the brain tissue. However, under systemic inflammation or metabolic stress, the blood-brain barrier will be damaged and its permeability will increase, making it easier for cytokines and immune cells in the blood to enter the brain tissue, especially the hypothalamus. A high-fat diet or metabolic damage can also reduce the expression of tight junction proteins (such as claudin-5), promoting microglial proliferation and white blood cell infiltration.

Some brain regions, such as the periventricular organs (CVOs), become key channels for peripheral inflammatory signals to enter the brain due to the lack of a complete blood-brain barrier, such as the median bulge and the posterior brain region. These regions can sense peripheral metabolic and immune status and transmit information to the central regulatory network (Bourhy et al., 2022).

In addition to the humoral pathway, neural reflexes are also involved in the transmission of inflammatory signals. The vagus nerve contains various cytokine receptors, which can rapidly transmit systemic inflammatory information to the brainstem (such as the nucleus solitarius), thereby affecting the hypothalamus and limbic system. These pathways together enable peripheral inflammatory mediators to affect central regulation, laying the foundation for hypothalamic inflammation associated with metabolic syndrome (Bourhy et al., 2022).

4.2 Inflammatory response of the hypothalamus

After peripheral inflammatory signals are transmitted to the hypothalamus, they will trigger a series of reactions and interfere with the regulation of energy balance. Metabolically sensitive regions such as the bow-shaped nucleus (ARC) are particularly sensitive to inflammatory stimuli due to direct exposure to circulating cytokines and fatty acids (Lee et al., 2020). After activating inflammatory pathways such as TLR4, NF-κB, and JNK, the expressions of pro-inflammatory factors such as IL-1β, IL-6, and TNF-α in the hypothalamus increase.

These inflammatory factors weaken insulin and leptin signaling by inducing inhibitory molecules such as SOCS3 and PTP1B, reduce the ability of neurons to perceive the body's energy state, and affect appetite regulation, energy expenditure and glucose metabolism (Lee, 2025). Long-term inflammatory stimulation can also lead to neuronal dysfunction, synaptic structural changes, and even a reduction in metabolism-related neurons, exacerbating insulin resistance and energy metabolism imbalance, and perpetuating metabolic abnormalities (Lee et al., 2020).

4.3 The role of glial cells

Microglia and astrocytes play a key role in the occurrence and maintenance of hypothalamic inflammation. Microglia are resident immune cells in the central nervous system. They are activated when encountering metabolic stress or peripheral inflammatory signals, transforming into a pro-inflammatory state and releasing factors such as IL-1β and TNF-α. This is an early event of diet-induced obesity and plays an important role in the early stage of inflammation (Lee, 2025).

Activated microglia produce inflammatory factors, recruit peripheral immune cells and amplify the inflammatory response (Figure 1) (Lee et al., 2020). Astrocytes undergo reactive changes in an inflammatory environment, releasing pro-inflammatory mediators. Abnormal function of astrocytes weakens support for neurons and impairs the hypothalamus' ability to regulate energy balance (Lee, 2025).

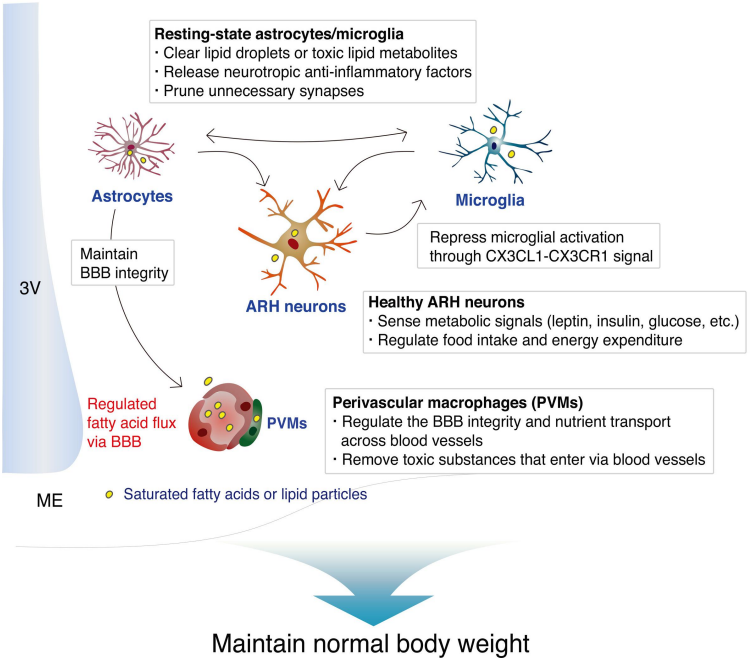

Figure 1 Homeostatic interactions between neurons and glia (microglia, astrocytes, and perivascular macrophages) in the hypothalamic ARH (Adopted from Lee et al., 2020)

Image caption: 3V, third ventricle; ME, median eminence (Adopted from Lee et al., 2020)

It is notable that there is a bidirectional regulatory relationship between microglia and astrocytes. The mutual activation of the two forms a continuous inflammatory cycle, which is an important driver of chronic hypothalamic inflammation and also provides a potential target for MetS intervention (Lawrence et al., 2023).

5 Key pathways and targets of central inflammatory cytokines

5.1 Up-regulating SOCS3 and PTP1B triggers leptin resistance

Leptin is a key hormone secreted by fat cells, which regulates appetite and energy expenditure through the hypothalamus to maintain energy balance. The leptin levels in the blood of obese and MetS patients are always high, but the hypothalamus is not sensitive to leptin, resulting in leptin resistance. This is directly related to the increase of SOCS3 (cytokine signal suppressor 3) and PTP1B (protein tyrosine phosphatase 1B)-SOCS3 weakens leptin signaling by inhibiting the JAK2/STAT3 pathway PTP1B further blocks the signal by dephosphorylating JAK2 (Mezzasoma et al., 2023).

An increase in SOCS3 and PTP1B in the afferent neurons of the hypothalamus and vagus nerve will reduce leptin sensitivity, resulting in increased appetite and weight gain (Zieba et al., 2020). Endoplasmic reticulum stress can exacerbate this condition. For instance, a high-fat diet can induce endoplasmic reticulum stress in the hypothalamus, leading to an upregulation of PTP1B expression.Animal studies have shown that inhibition or knockdown of SOCS3/PTP1B can restore leptin sensitivity and reduce obesity, indicating that these molecules are important targets for intervention of central leptin resistance (Roy et al., 2025).

5.2 The NF-κB/JNK pathway mediates central insulin resistance

Central insulin signaling is crucial for regulating blood sugar, appetite and energy expenditure. Under inflammatory conditions, pro-inflammatory factors activate stress pathways such as NF-κB (nuclear factor κB) and JNK (c-Jun N-terminal kinase), interfering with insulin signaling (Park et al., 2022). These kinases promote serine phosphorylation of insulin receptor substrates (IRS), inhibit downstream signals, and lead to central insulin resistance.

The continuous activation of the NF-κB/JNK pathway is driven by pro-inflammatory factors such as TNF-α and IL-1β, forming a vicious cycle of inflammation and insulin resistance (Khalid et al., 2021; Garg et al., 2023; Mobeen et al., 2025). Central insulin resistance can aggravate blood sugar disorders and increase appetite. Preclinical studies have shown that interventions targeting this pathway (such as antioxidants and kinase inhibitors) can improve insulin sensitivity (Park et al., 2022; Mobeen et al., 2025).

5.3 TLR4/NLRP3 activation promotes the maturation and release of IL-1β

The continuous amplification of central inflammatory responses is closely related to the activation of innate immune receptors TLR4 and NLRP3 inflammasomes. TLR4 can be activated by danger signals such as saturated fatty acids, initiating the NF-κB/ JNK-mediated inflammatory cascade, promoting the transcription of pro-inflammatory factors and inducing the assembly of NLRP3 inflammasome (Khalid et al., 2021). After NLRP3 activation, caspase-1 mediates the cleavage of the precursor IL-1β into active IL-1β.

The release of IL-1β is the key to the spread of central inflammation, which further weakens insulin and leptin signaling, aggravates neuronal dysfunction, and maintains the inflammatory environment (Xu and Nunez, 2022). The activation of NLRP3 is regulated by metabolic status, post-translational modifications and molecular chaperone proteins (such as p58IPK), among which p58IPK can inhibit inflammasome activity and limit the production of IL-1β. TLR4 and NLRP3 play a core role in inflammatory amplification and are potential therapeutic targets for intervening in neuroinflammation and metabolic disorders related to metabolic syndrome (Figure 2) (Mezzasoma et al., 2023; Unterberger et al., 2023).

6 The Development Process of Metabolic Syndrome

6.1 Increased food intake, reduced heat production and energy imbalance

The development of metabolic syndrome is often characterized by long-term energy excess, that is, energy intake consistently exceeds expenditure. Inflammatory factors in the brain can interfere with the hypothalamus'

regulation of appetite and satiety, leading to increased food intake and abnormal eating behavior. For instance, abnormal central estrogen signaling (such as decreased activity of amygdala aromatase) can enhance the motivation to eat and the amount of food consumed, making it more likely for women to gain weight (Maric et al., 2025). Furthermore, irregular eating (such as eating at night) intensifies hunger signals, alter the levels of appetite-related hormones, and makes adipose tissue more inclined to store fat rather than break it down, thereby accelerating fat accumulation (Vujovic et al., 2022).

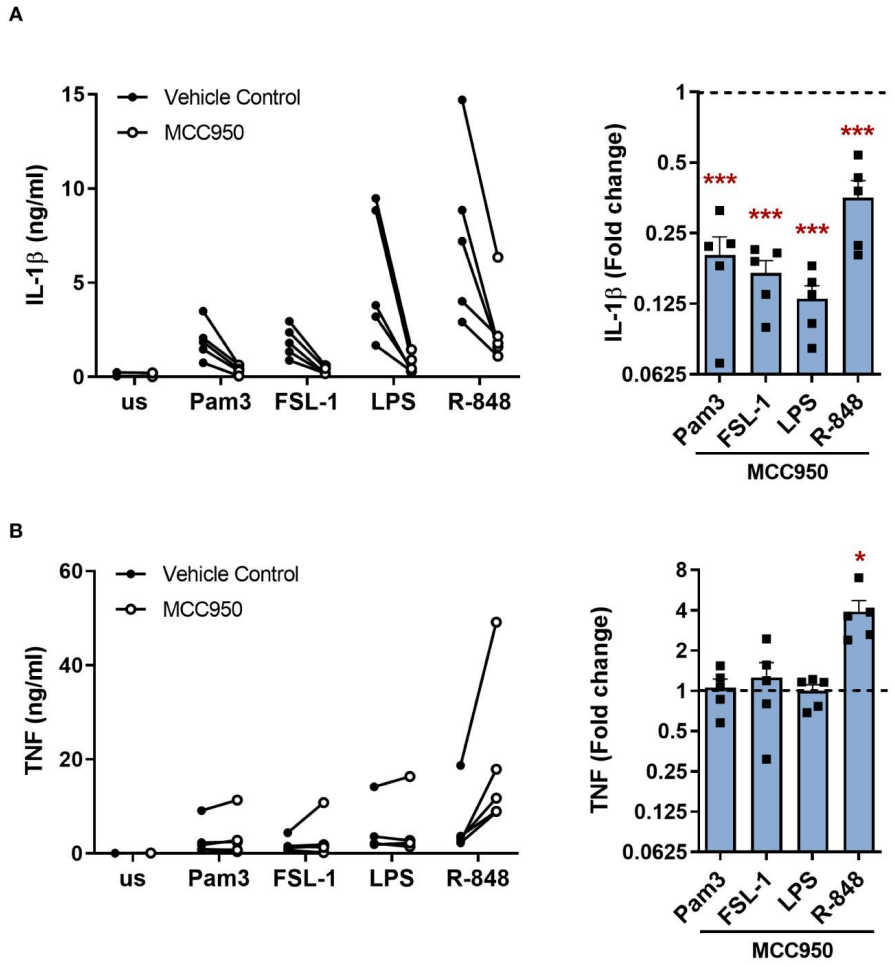

Figure 2 NLRP3 is required for TLR induced release of IL-1β in primary human monocytes (Adopted from Unterberger et al., 2023)
Image caption: Monocytes were unstimulated (us) or stimulated for 24h with 100 ng/mL Pam3, 1ng/mL FSL-1, 10 ng/mL LPS or 2 μg/mL R-848 in the presence of 10μM MCC950 or a vehicle control; Secretion of (A) IL-1β and (B) TNF were measured. Data are displayed as mean of technical triplicates (left) and as the fold change normalised to the corresponding TLR activation without MCC950 (dotted line) and pooled as the mean±SEM (right) from 5 individual donors; Significance was determined using two-tailed one sample t-test against the response without MCC950 treatment (*$p \leq 0.05$, ***$p \leq 0.001$) (Adopted from Unterberger et al., 2023)

In addition to increased intake, decreased energy expenditure and heat production capacity can also contribute to the progression of obesity. Weakened IL-6 signaling in the brain and impaired brown fat function are closely related to reduced energy expenditure and weight gain. Meanwhile, impaired central thermoregulatory pathways (such as decreased function of the cold-sensing TRPM8 channel or decreased IL-6 level in the lateral arm nucleus) will further inhibit thermogenesis of brown fat, resulting in a continuous tilt of energy balance towards weight gain (Mishra et al., 2019).

6.2 Increased liver glycogen output and abnormal lipid metabolism

Metabolic syndrome is often accompanied by disorders of glucose and lipid metabolism, with the core mechanisms being insulin resistance and chronic inflammation. Insulin resistance weakens the effect of insulin in inhibiting liver glucose production, resulting in increased liver glucose output and elevated fasting blood glucose

(Liu et al., 2025); Meanwhile, the release of free fatty acids from adipose tissue increased, the synthesis of new fat in the liver became stronger, and a large amount of lipids deposited in the liver (Chao et al., 2019).

Excessive lipids in the liver can activate kupffer cells, causing them to secrete pro-inflammatory factors, further inhibiting insulin signaling in liver cells and promoting the development of simple fatty liver into non-alcoholic steatohepatitis (NASH) and fibrosis (Bhat and Mani, 2023). Disorders of glycolipid metabolism promote each other and are key to the occurrence of non-alcoholic fatty liver disease (NAFLD) (Chao et al., 2019), and aggravated insulin resistance increases the risk of dyslipidemia and cardiovascular diseases (Liu et al., 2025).

6.3 Sympathetic nerve activation and vascular function impairment

Hypertension is an important manifestation of metabolic syndrome and is related to central and peripheral inflammation. Chronic mild inflammation of the brainstem and hypothalamus can enhance sympathetic nerve activity, leading to vascular tension and persistent elevated blood pressure. Both animal and human studies have confirmed this (Kalos et al., 2025; Venugopal et al., 2025).

Excessive activation of the sympathetic nerve can impair endothelial function, reduce vasodilation ability and promote the formation of hypertension (Ding et al., 2025). In metabolic syndrome, obesity, insulin resistance and chronic inflammation amplify this mechanism, creating a vicious cycle of elevated blood pressure and significantly increasing the risk of cardiovascular events.

7 Evidence and Impact

7.1 Evidence from animal experiments

Animal experiments provide important evidence for studying the role of inflammatory factors in metabolic syndrome. For instance, in experiments on high-fat diets in mice, long-term consumption of high-fat foods can lead to hypothalamic inflammation, manifested as elevated pro-inflammatory factors such as TNF-α and IL-1β. This activates microglia and astrocytes in the hypothalamus, thereby interfering with leptin and insulin signals, resulting in increased appetite, weight gain, and systemic insulin resistance. The hypothalamus is particularly sensitive to inflammatory stimuli due to its high permeability of the blood-brain barrier and its ability to sense peripheral metabolic signals (Robison et al., 2020).

Interventions targeting inflammatory pathways have shown significant effects in animal experiments. Inhibiting key inflammatory signals through genetic or drug means (such as blocking the JAK2/STAT3 pathway or neutralizing IL-1β) can significantly alleviate hypothalamic inflammation and improve metabolic balance (Robison et al., 2020; Wang et al., 2021). These intervention measures, accompanied by improvements in glucose tolerance, insulin sensitivity and weight regulation ability, confirmed the causal role of central inflammation in the occurrence of metabolic syndrome.

7.2 Evidence from human studies

Human studies have shown that elevated levels of inflammatory factors are closely related to the presence and severity of metabolic syndrome. The pro-inflammatory indicators such as IL-6, TNF-α and CRP in the blood of patients were significantly higher than those of healthy people (Ferreira et al., 2022), and were directly involved in insulin resistance and vascular injury (Ion et al., 2023). Meanwhile, the level of the anti-inflammatory factor IL-10 in the body was relatively low, aggravating the immune imbalance. The study also found that cytokine levels were significantly associated with metabolic syndrome characteristics such as abdominal obesity and insulin resistance (Ferreira et al., 2022). For instance, elevated MCP-1 and TNF-α levels are associated with visceral fat accumulation and insulin resistance, and people with low IL-10 levels have a higher metabolic risk (Sumerkina et al., 2022). This indicates that cytokine profiles can serve as potential biomarkers for assessing the risk of metabolic syndrome and monitoring disease progression.

7.3 Evidence of intervention measures

Intervention studies have shown that lifestyle adjustments and drug treatments can effectively reduce inflammation levels and improve metabolic indicators. Weight loss (calorie restriction or surgery) can significantly reduce pro-inflammatory factors such as IL-6 and TNF-α, and improve insulin sensitivity (Ion et al.,

2023; Bosch-Sierra et al., 2024); Exercise intervention (such as aerobic and strength training) can reduce TNF-α and CRP, increase IL-10 expression, and has anti-inflammatory effects even without significant changes in body weight (Yousefabadi et al., 2020; Rahimi et al., 2021).

Dietary intervention is also very important. Adopting a Mediterranean diet or a plant-based diet can reduce inflammation and improve metabolism (Onu et al., 2025; Suarez et al., 2025). In addition, drugs such as GLP-1 receptor agonists can reduce abdominal fat and inflammation and lower the severity of the disease (Sandsdal et al., 2023). In conclusion, lifestyle intervention combined with drug treatment is an effective strategy for improving the prognosis of metabolic syndrome.

8 Interventions and Outlook

In recent years, the treatment of metabolic syndrome has increasingly focused on inflammatory pathways in the brain, especially the IL-1-related pathway, the NF-κB/JNK signaling axis and the NLRP3 inflammasome. The NLRP3 inflammasome plays a key regulatory role in the production of pro-inflammatory factors. Inhibiting it can alleviate metabolic problems such as obesity and insulin resistance. The NF-κB and JNK pathways are at the core of chronic inflammation and metabolic disorders, and their continuous activation is closely related to insulin resistance and adipose tissue inflammation. In addition, the regulation of glial cell activity has also drawn attention. The neuroinflammation it triggers can damage hypothalamic function and lead to systemic metabolic disorders. These targets provide potential directions for the development of anti-inflammatory drugs.

In addition to drug treatment, comprehensive lifestyle management is still the fundamental way to reduce the burden of inflammation. Regular exercise (especially moderate-intensity) can reduce pro-inflammatory factors such as IL-1β and TNF-α and increase anti-inflammatory substances such as IL-10, which is effective even with little change in weight. The Mediterranean diet and plant-based diets can reduce systemic inflammation, improve metabolism, and the effect is even better when combined with exercise. In addition, regulating sleep and circadian rhythms is also crucial. Regular diet helps regulate inflammatory pathways and improve metabolism.

Future research should further clarify the causal relationship between central inflammatory factors and the progression of metabolic syndrome, and determine the best intervention timing. Given the individual differences in metabolic syndrome, there is an urgent need to develop reliable biomarkers for the early identification of high-risk populations, stratification of patients and evaluation of therapeutic effects. Multi-omics technology provides a new tool for analyzing individual inflammatory and metabolic characteristics. Mechanism research combined with biomarker strategies is a key direction for promoting anti-inflammatory intervention towards precise individualized treatment.

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Conflict of Interest Disclosure

The authors affirm that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case Study Open Access

Association Between Treatment Failure Cases and Individual Genetic Background in Patients With Drug-Resistant Tuberculosis

Yan Lou
Physicov Med. Tech. Ltd., Zhejiang, Zhuji, 311800, Zhejiang, China
Corresponding email: yan.lou@pmtcl.org

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Abstract This study explored the association between treatment failure and individual genetic background in patients with drug-resistant tuberculosis, aiming to reveal the role of host genetic factors in the treatment outcomes of drug-resistant tuberculosis (DR-TB). The study included tuberculosis patients with multidrug-resistant (MDR) and extensively drug-resistant (XDR) confirmed by drug sensitivity tests. By combining whole-genome sequencing (WGS), targeted gene analysis and clinical follow-up data, the relationship between host gene polymorphisms and drug metabolism, immune response and treatment outcomes was systematically evaluated. The results showed that the polymorphisms of drug metabolism genes (*NAT2*, *CYP2E1*, *CYP3A4*), drug transport genes (*ABCG2*, *SLCO1B1*), and immune regulatory genes (*PDCD1*, *VDR*, *PI3K/AKT*) significantly affected drug exposure levels, efficacy, and adverse reactions. Patients with slowly acetylated NAT2 are more prone to hepatotoxicity, while those with rapidly acetylated NAT2 have an increased risk of recurrence due to insufficient drug exposure. ABCG2 and VDR variations are associated with delayed sputum conversion to negative and adverse reactions. In addition, immune gene polymorphisms may affect the host's immune clearance ability, leading to persistent positivities or relapses in some patients even under the standard protocol. Based on this, this study proposes genotype-guided individualized treatment strategies, including drug selection and dosage optimization, dynamic monitoring of high-risk genotypes, and a comprehensive "gene-clinical-pharmacokinetic" evaluation model. Although pharmacogenomics is still limited by cost and validation in the clinical application of drug-resistant tuberculosis, it has great potential in precision treatment. In the future, through multi-omics integration and intelligent analysis, pharmacogenomics is expected to increase the cure rate, reduce toxicity and curb the spread of drug resistance.

Keywords Drug-resistant tuberculosis; Pharmacogenomics; Host genetic polymorphism; Treatment failure; Individualized treatment

1 Introduction

Drug-resistant tuberculosis (DR-TB) remains a major problem in the field of global health to this day. It not only makes the problem of antibiotics being ineffective more serious, but also slows down the pace of tuberculosis prevention, control and eradication. The latest data shows that in 2022, 410 000 cases of multidrug-resistant tuberculosis (MDR/DR-TB) or rifampicin-resistant tuberculosis were reported worldwide. At present, the pressure brought by multidrug-resistant and extensively drug-resistant tuberculosis (XDR-TB) is still increasing, and this problem is particularly prominent in regions with average economic conditions and among adolescents and young people (Gao et al., 2024). Insufficient medical resources, untimely diagnosis and the gap in economic conditions have made the burden brought by diseases even heavier. Some models predict that if there is no effective intervention, the number of cases and deaths of drug-resistant tuberculosis may still increase in the coming decades (Lü et al., 2024; Guo et al., 2025; Cui et al., 2025). In addition, drug-resistant strains can not only be directly transmitted among humans but also gradually change within patients' bodies. This implies that we urgently need more comprehensive public health strategies, such as rapid diagnosis, contact tracing, and targeted preventive measures (Liebenberg et al., 2022; Farhat et al., 2024).

With the emergence of new drugs and the application of short-term all-oral regimens (such as bedaquinolin-centered regimens), the treatment options for multidrug-resistant tuberculosis are increasing day by day. Compared with traditional long-term regimences, these new regimences usually bring a higher probability of cure and can reduce patient mortality (Fekadu et al., 2025; Michalik et al., 2025). The treatment outcome for

multidrug-resistant tuberculosis remains unsatisfactory. Globally, the cure rate of multidrug-resistant/rifampicin-resistant tuberculosis is only 60%~65%, significantly lower than that of common sensitive tuberculosis (Bartholomay et al., 2021). During the treatment process, treatment failure, loss to follow-up, and adverse reactions after medication are still relatively common. These problems are often associated with factors such as co-infection with HIV, malnutrition, previous tuberculosis history, and difficulty in controlling drug side effects (Dlatu et al., 2025). Treatment failure not only increases the risk of recurrence, severe illness and even death for patients, but also may promote the further spread of drug-resistant strains and generate new drug resistance, thereby weakening the overall effectiveness of tuberculosis prevention and control efforts (Liebenberg et al., 2022; Farhat et al., 2024). Therefore, it is of great significance to promote individualized treatment and seek reliable indicators to predict the treatment effect.

This study will explore the strain characteristics of Mycobacterium tuberculosis and the possible impact of human genetic factors on therapeutic effects. Some specific genetic changes in Mycobacterium tuberculosis may cause the bacteria to develop varying degrees of drug resistance, thereby increasing the risk of treatment failure and death. These bacterial characteristics may also interact with human genes and immune-related substances, thereby influencing disease progression and treatment outcomes. As for the specific role of human genetic background in the therapeutic effect of drug-resistant tuberculosis, further exploration is still ongoing. Due to the differences in the study population, treatment plans and diagnostic conditions, the conclusions of each study are not completely consistent. This study aims to integrate relevant research ideas, promote the application of precision medicine, form more targeted treatment strategies, increase the cure rate, and alleviate the burden brought by drug-resistant tuberculosis worldwide.

2 Clinical Characteristics and Causes of Treatment Failure of Drug-resistant Tuberculosis

2.1 Definition, criteria and main clinical manifestations of treatment failure

The World Health Organization (WHO) defines treatment failure for drug-resistant tuberculosis (DR-TB) as: after completing standard treatment, no pathogen is detected, the condition turns negative, and there is no significant improvement. This can usually be confirmed by sputum cultures and sputum smears that remain positive during or after treatment (Gunther et al., 2021). Common criteria for judging treatment failure include: sputum culture remaining positive after 5 months of treatment, or being negative first and then positive; Imaging studies show that the lesion and clinical condition have not improved significantly. And new drug resistance emerged during the treatment process (Gunther et al., 2021; Kherabi et al., 2025). Common symptoms are often manifested as coughing, hemoptysis, persistent fever and weight loss, etc., indicating poor disease control. Meanwhile, the imaging also shows the progression of lung lesions, such as new cavities and pleural effusion signs (Miiro et al., 2023; Li et al., 2025).

In the treatment of drug-resistant tuberculosis, there are many reasons for the failure of treatment. Some conditions are very similar to the side effects of the drugs, making it difficult to distinguish them when seeing a doctor. For patients with multidrug-resistant tuberculosis or those who have had related diseases before, the risk of treatment failure is significantly higher, with the failure rate reaching 44%, and the subsequent recovery effect is often poor (Kherabi et al., 2025). If the patient also has other diseases such as AIDS and diabetes, the possibility of treatment failure will be even greater. Doctors usually make a judgment on the condition based on the examination results and changes in symptoms, and also take into account the patient's own risk situation. Only by doing so can they have a more comprehensive understanding of the illness.

2.2 Non-genetic factors

In addition to genetic factors, many non-genetic factors can also have a significant impact on the treatment outcome of tuberculosis. Failure of patients to take medicine as prescribed is a common cause of treatment failure. Long treatment cycle, a wide variety of drugs to be taken, prominent drug side effects, coupled with high economic pressure, all these make it very difficult for patients to adhere to the regular medication (Bartholomay et al., 2021). In areas with backward medical conditions, it is not uncommon and even very common for patients who have received long-term treatment to lose contact during subsequent follow-ups. Meanwhile, if the

medication is not adjusted based on the results of the drug sensitivity test, or if the medication combination is unreasonable and other non-standard treatment plans are adopted, it will directly reduce the treatment effect and may also make the drug resistance problem more serious (Kherabi et al., 2025).

HIV infection, diabetes, malnutrition and other conditions all increase the risk of treatment failure and death. Among them, patients who are simultaneously infected with HIV often have a relatively low chance of successful treatment due to poor immune system function and possible mutual influence among different drugs. In addition, factors such as excessive alcohol consumption, smoking, advanced age, and previous tuberculosis may also prevent patients from taking medicine on time or affect their overall health, thereby leading to poorer treatment outcomes (Feng et al., 2025; Li et al., 2025). Poverty and insufficient medical resources will make these risks more obvious. Therefore, it is necessary to combine medical assistance with social support to provide patients with more comprehensive help (Bartholomay et al., 2021).

2.3 Significant individual differences in clinical practice and their significance

Even if there are unified treatment standards, the symptoms and treatment outcomes of patients with multidrug-resistant tuberculosis may still vary greatly. These differences are usually associated with many factors (Kherabi et al., 2025). During the medical treatment process, even if patients have similar drug resistance and take the same medications, the final treatment outcomes may still vary. This indicates that some factors that cannot be directly observed (such as genetic conditions, the body's immune response, etc.) may be crucial (Li et al., 2025).

This situation where everyone is different indicates that it is not feasible to treat all patients with exactly the same treatment plan. When formulating the treatment plan, the patient's own risk factors such as genetic characteristics should be considered to make the treatment more tailored to the individual situation (Kherabi et al., 2025; Li et al., 2025). To alleviate the troubles caused by the failure of treatment for multidrug-resistant tuberculosis, molecular diagnosis, personalized treatment and social assistance should be combined to better solve the problems of different patients.

3 Key Genes and Pathways Influencing Treatment Outcomes

3.1 Drug metabolism genes and their polymorphisms

Drug metabolism plays a core role in determining the pharmacokinetics and therapeutic effects of anti-tuberculosis drugs, and genetic variations encoding metabolic enzymes are an important source of individual differences in treatment outcomes, especially more prominent in patients with drug-resistant tuberculosis. Among them, the polymorphisms of the N-acetyltransferase 2 (NAT2) and cytochrome P450 (CYP) gene families have been studied most deeply. The NAT2 acetylation phenotype directly affects the metabolism of isoniazid (INH) : those with slow acetylation are more likely to have higher plasma INH levels and an increased risk of hepatotoxicity, while those with rapid acetylation may have insufficient drug exposure, thereby reducing efficacy and promoting drug resistance. Meanwhile, polymorphisms of genes such as *CYP2E1*, *CYP2C19* and *CYP3A4* can alter the metabolic clearance rates of various anti-tuberculosis drugs, thereby affecting the balance between efficacy and toxicity. Studies of populations in Indonesia and China suggest that *CYP2E1* and NAT2 polymorphisms are closely related to drug-induced liver injury during treatment, indicating that these genetic differences will shape the treatment outcomes of drug-resistant tuberculosis to a certain extent.

The impact of the differences in the *CYP450* gene is not only reflected in the "rate of drug metabolism", but also affects the overall therapeutic effect by altering the interactions between drugs. Enzymes like *CYP3A4* and *CYP2D6* are involved in the metabolism of both the body's own substances and various substances that enter the body from the outside. So, when they encounter other drugs being taken simultaneously or when their own genes undergo mutations, leading to inhibition or enhancement of activity, it may cause significant changes in the concentration of the drugs in the body and their toxic and side effects. Studies have mentioned that even components in daily diet (such as polyphenols in herbal tea) may inhibit the metabolic processes involved in *CYP3A4*, thereby indirectly affecting the metabolism of anti-tuberculosis drugs in the body. Therefore, the differences in these metabolism-related genes are not only related to whether patients are prone to adverse drug reactions, but also closely associated with poor treatment outcomes and the emergence of drug resistance.

Incorporating these related genetic differences into pharmacogenomic screening is expected to help formulate more precise medication management and monitoring plans, reduce the drug toxicity burden on patients with drug-resistant tuberculosis, and lower the risk of treatment failure.

3.2 Genes related to drug transport and excretion

Efflux transporters are one of the key factors influencing the absorption and utilization of anti-tuberculosis drugs in the body, their distribution in tissues, and the risk of treatment failure. Members of the ATP-binding cassette (ABC) transporter family (such as ABCB1 [also known as P-glycoprotein] and ABCG2) can regulate the concentrations of various anti-tuberculosis drugs within cells. When the activity of these transport proteins is too high or there are functional genetic differences, the effective drug concentration at the lesion site may decrease, thereby affecting the treatment outcome and increasing the probability of treatment failure. Research has found that among Chinese people, differences in the *ABCG2* gene (especially at the rs2622605 locus) are associated with an increased risk of liver damage caused by anti-tuberculosis drugs, indicating that differences in transporter genes not only affect the metabolic process of drugs in the body It will also make people more prone to drug toxicity reactions. Therefore, the genetic differences of transporters not only relate to the therapeutic effect but also affect the safety of medication, having a dual significance of "efficacy and safety", and deserve special attention when conducting risk assessment.

In addition, the drug efflux mechanism also intersects with cellular signaling and immune regulation processes: the activation of pathogen efflux pumps can directly contribute to bacterial resistance, while variations in host efflux related genes may further weaken drug efficacy. Changes in the activity of ABC transporters can affect the disposal process of key drugs such as rifampicin and bedaquinoline, and may alter the intracellular drug accumulation levels of drug-resistant strains, thereby influencing the treatment response (Figure 1) (He et al., 2022). Given that extraining-related genetic factors can simultaneously act on the host pharmacodynamic environment and bacterial resistance phenotypes, a systematic understanding of their effects is helpful for optimizing protocol design and reducing the risk of further expansion of drug resistance.

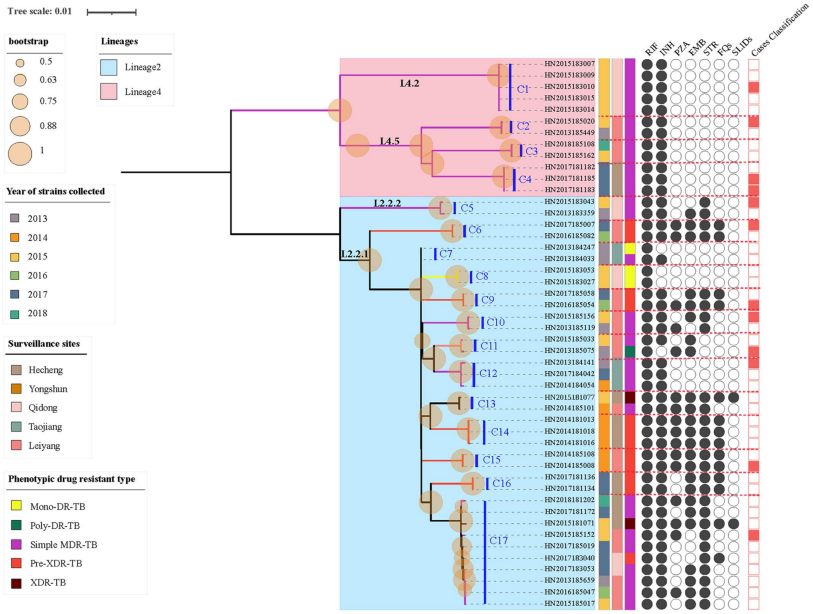

Figure 1 Maximum-likelihood tree of 44 rifampicin-resistant tuberculosis strains within 17 clusters and their phenotypic drug-resistant profiles (Adopted from He et al., 2022)

Image caption: The red dotted lines indicate boundaries of individual clusters; Cluster 1–17 was labeled as C1-C17; RIF, rifampicin; INH, isoniazid; PZA, pyrazinamide; EMB, ethambutol; STR, streptomycin; FQs, fluoroquinolones, including moxifloxacin and ofloxacin in this study; SLIDs, second-line anti-TB drugs, including kanamycin and amikacin in this study; Circles filled with black indicate drug-resistant strains, while empty circles indicate drug-susceptible strains; Rectangle filled with red indicate strains collected from cases with previously treatment history, while empty rectangles indicate strains collected from new cases; Scale bar indicates the genetic distance proportional to the total number of single nucleotide polymorphisms (Adopted from He et al., 2022)

3.3 Immune response-related genes and their impact on pathogen clearance

Host immune response is an important determinant of the treatment outcome of tuberculosis, and polymorphisms of immune-related genes can change the pathogen clearance ability and the probability of treatment success or failure by influencing the anti-tuberculosis immune effect and the intensity of inflammatory response. At present, the genes that have been studied more mainly focus on cytokine signaling and immune regulatory networks, such as *IL6*, *STAT3*, *PDCD1 (PD-1)*, *CTLA4*, *HAVCR2 (TIM-3)*, *mTOR* and *VDR (vitamin D receptor)*. During the treatment process, variations related to the IL-6/STAT3 pathway were associated with changes in cytokine responses and susceptibility to drug-induced hepatotoxicity. Meanwhile, the polymorphisms of mTOR and PI3K/AKT pathway genes involved in macrophage activation and bacterial clearance are also associated with increased susceptibility to tuberculosis and differences in treatment response (Wu et al., 2023)

The differences in immune-related genes can affect the efficacy of immunotherapy for tuberculosis. Genes like *PD-1, CTLA-4* and *TIM-3* are different and may affect the working state of T cells and the strength of immune responses, thereby influencing a person's ability to resist tuberculosis and control the condition. Studies have found that changes in the rs7568402 locus of the PDCD1 gene and the rs13170556 locus of the *HAVCR2* gene are both associated with the risk of tuberculosis, and this relationship may be different between men and women (Wang et al., 2021; Liu et al., 2024). Meanwhile, variations at the FokI locus of the *VDR* gene have also been proven to increase the risk of tuberculosis, indicating that the immune regulation involved in vitamin D is very important for controlling infection (Yadav et al., 2021). These genetic differences related to immunity may further alter patients' responses to treatment by influencing the body's ability to clear bacteria.

4 Case Study Design and Data Sources

4.1 Inclusion and exclusion criteria

This study adopted a case-control design to evaluate the association between genetic background and treatment failure in patients with drug-resistant tuberculosis (DR-TB). The included subjects were adults aged 18 years and above with tuberculosis who were confirmed to be multidrug-resistant (MDR) or extensively drug-resistant (XDR) by molecular or phenotypic drug sensitivity tests: MDR was defined as resistance to at least rifampicin and isoniazid, and XDR was defined as additional resistance to any fluoroquinolone drug and at least one second-line injection drug (such as amicacin or capreomycin) on this basis. Those WHO meet the conditions need to complete the standardized second-line treatment protocol as recommended by the WHO and be managed under direct observation treatment. The treatment plan usually includes the combination of bedaquiline, linezolid, levofloxacin and cycloserine, etc. To reduce confounding effects, patients with incomplete treatment records, co-infection with HIV, severe liver dysfunction or other chronic infectious diseases were excluded.

After the treatment commences, the patient will be followed up for 24 months, mainly to observe the negative sputum culture, disease recurrence and death. If the sputum culture remains positive after 6 months of treatment, or if it recurs within 1 year after the end of treatment, or if the patient dies of tuberculosis, it is regarded as treatment failure. The basic information, clinical data and microbiological test results of the patients mainly come from the national tuberculosis surveillance system and hospital databases. The inclusion criteria of this study were consistent with those of the relevant cohort studies in China and South Korea. Both used similar criteria to evaluate the relationship between genetic factors and treatment effects (Che et al., 2021).

4.2 Collect clinical data, follow-up records and laboratory test results

Clinical and laboratory information is collected through the standardized electronic medical record system of the designated tuberculosis hospital. Baseline variables include age, gender, smoking history, nutritional status, comorbidities, previous tuberculosis treatment history and drug resistance spectrum, etc. At the same time, record the treatment plan, compliance rate, adverse events and culture results, and extract them at the predetermined frequency (once a month during the intensive period and once every quarter thereafter). Sputum specimens were collected at both the baseline and follow-up stages for smear, culture and GeneXpert MTB/RIF detection. First-line and second-line drug sensitivity tests (DST) were performed using the proportional method on Lowenstein-Jensen medium. Meanwhile, combined with molecular line probe method (LPAs) for rapid detection of drug resistance-related mutations.

Some studies use whole-genome sequencing to identify genetic changes related to drug resistance and thereby determine the types of bacterial branches. When conducting the analysis, researchers not only focus on drug resistance genes, but also take into account the variations of compensation genes such as rpoA, rpoC, and gyrA. This can more comprehensively explain the connection between different bacterial characteristics and therapeutic effects (Figure 2) (Song et al., 2023). During the follow-up process, doctors will record the time when sputum bacteria turn negative (bacteria disappear), whether there is a recurrence, and changes in clinical scores. The death and recurrence of patients will be verified through the National tuberculosis Registry system. All data collection adheres to ethical requirements and has been approved by the institutional review board.

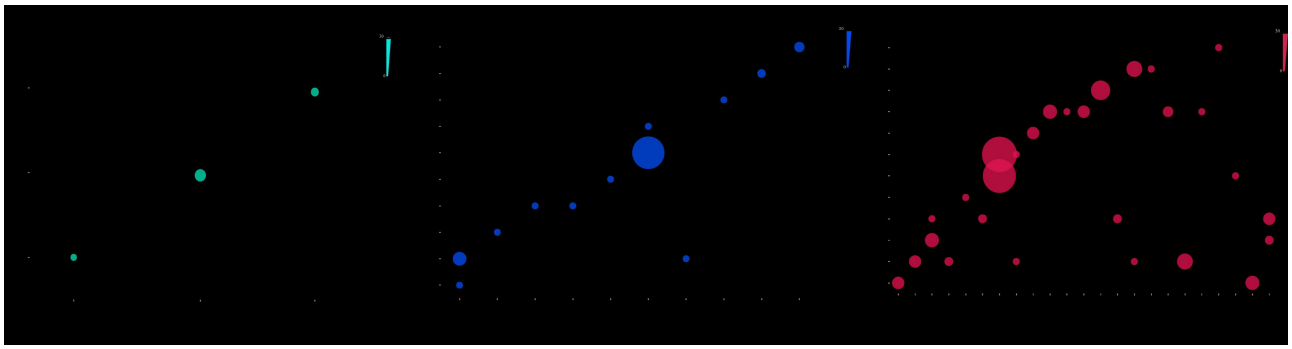

Figure 2 Putative compensatory mutations in the rpoA, rpoB, and rpoC genes were identified in this study (Adopted from Song et al., 2023)

Image caption: Each putative compensatory mutation was supported by at least two independent evolution events on the phylogenetic tree (Adopted from Song et al., 2023)

4.3 Overall framework of genetic testing and statistical analysis methods

Some studies have combined whole-genome sequencing with targeted sequencing and also used bioinformatics technology to identify genetic changes that may be related to therapeutic effects. Whole genome sequencing was performed on the Illumina HiS1eq platform, with an average sequencing depth of over 100×. Researchers compared the data obtained from sequencing with the reference genome of *H37Rv.* GATK is used to identify single nucleotide polymorphisms, that is, situations where a single base on a gene is altered. Researchers used the PhyloTB and TB-Profiler tools to jointly analyze the branch types and genetic characteristics of the strains. This research process is consistent with the commonly used genomic monitoring methods at home and abroad (He et al., 2022; Liang et al., 2023). Next, an in-depth analysis of the known drug-resistant genes will be conducted, with a focus on common genetic variations and potential new variations.

Statistical analysis was conducted using SPSS and R: descriptive statistics were used to summarize clinical features, and chi-square test and t-test were used to compare the classification and continuous variable differences between the successful treatment group and the failed treatment group. Logistic regression was used to evaluate the association between host genetic polymorphism and treatment outcomes, and confounding factors such as age, gender, comorbidities and drug resistance patterns were adjusted. The sputum transformation time and mortality risk were estimated by Kaplan-Meier and Cox proportional hazards models, and the methods were consistent with the designs of recent genomic and cohort studies. Genome-wide association analysis was conducted using tools such as PLINK and admix, and error detection rate correction was adopted to control multiple comparisons. The result interpretation emphasizes the significance at the functional pathway level and its potential value for precise anti-tuberculosis treatment strategies.

5 Review of Cases of Failed Treatment for Drug-Resistant Tuberculosis

5.1 Basic case information, drug resistance overview and initial treatment plan

This study focuses on patients with drug-resistant tuberculosis. Multidrug-resistant tuberculosis usually refers to tuberculosis that is resistant to both isoniazid and rifampicin. On this basis, extensively drug-resistant tuberculosis may also be resistant to fluoroquinolones and at least one second-line injection drug. Among our group of patients, the majority are aged between 25 and 60, and the proportion of men is also higher. This is the same as the

population characteristics of drug-resistant tuberculosis patients worldwide (Varshney et al., 2021). Among patients diagnosed with drug resistance from the very beginning, the proportion of multidrug resistance is the highest, approximately 70%. In addition, the resistance rate of fluoroquinolone drugs among patients is also not low, which is consistent with the rising trend of resistance to second-line drugs in some parts of Asia (Samad et al., 2024).

The treatment plan is formulated in accordance with the guiding principles of the World Health Organization and in combination with the actual condition of the patient. The treatment mainly adopts an all-oral regimen or a combination of several second-line oral drugs. Commonly used drugs include bedaquiline, linezolid, levofloxacin, etc. The treatment period for most patients is between 18 and 24 months. Patients with severe drug resistance or those whose drug resistance is detected late often find it difficult to achieve the desired therapeutic effect. Studies have shown that patients who were resistant to fluoroquinolones and injectable drugs before treatment usually have poor recovery after treatment (Venkatesh et al., 2021). Patients who have received treatment before but failed, or whose condition relapsed, are more likely to develop multidrug resistance and have less favorable treatment outcomes (Soedarsono et al., 2023).

5.2 Description of the treatment process, outcome and major adverse reactions

The treatment process is usually advanced in stages (intensive period and continuous period), and dynamic monitoring is carried out through monthly sputum smears and cultures. In this cohort, approximately 60% of the patients achieved sputum culture transformation within 6 months, 25% experienced transformation delay, and another 15% remained consistently positive and indicated treatment failure. Overall, the global success rate of multidrug-resistant tuberculosis treatment is still often lower than 60%, and the average success rate of XDR-TB is even lower, approximately 45%. Insufficient compliance, comorbidities (such as diabetes), and drug toxicity are the main driving factors leading to treatment interruption, recurrence or failure.

Adverse drug reactions (ADR) are quite common during the treatment process. The common types include hepatotoxicity, gastrointestinal reactions, ototoxicity and peripheral neuropathy. The introduction of new drugs such as bedaquiline and linezolid has generally improved the outcomes of some patients, but it has also brought risks such as cardiotoxicity and bone marrow suppression, which require more rigorous monitoring and management (Adhvaryu and Vakharia, 2011). Even if the plan is standardized, long-term treatment, insufficient socio-economic burden and psychological support will still affect the completion rate. Project reviews from Eastern Europe and Central Asia have shown that economic hardship, homelessness and alcoholism significantly increase the probability of poor compliance and adverse outcomes.

5.3 Screening and preliminary assessment of major non-genetic risk factors

In addition to the drug resistance spectrum and genetic susceptibility, multiple non-genetic factors can also contribute to the failure of treatment for drug-resistant tuberculosis. Socio-economic pressures (such as unemployment, low income and insufficient access to medical care) are closely related to non-compliance and high default rates. Studies from multiple Eastern European countries have pointed out that lack of income during treatment is a strong predictor of default and failure, and the probability of those without income discontinuing treatment is nearly three times that of others. In terms of clinical factors, diabetes, malnutrition and advanced age are also associated with poor prognosis. Among them, diabetes may increase the risk of multidrug resistance by prolonging sputum transformation time and increasing bacterial persistence.

Behavioral and execution issues during the treatment process, such as discontinuing medication halfway, insufficient dosage, and inadequate implementation of direct face-to-face medication (DOTS), can increase the probability of treatment failure. Studies conducted using machine learning have found that being underweight (low BMI), having had tuberculosis before, and untimely diagnosis are the most reliable predictors of poor treatment outcomes. Moreover, even without considering genetic factors, the different metabolic conditions of drugs in the body and the patients' own conditions (such as slow drug metabolism, low drug concentration in the blood, and insufficient drug effect in diabetic patients after taking rifampicin are typical cases) may also have a significant impact on the treatment outcome (Kadhiravan, 2022). Therefore, it is necessary to carry out and

combine the analysis of social and economic conditions, clinical conditions, drug effects and genetic testing simultaneously. Only in this way can the risk of treatment failure for drug-resistant tuberculosis be predicted more comprehensively and reduced.

6 The Relationship Between the Genetic Background of Individuals and Treatment Failure

6.1 Key genetic variations identified in typical cases

The genes responsible for drug metabolism are different from those related to immunity, which have a significant impact on the therapeutic effect of drug-resistant tuberculosis (DR-TB). For instance, if genes such as cytochrome P450 (CYP) and N-acetyltransferase 2 (NAT2) change, it may alter the metabolic rate of major anti-tuberculosis drugs, thereby affecting the treatment outcome and possibly causing varying degrees of side effects. Studies on Chinese people have found that some *CYP2E1* gene types have no significant association with the incidence of liver injury. In contrast, the relationship between the drug transport gene *ABCG2* and the risk of liver injury and changes in serum enzyme indicators caused by anti-tuberculosis drugs is much clearer.

Genes related to immune regulation can also affect the treatment response and the ability to eliminate bacteria. If genes related to the PI3K/AKT signaling pathway mutate, it may make macrophages difficult to be fully activated and weaken their bactericidal ability. As a result, the risk of tuberculosis will increase (Wu et al., 2023). In addition, variations at the rs7568402 site of the immune checkpoint molecule PDCD1 (also known as PD-1) can also increase the risk of tuberculosis. This indicates that abnormal immune function may lead to more difficult clearance of bacteria and persistent infection (Wang et al., 2021). Changes in genes related to drug metabolism and transport as well as immune-related genes may interact with each other to jointly determine the therapeutic effect. These genes can also serve as candidate biomarkers for clinical stratified risk assessment.

6.2 The relationship between genotype and drug blood concentration/adverse reactions

The absorption and utilization of anti-tuberculosis drugs in the body and their toxic and side effects are closely related to genetic variations that affect the activity of metabolic enzymes and the drug transport capacity. Take the NAT2 gene as an example. People carrying the slow-metabolism type gene usually have a higher concentration of isoniazid in their blood, and their risk of liver damage also increases. For people carrying fast-metabolizing type genes, the concentration of the drug in their bodies may not meet the therapeutic requirements, thereby reducing the effect of eliminating bacteria. During the metabolism of drugs such as rifampicin and pyrazinamide, variations in the *CYP2E1* and *CYP3A4* genes can also cause differences in drug concentrations among patients with different genotypes, leading to situations such as drug accumulation in the body or rapid excretion. Pharmacogenomic studies also support this conclusion, indicating that variations in the *CYP* gene can simultaneously affect the efficacy and safety of anti-tuberculosis treatment regimens (Yang and Wang, 2025).

Genetic differences related to drug transport can significantly affect the distribution of drugs in the body, making people more prone to drug poisoning. Patients with specific *ABCG2* gene variations may be more prone to accumulate toxic metabolites in the liver, thus having a higher risk of liver damage and possibly leading to elevated alkaline phosphatase. Some immune-related variations in the vitamin D receptor (VDR) gene can also alter the strength of the immune response. In the Asian population, certain genetic types not only increase the risk of tuberculosis but may also reduce the probability of recovery after treatment (Li et al., 2022). The genes of different patients vary, which not only affect the metabolism and transport of drugs but also influence the process by which drugs take effect by altering immune function, ultimately determining the treatment outcome of drug-resistant tuberculosis.

6.3 The relationship between genotype and treatment outcomes

When immune-related genes change, it will affect the treatment effect of tuberculosis. Specifically, the tuberculosis bacteria in the sputum cannot turn negative for a long time, or the speed of turning negative is extremely slow, or it will recur after being cured. Some immune genes mutate, which may reduce the body's ability to eliminate bacteria, making it even more difficult to completely eradicate them. Therefore, even with the standard chemotherapy regimen, patients with relatively weak immune function may not achieve the desired therapeutic effect (Wang et al., 2021; Wu et al., 2023). Mutations in the *VDR* gene may increase the risk of

recurrence and slow down the rate at which sputum bacteria turn negative. This connection is more prominent in people with low vitamin D levels (Yadav et al., 2021).

Meanwhile, CYP2E1 and NAT2 polymorphisms may indirectly affect treatment success by altering plasma drug levels: Metabolic features such as rapid acetylation may lead to subtreatment exposure and be associated with an increase in persistent posipositive and recurrence rates, while insufficient metabolism may cause treatment interruption due to increased toxicity. Variations in efflux transport genes (such as *ABCG2*) may also lead to insufficient intracellular drug accumulation, which is conducive to the survival of bacteria under therapeutic stress. Overall, the interaction between pharmacogenetic factors and immunomodulatory factors provides a reasonable explanation for the heterogeneous outcomes that still occur in patients with drug-resistant tuberculosis under a uniform protocol. In the future, if the host genomic characteristics can be combined and integrated with the monitoring of therapeutic drugs and immunophenotypes, it is expected to establish more precise treatment algorithms to increase the cure rate and reduce the risk of recurrence.

7 Develop Individual Treatment Plans Based on Genetic Characteristics

7.1 Select anti-tuberculosis drugs and adjust medication based on genotypes

Everyone's genes are different, which leads to varying treatment outcomes for drug-resistant tuberculosis. The differences in drug metabolism genes can affect the concentrations of drugs such as isoniazid and rifampicin in the body. People with a slower metabolism rate of the *NAT2* gene tend to have drugs stay in their bodies for a longer time and have a greater risk of liver injury. People with fast gene metabolism have lower drug concentrations in their blood, and the possibility of developing drug resistance increases. By integrating the monitoring results of therapeutic drugs with pharmacogenomic information, more reliable medication plans can be formulated, which not only can kill bacteria more effectively but also reduce the toxic and side effects brought by drugs (Igumnova, 2025).

Genetic information can also help improve the safety of using second-line anti-tuberculosis drugs. For instance, hearing loss after taking aminoglycoside drugs may be related to the variation of the *MT-RNR1* gene. If genetic testing could be done earlier, there would be a chance to avoid irreversible damage (Igumnova, 2025). In addition, different *CYP3A4* genes can affect the metabolism of bedaquiline, making it easier for this drug to accumulate in the body and thereby increasing the risk of prolonged QT interval. Pharmacogenomics can also provide more appropriate medication guidance for new drugs like pretomanib.

7.2 Strengthen the monitoring and management methods for high-risk genotypes

Patients who are prone to treatment failure or severe side effects can be identified through genetic markers. People carrying genes related to *CYP2E1* or *NAT2* slow metabolism are more prone to drug-induced liver injury. They should enhance liver function tests and adjust the dosage in a timely manner. For individuals with mutations in the *ABCG2* and *SLCO1B1* genes, there may be insufficient drug absorption or increased toxicity, making it more suitable to use drugs flexibly based on blood drug concentration and therapeutic effect. The use of pharmacogenomic data in conjunction with routine biochemical tests can provide more timely risk warnings for clinical practice.

Therapeutic drug monitoring and population pharmacokinetic models are a good approach to managing critically ill patients. They can flexibly adjust the dosage of medication during treatment and reduce risks. Drug proteomics studies have found that biomarkers at the protein level can make up for the shortcomings of gene screening and more comprehensively reflect the differences in drug responses among different people (Kumar et al., 2025). These methods can help form a management model of "risk classification+dynamic adjustment", making the treatment process more flexible and efficient.

7.3 Application of gene and clinical comprehensive evaluation model in treatment decision-making

Putting genetic information, clinical manifestations and drug metabolism data in the same decision-making tool is a key approach to improving the accuracy of treatment for multidrug-resistant tuberculosis. Gene-clinical models can take into account gene differences such as *NAT2* and *CYP2E1* along with factors like age and comorbidities,

to estimate drug concentrations, the risk of liver damage, and the possibility of successful treatment. Studies have found that machine learning models trained with relevant data can screen out high-risk patients with "specific genotype+liver disease", and suggest that the prognosis of such patients may be worse.

This system conforms to the host-centered precision treatment direction. Combining the genetic characteristics of patients, genetic information of pathogens and drug metabolism data can help formulate more reasonable plans and reduce the chance of drug resistance. Pharmacogenomics should also be used for the medication guidance of new drugs such as bedaquiline to improve efficacy and reduce adverse reactions (Espino-Pereiro et al., 2022; Motta et al., 2023). In the future, clinical decision-making platforms that integrate multi-omics data may shift the management approach from "dealing with problems only when they arise" to "continuous adjustment during the treatment process", thereby further promoting individualized treatment.

8 Discussion and Outlook

The results of this study and the increasing evidence worldwide both indicate that an individual's genetic status can significantly affect the therapeutic effect of drug-resistant tuberculosis (DR-TB). The differences in genes such as drug-metabolizing enzymes (such as *NAT2*, *CYP2E1*, *CYP3A4*), drug transporters (such as ABCG2, SLCO1B1), and immune-related genes (such as *PDCD1*, *VDR*, *PI3K/AKT*) It can lead to different therapeutic effects by altering the metabolism of drugs in the body, the body's tolerance to drugs, and the immune regulatory capacity. Common situations include: People with slow drug metabolism caused by the NAT2 gene are more likely to suffer liver damage due to drug accumulation in the body. For those with a fast drug metabolism, the risk of treatment failure may increase due to insufficient drug concentration in the body. At the same time, mutations in the *ABCG2* and *VDR* genes will also make people more prone to adverse drug reactions, and the speed at which sputum bacteria turn negative will also slow down. It is precisely because of these differences determined by genes that even if a uniform treatment plan is used, patients' treatment responses can still vary greatly. Overall, identifying these key genetic influencing factors can lay the foundation for formulating personalized treatment plans, help doctors assess the efficacy and drug toxicity risks before the start of treatment, and promote the development of drug-resistant tuberculosis treatment towards precision.

Although pharmacogenomics research has made considerable progress, it still faces many difficulties. Current research often leads to unstable validation results from different research teams due to issues such as small sample sizes, most of the research subjects being of the same race, and inconsistent definitions of treatment effects. Moreover, the occurrence of drug-resistant tuberculosis is the result of the combined effect of multiple factors such as the patient's genes, pathogen mutations, living environment and drug metabolism. These factors are intertwined, making it difficult to accurately calculate the independent impact of a single genetic variation on treatment failure. In practical applications, the high cost of genetic testing, the insufficient popularization of testing technology, and the lack of a unified clinical interpretation standard all limit the use of pharmacogenomics in first-line treatment. In those low-and middle-income countries where the problem of drug-resistant tuberculosis is relatively serious, local medical systems often lack the basic conditions for standardized genetic testing and drug efficacy monitoring. In addition, many of the reported associations between genes and therapeutic effects still lack verification from large-scale actual diagnosis and treatment data and long-term follow-up studies. Therefore, it is difficult to directly use these conclusions to guide clinical treatment decisions.

Future research should prioritize the integration of multiple omics and large-scale population studies, and enhance the systematic validation of genotype-phenotypic associations in clinical scenarios to screen for scalable pharmacogenomic markers. Linking the host genome, bacterial genome and pharmacokinetic data is expected to provide a more complete explanation of treatment dynamics and the mechanism of drug resistance evolution. Meanwhile, machine learning models that integrate genetic, clinical and biochemical data may also become effective decision-making tools for optimizing individualized plans. To promote the implementation in resource-limited areas, subsequent work still needs to develop more economical and rapid real-time genotyping methods and explore the connection path with the conventional monitoring system. The integration of pharmacogenomics into the national tuberculosis control program cannot be achieved without interdisciplinary

collaboration among clinical, molecular biological and public health decision-making to establish evidence-based guidelines and training systems. Overall, if pharmacogenomics can be systematically introduced into the routine management of DR-TB, it is expected to increase the cure rate, reduce toxicity and decrease the spread of drug-resistant strains, thereby promoting the upgrading of global tuberculosis prevention and control strategies.

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Conflict of Interest Disclosure
The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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Feature Review Open Access

Mechanistic Research and Biomarker Characteristics of Immune Storms in Severe Dengue

Manman Li
Hainan Institute of Biotechnology, Haikou, 570206, Hainan, China
Corresponding email: manman.li@hibio.org

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Abstract This study explored the key mechanisms of the immune storm in severe dengue fever, the progress of biomarkers, and potential intervention ideas. Immune storm mainly results from the imbalance between innate immune and adaptive immune responses. Common manifestations include excessive activation of pattern recognition receptor pathways such as TLR, antibody-dependent enhancement (ADE), and abnormal T-cell responses, etc. These changes can cause a large amount of cytokine release, further leading to increased vascular permeability, coagulation disorders, and may develop into multiple organ dysfunction. This study reviewed the research progress of multiple types of biomarkers. The existing evidence suggests that these indicators have application potential in the early identification of severe cases, risk stratification, and monitoring of therapeutic efficacy or disease course. Meanwhile, the research also discussed possible therapeutic exploration directions, such as anti-inflammatory and immunomodulatory therapy, endothelial protection-related drugs, and a comprehensive management model of "supportive treatment+targeted intervention". It should be pointed out finally that the current research on biomarkers still has limitations such as small sample sizes and inconsistent research standards, which affect the comparability and promotion of the results. In the future, larger-sample and multi-center studies should be carried out, more standardized biomarker combinations should be established and clinical applications promoted, so as to achieve more accurate risk assessment and earlier intervention, and reduce the risk of death from severe dengue fever.

Keywords Severe dengue fever; Immune storm; Cytokine; Biomarker; Pathogenesis

1 Introduction

Dengue fever is one of the common mosquito-borne viral diseases worldwide. In recent years, the number of cases has continued to rise and the range of transmission has been expanding, making it a prominent public health issue. As of 2021, there were approximately 59 million new cases and nearly 29 000 deaths worldwide each year (Zeng et al., 2021). This disease has been prevalent for a long time in regions such as South Asia, Southeast Asia and Latin America, imposing a considerable burden on society and the economy. Among them, low-and middle-income countries are more affected. Climate change, accelerated urbanization and increased population mobility have further promoted the spread of diseases (Zhang et al., 2025).

The symptoms of dengue fever virus infection vary greatly. It may have no obvious symptoms or only mild discomfort, or it may develop into a serious condition characterized mainly by blood exudation, massive bleeding and organ function damage. In severe cases, shock or even death may occur (Tejo et al., 2023). The elderly and those with underlying diseases have a higher probability of adverse outcomes (Mendez et al., 2025). In clinical observations, the indicative risk signals mainly include repeated vomiting, abdominal pain, mucosal bleeding, liver enlargement, rapid decrease in platelet count, etc. (Dash et al., 2024; Azra et al., 2025; Jeng et al., 2025). Some patients with mild early symptoms may rapidly worsen within a short period of time, which makes disease assessment more uncertain and continuously increases the pressure on clinical judgment and allocation of medical resources (Tsheten et al., 2021; Yang et al., 2025).

This study will focus on the core cause of severe dengue fever, immune storm (also known as cytokine storm). Simply put, it is an imbalance between innate and adaptive immune responses, releasing a large amount of pro-inflammatory cytokines. At present, there are no specific antiviral drugs for the treatment of dengue fever.

Although there have been advancements in supportive treatment, the lack of reliable early detection indicators often affects the timely intervention of severe cases. Understanding the occurrence mechanism of immune storm and finding effective detection indicators can assess the risk of patients, enable early treatment, and reduce the mortality rate of severe dengue fever.

2 Pathological Process and Immune Response of Severe Dengue Fever

2.1 Basic characteristics of viruses

Dengue virus belongs to the Flaviviridae family of single-stranded RNA viruses and is divided into four serotypes from DENV-1 to DENV-4. There is a certain association between the genetic differences and the clinical severity (Khanam et al., 2022; Sinha et al., 2024). After the virus enters the human body through the bites of Aedes aegypti and Aedes albopictus, it first infects local immune cells in the skin and then spreads to lymph nodes and blood circulation to form viremia (Tejo et al., 2023; Cloherty et al., 2024). During the replication process within host cells, viral RNA mediates the synthesis of various proteins, among which the non-structural protein NS1 is closely related to immune evasion and vascular injury processes.

The replication and pathogenicity of the virus are simultaneously influenced by the characteristics of the virus itself and the genetic factors of the host. For example, types such as DENV-2 have stronger replication ability and more obvious immune interference, and may be more likely to cause severe illness (Samune et al., 2024). During the infection process, the interaction between the virus and the host protein can also change the infection process (Cloherty et al., 2024; Sinha et al., 2024). Furthermore, when reinfected with different serotypes, antibody-dependent enhancement (ADE) may occur, significantly increasing the risk of severe illness, which is an important mechanism for disease aggravation (Puc et al., 2021; Khanam et al., 2022).

2.2 Main differences in immune responses between mild and severe patients

The immune response is a key link in eliminating the dengue virus. When the immune regulatory function is out of balance, immune pathological changes characterized by tissue damage in the human body may occur. Patients with milder symptoms usually exhibit an effective combination of innate immunity and adaptive immunity, thereby inhibiting viral reproduction and maintaining tissue damage at a low level (Dash et al., 2024). Abnormal immune regulation is more common in critically ill patients, especially those who are reinfected with different serotypes of viruses. The excessive release of pro-inflammatory factors can trigger a cytokine storm, causing the condition to worsen rapidly (Jiravejchakul et al., 2025).

Severe patients often have significantly elevated inflammatory factors such as IL-6 and IL-8, and their immune cells remain in a highly active state. Antibody-dependent enhancement enables some non-neutralizing antibodies to assist the virus in entering more target cells, thereby expanding and exacerbating the uncontrolled inflammatory response (Khanam et al., 2022; Dash et al., 2024; Jiravejchakul et al., 2025). When the immune regulatory capacity is insufficient, inflammation is difficult to subside, and there may also be an increase in vascular permeability. The risk of organ damage will also rise accordingly. The dynamic balance between pro-inflammatory and anti-inflammatory responses is closely related to the development process of the disease and the recovery effect.

2.3 The overall framework of increased vascular permeability, coagulation imbalance, fibrinolysis and organ damage

A sudden increase in vascular permeability is one of the main characteristics of severe dengue fever. In severe cases, it can cause plasma extravasation, blood concentration and even shock (Nanaware et al., 2021). This situation is related to both the direct destruction by the virus and immune damage: Dengue virus can affect the function of vascular endothelial cells, and NS1 protein can also damage the vascular barrier and cause inflammation (Puc et al., 2021), while pro-inflammatory factors such as TNF-α will further increase vascular permeability (Tejo et al., 2023; Dash et al., 2024).

Patients with severe dengue fever often have abnormal coagulation function, specifically manifested as reduced platelet count and weakened coagulation ability, which greatly increases the possibility of bleeding (Tejo et al.,

2023). When the platelet count drops significantly and is accompanied by vascular endothelial injury, severe bleeding is more likely to occur. Blood leakage, direct damage of viruses to tissues, and overactivated immune responses can simultaneously affect the liver, kidneys, and central nervous system, leading to liver function problems, poor kidney function, and even multiple organ failure in some patients (Estrada-Jimenez et al., 2022; Dash et al., 2024; Teramoto, 2025).

3 Concept and Evidence of Severe Dengue Immune Storm

3.1 Definition and general characteristics of immune storm/cytokine storm

An immune storm refers to a state in which, under the stimulation of infection, cytokines increase significantly in a short period of time, triggering an uncontrolled inflammatory response. In patients with severe dengue fever, various interleukins and tumor necrosis factor -α will rapidly increase, keeping immune cells in an activated state all the time. During the critical period of the disease, a significant increase in vascular permeability and an increased risk of shock often occur simultaneously (Pal et al., 2024). The cytokines released by infected cells will continuously amplify the immune response, forming a self-reinforcing process, and thereby aggravating the damage to tissues and blood vessels (Kadi et al., 2025).

The immune storm of severe dengue fever is related to both innate immunity and adaptive immunity. It should be emphasized that although this intense inflammation is a response against the virus, it can, in turn, disrupt the normal functions of blood vessels and organs (Dash et al., 2024; Kadi et al., 2025). Compared with mild cases, the immune response of severe patients is more difficult to control in a timely manner, and thus they are more likely to lose control of their condition.

3.2 The relationship between abnormal cytokines and disease progression in critically Ill patients

Patients with severe dengue fever often experience abnormal changes in the types and quantities of cytokines, and such changes are closely related to the disease's development process and clinical outcomes. The levels of inflammatory factors IL-6, TNF-α, anti-inflammatory factor IL-10 and various chemokines in critically ill patients are generally elevated, and they persist in the early stage of the disease. They are often accompanied by severe symptoms such as blood leakage and impaired organ function (Dash et al., 2024; Masyeni et al., 2024), among which the elevated levels of IL-6 and IL-8 are closely related to the increased risk of bleeding (Bhatt et al., 2024), and the abnormal changes in IL-10 levels are more obvious in disease types mainly characterized by liver injury.

The dynamic changes of cytokines in the disease course have indicative significance. The peak of some factors at a specific stage can indicate disease progression. Compared with the absolute level of a single indicator, the imbalance of pro-inflammatory and anti-inflammatory responses can better reflect the risk of severe illness (Bhatt et al., 2024). Secondary infections and individual genetic differences can change the intensity of immune responses and increase the possibility of excessive initiation of inflammatory responses (Dash et al., 2024; Masyeni et al., 2024; Pal et al., 2024)

3.3 Mechanisms of leakage, shock and organ damage caused by excessive inflammation

When a patient with severe dengue fever experiences vascular leakage and shock, it indicates a serious inflammatory state. The excessive release of cytokines such as TNF-α and IL-6 can directly damage vascular structure, aggravate abnormal vascular endothelial function, promote blood exudation, reduce the amount of effectively circulating blood, and some patients may develop shock. This process is regarded as one of the important fatal causes in disease progression (Dash et al., 2024; Kurosu et al., 2024).

Long-term uncontrolled inflammatory responses can also affect coagulation and metabolic processes, manifested as thrombocytopenia accompanied by multiple organ damage, excessive IL-10, and related to liver function impairment. Some chemokine changes are associated with renal and lung disease phenotypes. Specific cytokine intervention studies can alleviate clinical manifestations to a certain extent, supporting the key role of excessive inflammation in the progression of severe cases (Kadi et al., 2025). Early suppression of abnormal inflammatory responses helps reduce the risk of severe complications and death

4 The Key Mechanisms of the Severe Dengue Fever Immune Storm

4.1 Overactivation of innate immunity and pattern recognition receptor pathways

Innate immunity is the first line of defense of the human body against the dengue virus (DENV). Pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), are responsible for recognizing the virus and initiating an inflammatory response. After DENV infection, TLR2, TLR4 and TLR6 in immune cells are often activated, leading to an increase in pro-inflammatory factors such as IL-6 and TNF-α. Among them, the NS1 protein of DENV can activate TLR2, TLR4 and TLR6, directly promoting immune cells to release cytokines, intensifying immune storm and tissue damage (Fernandez-santos and Azeredo, 2022). The strong response of innate immunity can initially fight viruses, but if it goes too far, it will get out of control. Excessive TLR signals will increase vascular permeability, which is an important feature of severe dengue fever.

Plasma leakage often occurs after a decrease in viral load, suggesting that severe manifestations are more due to uncontrolled host immunity rather than direct cell destruction by the virus (Fernandez-Santos and Azeredo, 2022). If pattern recognition receptors (PRRs) are overly or abnormally activated, they will rapidly trigger a series of inflammatory responses, which is precisely the basis for the formation of an immune storm.

4.2 Antibody-dependent enhancement and abnormal T-cell response

Antibody-dependent enhancement (ADE) is regarded as one of the important reasons for the aggravation of dengue fever, especially when reinfected with different serotypes of viruses. During the ADE process, antibodies that cannot neutralize the virus will "bring" the virus into immune cells expressing Fcγ receptors (such as monocytes), thereby increasing the replication level of the virus in the body and inducing overactivation of the immune system (Figure 1) (Sun et al., 2025). Subsequently, a large number of inflammation-related cytokines are released, further promoting the development of the immune storm, which can eventually lead to vascular leakage and shock (Shabbir and Linh, 2024).

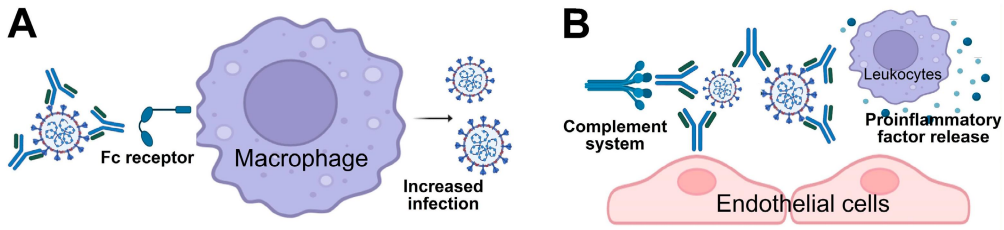

Figure 1 Two proposed mechanisms of ADE in viral disease exacerbation (Adopted from Sun et al., 2025)

Image caption: This figure illustrates two potential mechanisms of ADE contributing to viral disease pathogenesis, as suggested by previous studies; (A) In ADE via increased infection, non-neutralizing or sub-neutralizing antibodies enhance the viral infection of macrophages or other Fc-receptor-bearing cells through Fc-receptor-mediated endocytosis. This process leads to increased viral replication and a more severe disease phenotype; (B) In ADE via enhanced immune activation, non-neutralizing antibodies form immune complexes with viral antigens within tissues such as blood vessels or airways. These immune complexes trigger the release of proinflammatory cytokines, the recruitment of immune cells, and the activation of the complement cascade, resulting in localized tissue damage and inflammation (Adopted from Sun et al., 2025)

Abnormal T cell function also increases the risk of severe illness. Some memory T cells formed by previous infections can "recognize" different serotypes of viruses, but their response to secondary infections is often inefficient - these cells tend to release pro-inflammatory factors but have difficulty effectively eliminating the virus. This phenomenon is known as "original antigen imprinting". When the ADE effect superimposed with this abnormal T-cell response, it would promote an increase in viral load and aggravation of inflammation, forming a vicious cycle (Shabbir and Linh, 2024).

4.3 Vascular endothelial injury leading to complement and coagulation abnormalities and vascular stability disruption

Vascular endothelial injury is an important pathological feature of severe dengue fever. After entering endothelial cells, the dengue virus triggers an inflammatory response, increases the expression of various chemokines, promotes the aggregation of immune cells, and causes significant cellular damage during the disease's progression.

The NS1 protein can increase the release of inflammatory factors through the TLR4 pathway and reduce vascular barrier function (Fernandez-Santos and Azeredo, 2022). Some autoantibodies produced during infection can also bind to endothelium-related targets, further aggravating endothelial damage.

During the critical stage of illness, the complement system and the coagulation system are often overactivated. Excessive complement response can amplify inflammation and increase vascular leakage. Coagulation dysfunction is prone to cause thrombocytopenia and increase the risk of bleeding. Meanwhile, platelets interact with white blood cells, releasing more pro-inflammatory substances and continuously damaging endothelial cells. Under the superposition of multiple abnormalities, vascular stability is disrupted, which may eventually lead to plasma leakage, shock and multiple organ failure (Amin et al., 2025).

5 Research Progress of Biomarkers Related to Immune Storm

5.1 Pro-inflammatory and Anti-inflammatory cytokines

The changes in cytokine levels have important reference value in the disease assessment of severe dengue fever. The increase of pro-inflammatory factors such as IL-6 and TNF-α in critically ill patients is often associated with increased vascular permeability and increased risk of bleeding (Paul et al., 2025). Among them, a significant increase in IL-6 is considered closely related to the increased demand for intensive care and the elevated risk of death (Sivasubramanian et al., 2022; McBride et al., 2024).

Among anti-inflammatory factors, the role of IL-10 is rather complex. When the inflammatory response is too intense, IL-10 will increase, which may help "suppress" the inflammation. But if it increases too much, it will suppress the body's immune response against the virus, making it more difficult to clear the virus (Masyeni et al., 2024; Prajapati et al., 2024). The key lies not in the level of a single cytokine, but in whether the effects of pro-inflammatory factors and anti-inflammatory factors are balanced. Once out of balance, patients may present with severe symptoms (Figure 2) (Dash et al., 2024). Recent studies have pointed out that the imbalance in the combined changes of IL-6, IL-8, and IL-10 may be related to early bleeding, which indicates that the "combination of cytokines" is of great value in judging the prognosis of patients.

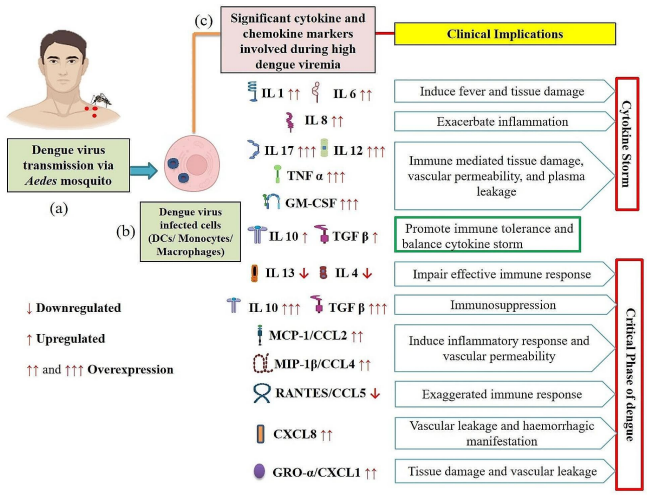

Figure 2 Mechanistic effects of complex interplay between pro-inflammatory and anti-inflammatory cytokines and chemokines during dengue virus (DENV) infection (Adopted from Dash et al., 2024)

Image caption: (a) Infection of DENV to host via Aedes mosquito during blood meal. (b) DENV infects target cells including dendritic cells, macrophages, and monocytes, initiating host immune response. (c) Infected cells release pro-inflammatory cytokines, such as IL-1, IL-6, IL-8, IL-17, IL-12, TNF-α, and GM-CSF and chemokines such as MCP-1/CCL-2, MIP-1β/CCL-4, CXCL-8, and GRO-α/CXCL-1. Proinflammatory cytokines activate other immune cells and promote the release of anti-inflammatory cytokines, such as IL-10 and TGF-β that limits the extent of immune responses. During high dengue viremia, excessive release of pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-17, IL-12, TNF-α, and GM-CSF) and chemokines (MCP-1/CCL-2, MIP-1β/CCL-4, CXCL-8, and GRO-α/CXCL-1), upregulation of anti-inflammatory cytokines (IL-10 and TGF-β), and downregulation of chemokine RANTES/CCL-5 lead to exaggerated immune response; This surge in immune response results in cytokine storm and contribute to SD manifestations (Adopted from Dash et al., 2024)

5.2 Markers of endothelial injury and vascular permeability

Severe dengue fever is mainly based on impaired vascular endothelial function. Relevant biomarkers have been widely used in clinical risk assessment. Among them, the applications of sICAM-1 and Ang-2 are relatively mature. Elevated levels of sICAM-1 indicate an increased risk of plasma extravasation or shock (McBride et al., 2024). In patients with dengue shock, Ang-2 has a closer relationship with pulmonary leakage and the risk of death, and has a higher predictive effect on disease progression. Elevated sICAM-1 and VCAM-1 mainly reflect that endothelial cells are in an activated state and are also related to the aggravation of the disease (Sivasubramanian et al., 2022; Yang et al., 2025).

5.3 New multi-group student physical markers

The development of multi-omics technology has provided more ideas for finding new markers and understanding the mechanism of immune storm. Transcriptomic studies have identified some gene expression characteristics related to severe illness, such as elevated MX2 in B cells and elevated CD163 in monocytes. These changes may occur before severe illness and can be used for early prediction (Zhang et al., 2023). Proteomics and metabolomics have also identified many candidate molecules that can reflect the host response intensity and immune activation level (Vairaperumal et al., 2025).

Indicators such as thrombin and sFlt-1 are often used to evaluate the degree of endothelial injury and abnormal coagulation function in critically ill patients. Standardized testing helps to identify high-risk groups at an early stage and guide targeted treatment and intervention. However, the current detection standards are not uniform. Personal factors such as age and underlying diseases may affect the stability and credibility of the results (McBride et al., 2024; Yang et al., 2025; Paul et al., 2025).

Molecules such as miRNAs and lncRNAs have great potential in regulating immune responses. For example, miR-584-5p in the blood can distinguish severe and non-severe dengue fever patients quite well. Some studies have shown that its discriminative ability (AUC) can exceed 0.8 (Katz et al., 2025). This type of new biomarker is expected to be used in clinical practice in the future, but it still needs to be further verified in different populations and the detection methods and determination criteria should be unified (Limothai et al., 2022; Paul et al., 2025).

6 Application Prospect of Biomarkers in Severe Dengue Fever

6.1 Early identification of high-risk patients and disease classification

Early detection of dengue fever patients who may develop into severe cases is very important for improving the treatment effect. In the early stage of fever, the changes of indicators such as CRP, AST, VCAM-1, IL-8, and TNF-α are closely related to the subsequent aggravation of the disease (Moallemi et al., 2025). Among them, elevated CRP and AST can be regarded as early risk signals. The increased expression of VCAM-1 and syndecan-1 indicates a greater possibility of blood leakage or bleeding (Moallemi et al., 2023). The combined use of multiple biological indicators with molecular markers such as lncRNA and miRNA can further improve the accuracy of risk assessment (Limothai et al., 2022).

A comprehensive assessment model based on biomarkers can identify high-risk groups in the early stage of diseases and also support enhanced monitoring and intervention measures. This method has high practical value in areas with dengue fever epidemic and environments with insufficient medical resources. It helps to rationally allocate intensive care resources and improve the overall diagnosis and treatment efficiency (Moallemi et al., 2023; Katz et al., 2025; Vairaperumal et al., 2025).

6.2 Dynamic monitoring of biomarkers and disease assessment

Continuous monitoring of biomarker changes during the disease process is helpful for judging the progression of the disease and treatment response. For instance, elevated levels of cfDNA and CRP during the acute phase of infection usually indicate an increased risk of shock and plasma leakage. Elevated liver enzymes or a continuous decline in platelets may indicate organ damage or a tendency to bleed. Doctors can adjust the treatment strategies in a timely manner based on the changes of these indicators, such as strengthening monitoring or performing fluid resuscitation in advance, to reduce the risk of further deterioration of the condition (Vairaperumal et al., 2025).

Bedside real-time detection technology can quickly obtain multi-index results, facilitating doctors to make quick decisions. By observing whether the indicators decrease or continue to increase, it is also possible to indirectly determine whether the treatment is effective and decide whether the intervention plan needs to be adjusted (Vairaperumal et al., 2025).

6.3 Utilize biomarkers to improve monitoring and guide treatment

Biomarkers can reflect the disease changes of patients with severe dengue fever and provide references for disease surveillance, fluid replacement plan formulation and treatment decision-making. Elevated endothelial injury, inflammation or metabolism-related indicators often suggest an increased risk of circulatory system complications and the need for intensive intervention (Ghosh et al., 2024). Dynamically adjusting the treatment strategy based on indicators is helpful for reasonably controlling the infusion volume and reducing the risk of infusion-related organ injury (Vairaperumal et al., 2025).

The combined evaluation of multiple biomarkers can be used to determine whether there is coagulation dysfunction or vascular injury and guide the initiation timing of supportive treatment. Its standardized detection and interpretation in clinical practice can help improve the accuracy of decision-making and the prognosis of patients (Ghosh et al., 2024; Katz et al., 2025).

7 The Immune Treatment and Intervention Study of the Storm

7.1 Potential directions of anti-inflammatory and immunomodulatory therapy

Severe dengue fever often presents as an immune storm type, characterized by disordered immune regulation and excessive release of pro-inflammatory factors. Enhanced or inhibited interferon signals related to antibodies will promote the further expansion of the inflammatory chain reaction. Anti-inflammatory treatment mainly works by intervening in key inflammatory pathways to reduce the excessive activation of immune cells. Studies have shown that IL-1 receptor antagonists and JAK inhibitors can reduce the level of inflammation, and immune checkpoint related regulation can help restore immune balance and alleviate vascular damage (Chermahini et al., 2025; Yoo et al., 2025).

Early use of corticosteroids combined with intravenous immunoglobulin can enhance anti-inflammatory effects and improve organ function. However, there are individual differences in therapeutic effects. The effect is more obvious in patients with compensatory shock, while it is relatively poor in the decompensated stage. The choice of treatment duration and applicable population has a significant impact on the treatment outcome (Mahashabde and Kumar, 2024; Shetty et al., 2025). The relevant basis and practice of immunomodulatory therapy in other infectious disease fields can also provide a reference for optimizing the treatment plan for dengue fever.

7.2 Drug strategies for protecting vascular endothelium and reducing leakage

Damage to vascular endothelium and increased permeability are the key basis for plasma leakage and shock formation. Therefore, endothelial protection and leakage control have become the focus of research. Existing studies have shown that some kinase inhibitors can alleviate vascular leakage related to viral infection and improve survival rate, and some receptor agonists can enhance vascular barrier stability. Their protective effects have been preliminarily confirmed in animal models (Modak et al., 2023; Mishra et al., 2025).

Anti-vegf antibodies can help reduce vascular leakage in terms of lowering vascular permeability. Drugs that inhibit mast cell activity can also reduce the risk of shock to a certain extent (Lim et al., 2024). Meanwhile, some natural compounds demonstrated antiviral and endothelial-protective activities in experiments and could inhibit viral protein-mediated vascular leakage (De Sousa et al., 2022). It can be seen that both synthetic drugs and natural ingredients are expected to play a role in maintaining the function of the vascular barrier.

7.3 A comprehensive strategy combining supportive treatment with targeted intervention

The pathological process of severe dengue fever is rather complex, and a comprehensive treatment strategy is often adopted in clinical practice. Standardized supportive treatment remains the basic measure, mainly including fluid management, circulatory monitoring and organ function support (Hasani et al., 2025), supplemented by intervention methods for immune disorders and endothelial injury. Relevant studies suggest that some drugs have certain effects in inhibiting viral replication and reducing inflammation (Abbasi, 2025).

Stratified treatment based on disease severity and biomarker levels helps improve the targeting of intervention. Patients with significantly elevated inflammatory indicators are more suitable for prioritizing immunomodulatory measures, while patients with early vascular leakage-related signals should focus on endothelial function protection (Shetty et al., 2025). The combination of targeted intervention on the basis of conventional supportive treatment is considered to help reduce the risk of death from severe dengue fever, but the relevant strategies still need further clinical research for verification and improvement.

8 Conclusion and Outlook

Immune storm is the key to the occurrence and deterioration of severe dengue fever. It can cause dengue fever to develop from a common fever into fatal conditions such as plasma leakage, bleeding and shock. The essence is that the immune response is out of order - too many cytokines are released, immune cells are overly active, and the function of endothelial cells is impaired, ultimately destroying the vascular barrier and causing organ problems. Recent studies have found that TNF-α, IL-6 and various chemokines are all involved in this process. Extracellular vesicles and non-coding Rnas may also regulate immune and endothelial responses, providing us with a more comprehensive understanding of the mechanism of severe illness development.

At present, biomarker research has identified many candidate indicators, such as gene expression characteristics, circulating proteins, cytokines, etc., which can be used for early disease prediction and risk stratification. The advantages of these studies lie in the use of multiple sets of data, more advanced molecular detection techniques, and the integration of machine learning to enhance prediction accuracy. However, the shortcomings are also quite obvious: many studies have a small sample size and only come from one institution. The case standards and sampling times are not uniform, making it difficult to replicate and promote the results. Moreover, the research endpoints are not uniform, and the process from experimental discovery to clinical application is unclear, which also hinders the progress of intervention treatment research.

Future research should focus on large sample sizes and multi-center research designs, so as to more confidently verify those candidate markers. At the same time, differences in regions and populations, as well as different types of viruses, should also be taken into account. We need to create a standardized combination of biomarkers, integrating genetic information, protein data and patients' clinical conditions. This will facilitate the comparison among different studies and promote the practical application of research results in clinical treatment. In addition, by integrating high-throughput detection, continuous sampling, and bedside rapid testing technologies, it can help doctors identify critically ill patients earlier and enhance the efficiency of treatment and management. In conclusion, the joint development and validation of a standardized marker system by all is the key to improving the treatment outcomes for patients in dengue fever endemic areas and optimizing intervention methods.

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Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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Review and Progress Open Access

The Role of the Gut-Brain Axis in the Pathogenesis of Parkinson's Disease and Its Clinical Application Prospects

Jingqiang Wang
Institute of Life Science, Jiyang College of Zhejiang A&F University, Zhuji, 311800, Zhengjiang, China
Corresponding email: jingqiang.wang@jicat.org

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Abstract This study explored the role of the gut-brain axis in Parkinson's disease (PD). PD is characterized by the degeneration of dopaminergic neurons in the substantia nigra and the aggregation of α-synuclein. Gastrointestinal non-motor symptoms such as constipation often occur earlier than motor symptoms, accompanied by the deposition of α -synuclein in the intestine, damage to the intestinal barrier and activation of mucosal immunity. Environmental toxins, diet, infection and antibiotics can cause intestinal flora imbalance, promote the misfolding of α-synuclein and its entry into the brain along the vagus nerve and humoral pathways, and work in synergy with mitochondrial dysfunction, oxidative stress and genetic susceptibility to form a multi-factor pathological network. In terms of early diagnosis, fecal microbiota and its metabolites, intestinal biopsy α-synuclein, tongue coating microbiota and multi-omics integrated models, combined with gastrointestinal symptom scales, are expected to form a non-invasive biomarker system for screening high-risk populations and risk stratification. In terms of treatment, the combined application of probiotics/synthetic bacteria, dietary intervention, fecal microbiota transplantation, intestinal-targeted anti-inflammatory and barrier repair, and vagus nerve regulation, along with dopamine replacement and deep brain stimulation, is expected to improve both motor and non-motor symptoms while partially influencing the course of the disease, providing new ideas for individualized intervention based on the gut-brain axis.

Keywords Parkinson's disease; Gut-brain axis; Gut microbiota; α-synuclein; Early diagnosis

1 Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder and the second most common movement disorder in the world. In the general population, about 1 to 2 people out of every 1 000 suffer from this disease. The proportion of people over 60 years old suffering from this disease is approximately 1%. After the onset of the disease, patients often experience problems related to movement, such as hand tremors, muscle stiffness, slow movement and physical instability. In addition, patients may also experience non-motor symptoms, which often appear several years earlier than the motor symptoms we are familiar with. This indicates that Parkinson's disease is not only complex but also affects the whole body (Santos et al., 2022). Relevant epidemiological investigations show that men have a higher risk of Parkinson's disease than women. The occurrence of this disease is related to both genetic factors and environmental risks (Ben-Shlomo et al., 2024). Nowadays, the aging of the population is becoming increasingly prominent, and the health pressure brought by Parkinson's disease on a global scale is also growing. It is estimated that the number of patients may double in the coming decades. This means that we urgently need to have a deeper understanding of this disease and improve its treatment and care methods (Menozzi et al., 2025).

The traditional view holds that PD is mainly caused by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the accumulation of misfolded α -synuclein in Louis' bodies. Its molecular mechanisms involve α -synuclein aggregation, mitochondrial dysfunction, oxidative stress, impaired protein clearance and neuroinflammation, etc. (Simon et al., 2020). Based on the above understanding, symptomatic treatments such as dopamine replacement represented by levodopa and deep brain stimulation have been developed. However, long-term application is often accompanied by reduced efficacy and motor and non-motor complications, and cannot prevent or reverse the progression of the disease (Xu et al., 2023; Menozzi et al., 2025),

also lacks truly disease-improving therapies and reliable early diagnostic biomarkers, highlighting the urgency of exploring novel treatment strategies to target the potential pathophysiology of PD.

This study will explore the crucial role of the gut-brain axis in the pathogenesis of PD. An increasing number of preclinical, clinical and postmordial studies suggest that gastrointestinal dysfunction and intestinal microbiome imbalance may precede and promote the occurrence and progression of the disease. Mechanically, intestinal ecological imbalance, increased permeability and immune activation can induce systemic and neuroinflammation, promoting the misfolding of α -synuclein in the intestinal nervous system and its transmission along the vagus nerve to the central nervous system. This study aims to provide new clues for the early detection and pathophysiology of PD, and also opens up prospects for disease improvement and individualized treatment strategies targeting the gut microbiota and gut-brain communication. It is expected to reshape the management model of PD and improve the prognosis of patients.

2 The Structure and Function of The Gut-Brain Axis

2.1 Central nervous system, enteric nervous system and autonomic nervous system

The gut-brain axis is basically constructed around a complex bidirectional communication network integrating the central nervous system (CNS), the enteric nervous system (ENS), and the autonomic nervous system (ANS) (Hattori and Yamashiro, 2021; Zheng et al., 2023). The CNS, composed of the brain and spinal cord, is the main processing center for neural information, while the ENS, known as the "second brain", is embedded in the gastrointestinal tract and is composed of a large number of neurons, responsible for autonomously regulating intestinal motility, secretion, absorption and local immune response (Suganya and Koo, 2020; Zheng et al., 2023). The ENS communicates extensively with the CNS simultaneously through pathways such as vagus nerve and spinal afferent fibers, enabling rapid transmission of sensory and motor signals between the gut and the brain, thereby achieving the regulation of the digestive process by the brain and the feedback effect of gut-derived signals on brain function and behavior (Hattori and Yamashiro, 2021; Zheng et al., 2023).

The autonomic nervous system (abbreviated as ANS) is composed of two parts: the sympathetic nerve and the parasympathetic nerve. It is a key intermediate transmitter between the central nervous system and the enteric nervous system (ENS), responsible for coordinating physiological activities that are not subjectively controlled, such as heart rate, digestion, and respiratory rate (Suganya and Koo, 2020). Among them, the nerve fibers of the sympathetic nerve usually inhibit intestinal peristalsis and secretion production, while the parasympathetic nerve fibers mainly promote the progress of the digestive process through the vagus nerve and play an anti-inflammatory role (Longo et al., 2023; Zheng et al., 2023). Through these neural conduction pathways, the metabolic products of the intestinal flora or the changes in the intestinal environment caused by inflammation can be rapidly transmitted to the brain. The stress response generated by the brain, in turn, affects the physiological state and microbiota composition of the intestines. This bidirectional interaction constitutes an important structural and functional basis of the gut-brain axis in both healthy and diseased states (Hattori and Yamashiro, 2021).

2.2 Regulatory networks: HPA axis, immune system and humoral factors

In addition to neural pathways, the gut-brain axis is also jointly regulated by the hypothalamic-pituitary-adrenal axis (HPA axis for short), the immune system, and various humoral factors (Hattori and Yamashiro, 2021). The hypothalamic axis is an important part of the central neuroendocrine system. It regulates the overall stress response of the body by controlling the secretion of glucocorticoids (such as cortisol) (Rusch et al., 2023). When the HPA axis is activated, it will change intestinal permeability, regulate immune responses, affect the composition and function of intestinal flora, thereby altering the physiological state of the intestine (Bertollo et al., 2025). Conversely, signals such as microbial metabolic products or inflammatory cytokines produced in the intestinal tract can also activate the HPA axis, thereby influencing the overall stress state of the body and brain function. When a person is ill, neuroendocrine signals play a crucial role in maintaining gut-brain balance and dealing with the problem of balance disruption (Rusch et al., 2023).

The immune system is not only an important channel for signal transmission between the intestine and the brain, but also a key target of this axial regulation. In the relevant lymphoid tissue (GALT for short) in the intestine,

immune cells constantly detect substances in the intestine. After interacting with microbial antigens, they produce signal molecules such as cytokines, thereby regulating the local and overall immune responses of the body. These substances can cross the blood-brain barrier or affect brain function through neural pathways, participating in the occurrence and development of neuroinflammation and neurological diseases (Hattori and Yamashiro, 2021). Meanwhile, humoral factors such as intestinal hormones and neuropeptides, as well as microbial metabolic products like short-chain fatty acids, further regulate the activities of the nervous and immune systems, which also reflects the complexity and integrity of the gut-brain axis regulatory network (Suganya and Koo, 2020).

2.3 Regulation of the nervous system by gut microbiota and its metabolites

The gut microbiota, composed of trillions of microorganisms, settles in the human gastrointestinal tract and is now regarded as the core regulatory part of the gut-brain axis (Suganya and Koo, 2020). They are involved in various metabolic processes and can produce many bioactive substances, such as neurotransmitters like serotonin and gamma-aminobutyric acid, as well as metabolites like short-chain fatty acids that have an impact on the nervous system. These substances can act directly or indirectly on the enteric nervous system, change its function, and also regulate the activities of the autonomic and central nervous systems (Zheng et al., 2023; Bakshi et al., 2024).

From the initial development of the nervous system to the aging process of human beings, various factors such as diet, antibiotic use, high mental stress, and infection may all change the composition and metabolic characteristics of the intestinal microbiota, thereby affecting the generation of important metabolites and the overall situation of signal transmission between the intestine and the brain (Suganya and Koo, 2020). Researchers are actively studying methods such as probiotics, prebiotics, and dietary adjustments to restore or regulate the gut microbiota, and taking this as a potential direction for the treatment of neurodegenerative diseases and neuropsychiatric disorders (Zheng et al., 2023; Bakshi et al., 2024). This type of research further demonstrates that the gut microbiota is of great significance for maintaining the health of the nervous system and developing new clinical intervention methods.

3 Evidence for the Role of the Gut and Gut Microbiota in Parkinson's Disease

3.1 The relationship between gastrointestinal non-motor symptoms and the occurrence and development of parkinson's disease

Gastrointestinal (GI) symptoms are now regarded as the most common and earliest group of non-motor manifestations in Parkinson's disease (PD), often emerging many years or even decades earlier than classical motor symptoms (Chiang and Lin, 2025). Constipation, drooling, dysphagia and urinary dysfunction are particularly common. About 60%~80% of PD patients have at least one GI symptom. These manifestations not only significantly impair the quality of life, but are also related to the duration and progression of the disease. It is suggested that GI dysfunction is closely related to the potential pathophysiology of PD (Montalban-Rodriguez et al., 2024). Among them, constipation and defecation dysfunction often occur before motor symptoms and are regarded as potential early clinical markers of PD, which are expected to provide clues for early identification and intervention (Khalaf et al., 2025).

Some studies have shown that Parkinson's disease patients with poor gastrointestinal function tend to have more severe motor symptoms and more obvious cognitive decline, which further indicates that gastrointestinal problems are associated with the progression of Parkinson's disease (Jones et al., 2020). Patients with Parkinson's disease often have changes in gut microbiota, that is, microbiota imbalance. This change is related to their gastrointestinal symptoms and neurological symptoms (Chiang and Lin, 2025). The gut-brain axis enables bidirectional signal transmission between the gut and the central nervous system, allowing signals from the gut to influence the processes of neuroinflammation and neurodegeneration. So, gastrointestinal symptoms may not only be incidental manifestations of Parkinson's disease, but an important part involved in the occurrence and development of the disease (Montalban-Rodriguez et al., 2024).

3.2 Deposition of α -synuclein in intestinal mucosa and enteric nervous system and braak hypothesis

One of the most core pathological features of Parkinson's disease (PD) is the accumulation of misfolded α -synuclein in nerve cells, forming Lewy bodies. This pathological change not only occurs in the brain, but also

widely exists in the enteric nervous system (ENS) and intestinal mucosa (Chiang and Lin, 2025). The Braak hypothesis suggests that Parkinson's disease may originate in the gut: misfolded α -synuclein first appears in the enteric nervous system and then spreads along the vagus nerve to the central nervous system like prions (Montalban-Rodriguez et al., 2024). Both human and animal experiments can support this view. For instance, α -synuclein aggregates can be detected in intestinal neurons several years before the onset of motor symptoms in patients with Parkinson's disease. Inoculation of α -synuclein fibrils into the intestines of mice can lead to lesions similar to Lewy bodies in their brainstems. In addition, this diffusion also relies on the complete vagus nerve pathway.

The evidence for the "gut origin" theory comes from environment-related studies. When the gut is exposed to toxic substances or when the gut microbiota is imbalanced, it may cause misfolding of local α -synuclein (Chiang and Lin, 2025). Intestinal glial cells play a key role in this process. Their activation and reactivity changes are closely related to the pathological changes and inflammatory responses of α -synuclein (Montalban-Rodriguez et al., 2024). In addition, a small amount of α -synuclein can also be found in intestinal endocrine cells. These abnormally folded proteins will directly contact intestinal neurons along neural pathways and gradually spread from the intestinal epithelium to the central nervous system. Overall, these findings provide strong support for the Braak hypothesis and also highlight the significant role of the enteric nervous system in the pathogenesis of Parkinson's disease.

3.3 Findings related to intestinal barrier dysfunction, "leaky gut", and mucosal immune activation

Poor intestinal barrier function, commonly known as "leaky gut", is regarded as an important cause of Parkinson's disease. Under normal circumstances, the intestinal epithelial barrier not only enables nutrients to be absorbed smoothly but also prevents harmful bacteria and toxins from entering the body. The intestinal barrier integrity of patients with Parkinson's disease is disrupted, specifically manifested as increased intestinal permeability, elevated levels of tight junction marker protein zonulin, and endotoxemia may also occur (Skjærbæk et al., 2021; Derkinderen et al., 2025). These changes are usually associated with intestinal flora disorders and chronic enteritis, which may trigger a systemic immune response and subsequently cause neuroinflammation in the central nervous system. These factors are regarded as important links connecting intestinal lesions and neurodegeneration (Dodiya et al., 2020; Metta et al., 2021; Munoz-Pinto et al., 2024).

Mucosal immune activation is another distinct feature of Parkinson's disease. Studies have found that the levels of pro-inflammatory cytokines increase in the intestines and peripheral blood of patients with Parkinson's disease, and immune cells such as monocytes and T cells can also invade the central nervous system. Toll-like receptors on the surface of small intestinal glial cells are crucial in immune responses and maintaining intestinal barrier function. Their functional disorders can aggravate inflammation and promote pathological changes in α -synuclein (Figure 1) (Montalban-Rodriguez et al., 2024). Animal experiments have shown that intestinal inflammation caused by intestinal barrier damage or microbiota disorder can accelerate neurodegenerative changes and make the symptoms of Parkinson's disease more severe. This indicates that restoring intestinal barrier function and regulating mucosal immunity may become methods for intervention and even change the disease process to a certain extent (Dodiya et al., 2020; Metta et al., 2021).

4 Examine the pathogenesis of Parkinson's disease from the perspective of the gut-brain axis

4.1 Environmental factors induce intestinal flora imbalance and misfolding of α -synuclein

Environmental conditions such as diet, toxic substances, infections and the use of antibiotics can significantly alter the flora in the intestines, causing an imbalance in the flora. This can cause lipopolysaccharide (LPS) produced by bacteria to enter the bloodstream, thereby triggering systemic and local immune responses (Klann et al., 2022; Mahbub et al., 2024; Oliver et al., 2025). When this immune response is activated, it will cause misfolding and accumulation of the core protein of Parkinson's disease - α -synuclein, leaving hidden dangers for subsequent pathological changes (Santos et al., 2022).

Abnormal aggregation of α -synuclein may first occur in the enteric nervous system (ENS). Experiments have confirmed that specific intestinal bacteria, environmental toxins and poor diet can all affect or exacerbate the

aggregation of α -synuclein (Klann et al., 2022; Santos et al., 2022; Mahbub et al., 2024). Several years before the onset of motor symptoms in PD patients, aggregates of this protein can already be detected in intestinal neurons, indicating that intestinal pathology may predate central lesions, and environmental factors that disrupt the intestinal microecology may be early triggers for the onset of PD.

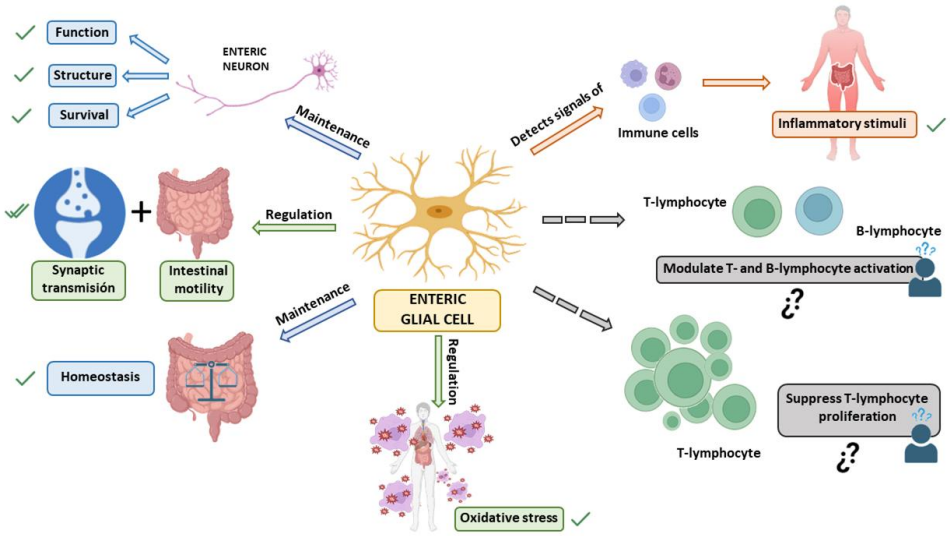

Figure 1 Functions of enteric glial cells (EGCs) (Adopted from Montalban-Rodriguez et al., 2024)

4.2 Pathological cascades of intestinal pathology that spread to the central nervous system through pathways such as the vagus nerve

The stepwise spread of α -synuclein pathology from the intestine to the brain is the core content of the gut-brain axis hypothesis. According to the Braak hypothesis, misfolded α -synuclein can be retroactive from the ENS to the central nervous system in a prion-like manner along the vagus nerve. It first affects the dorsal motor nucleus of the brainstem vagus nerve and then spreads to regions such as the substantia nigra, leading to the loss of dopaminergic neurons and the appearance of typical motor symptoms (Santos et al., 2022; Montalban-Rodriguez et al., 2024; Oliver et al., 2025). Clinical observations have shown that vagotomy is associated with a reduced risk of Parkinson's disease (PD) and that GI symptoms such as constipation occur earlier than motor symptoms, all of which provide indirect support for this model.

In addition to the vagus nerve, the humoral pathway may also be involved in the spread of intestinal pathology to the central nervous system: when the intestinal and blood-brain barriers are damaged, bacterial products and pro-inflammatory cytokines can enter the circulation, cross the barriers, induce neuroinflammation and promote further misfolding of α -synuclein in the central nervous system (Hill et al., 2021; Mahbub et al., 2024). Intestinal glial cells and various immune mediators play a key role in amplifying and transmitting enterogenic inflammatory signals to the brain. The interaction between neuro-humoral mechanisms highlights the complexity of the gut-brain axis pathology in PD and also suggests multiple potential therapeutic intervention targets (Santos et al., 2022; Montalban-Rodriguez et al., 2024).

4.3 The interaction among mitochondrial dysfunction, oxidative stress and genetic susceptibility

Dopaminergic neurons in the substantia nigra are inherently fragile and prone to injury. Pathological changes caused by intestinal flora disorder and abnormal folding of α-synuclein can be intertwined with mitochondrial dysfunction and oxidative stress to form a vicious cycle, jointly accelerating the degeneration and death of neurons (Lei et al., 2021). Microbial metabolites such as short-chain fatty acids and LPS can affect the working state of mitochondria and closely link the composition of the gut microbiota with the survival of neurons (Mahbub et al., 2024).

Genetic predisposition to the disease interacts with environmental and microbial factors, jointly altering the risk and progression rate of Parkinson's disease: Changes in related genes increase the risk of disease and also alter the

body's response to intestinal-derived damage. Therefore, the combined effect of genetics, environment and gut microbiota determines the complex pathogenesis of Parkinson's disease. In-depth study of these interrelationships is of great significance for the prevention and treatment of Parkinson's disease (Klann et al., 2022).

5 Early Diagnosis and Biomarkers Based on the Gut-brain Axis

5.1 Overview of fecal microbiota, metabolites and intestinal biopsy related indicators

Studies have found that the composition and function of the gut microbiota in PD patients are significantly different from those in healthy individuals, manifested as a reduction in butyric acidogenic bacteria, an increase in Akkermansia and Bilophila, the latter of which can serve as a potential diagnostic marker (Figure 2) (Zhao et al., 2024). These changes are often accompanied by a reduction in metabolites such as short-chain fatty acids in feces, which may exacerbate intestinal barrier damage and neuroinflammation (Tan et al., 2020; Nishiwaki et al., 2024). Fecal metagenomic and metabolomic analyses have a strong ability to distinguish PD, and the area under the curve (AUC) of some gene marker combinations can exceed 0.9 (Qian et al., 2020).

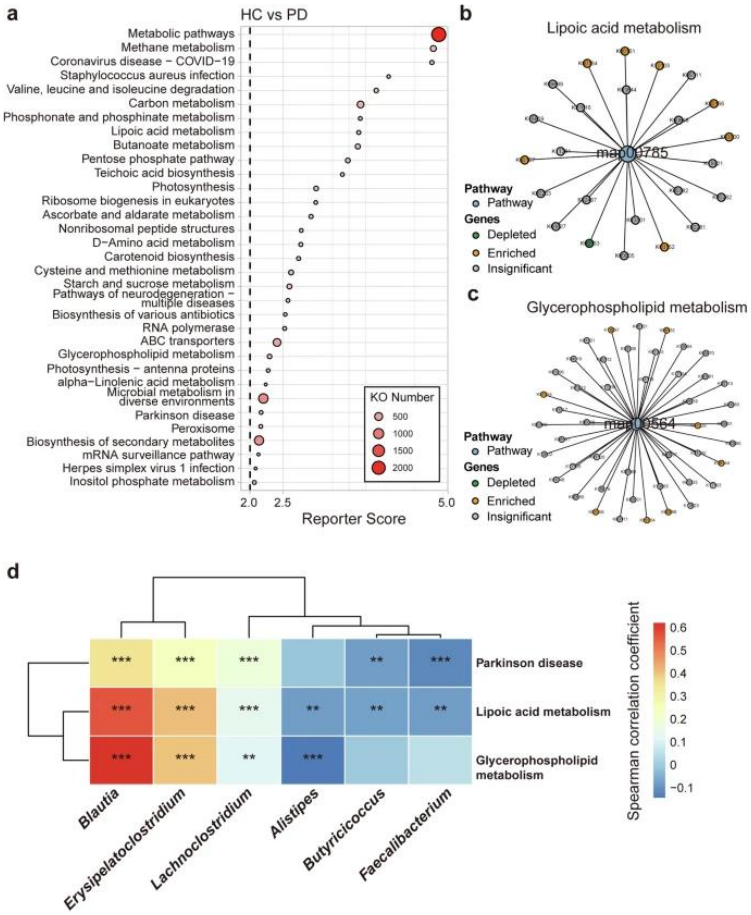

Figure 2 Changes in microbial functions of PD (Adopted from Zhao et al., 2024)

Image caption: (a) Reporter score for level-3 KEGG pathways showing functional enrichment in different groups; Reporter Score>0 represents enrichment of pathways in PD group, and Reporter Score=2 was set as the threshold for visualization; Network plots for (b) lipoic acid metabolism and (c) glycerophospholipid metabolism pathways; d Heatmap showing the associations between genus-level relative abundances and pathway abundances; The color gradient indicates the Spearman's rank coefficient of correlation; $^{**}P < 0.01$; $^{***}P < 0.001$; Statistical significance was calculated by Spearman correlation test (Adopted from Zhao et al., 2024)

During intestinal biopsy, α -synuclein deposition in the enteric nervous system is studied as an early diagnostic marker, but this examination is invasive and difficult to popularize (Qian et al., 2020). Non-invasive detection methods such as the tongue membrane microbiota have become good alternatives (Yang et al., 2025). Combining indicators from multiple sources is expected to further enhance the accuracy of diagnosis and monitoring of Parkinson's disease (PD).

5.2 Application of the gastrointestinal non-motor symptom scale in screening high-risk populations

Non-motor gastrointestinal symptoms such as constipation often appear many years earlier than motor symptoms and are important clues for the early screening of PD. Gastrointestinal symptom scales and questionnaires can assist in identifying high-risk populations, especially when combined with prodromal symptoms such as rapid eye movement sleep behavior disorder (Heinzel et al., 2021). The accuracy rate of multiple non-motor symptom combinations in predicting the prodromal stage of PD exceeds 80%.

Combining the gastrointestinal symptom scale with the intestinal microbiota map can enhance the accuracy of prediction. There are certain types of microbiota that are directly associated with the risk of Parkinson's disease (Heinzel et al., 2021). Combining the two is expected to enhance the identification effect of high-risk groups and facilitate early intervention, but more long-term follow-up studies are still needed to verify and improve this method.

5.3 Risk prediction and disease classification models based on microbiome and multi-omics integration

The integration of multiple omics such as microbiome with metabolomics and neuroimaging has promoted the establishment of PD risk prediction models and subtype classification frameworks (Zhou et al., 2025). The machine learning model based on multi-omics has high prediction accuracy, and the AUC value in some external cohorts is greater than 0.9 (Makarious et al., 2021; Yu et al., 2025).

The combination of multi-omics techniques can also help us distinguish different types of Parkinson's disease, understand the disease development process, and lay the foundation for personalized treatment (Luo et al., 2025). For instance, combining the results of neuroimaging examinations with the characteristics of the intestinal flora can make the staging of cognitive dysfunction in patients with Parkinson's disease more accurate. As related technologies become increasingly mature, they will play a key role in the early diagnosis and personalized treatment of Parkinson's disease.

6 Intervention and Treatment Strategies Based on the Gut-brain Axis

6.1 Probiotics, synthetic bacteria and dietary adjustments

Regulating the intestinal flora through probiotics, synthetic bacteria and dietary adjustments has become a promising approach to influencing the progression of Parkinson's disease (PD). Probiotics are active beneficial bacteria that can restore the balance of intestinal flora to a certain extent, reduce intestinal inflammation, and also promote the production of metabolites such as short-chain fatty acids (SCFAs) that have protective effects on the nervous system. Clinical and laboratory studies have shown that supplementing probiotics can help improve gastrointestinal function in patients with Parkinson's disease (PD), reduce neuroinflammation, and have a slight improvement in motor and non-motor symptoms. However, the effect in improving core motor symptoms is still relatively limited (Singh et al., 2022). Synthetic probiotics (that is, the combination of probiotics and prebiotics) can promote the growth of beneficial bacteria, enhance their metabolic activity, thereby better maintaining intestinal health, and may also enhance the protective effect on nerves (Kumar et al., 2025).

Dietary adjustments, especially the Mediterranean diet or high-fiber diet, can help reshape the intestinal microbiota, which is associated with an increase in the abundance of ScFas-producing bacteria and a reduction in pro-inflammatory flora, thereby helping to maintain the integrity of the intestinal barrier and alleviate systemic inflammation (Salim et al., 2022; Zhu et al., 2022). Nutritional interventions, including nutritional supplements and foods rich in polyphenols, have also been proven to affect the composition and function of gut microbiota, creating an internal environment with more neuroprotective characteristics, which may delay the progression of PD (Yao et al., 2024; Sobral et al., 2025). Although the above-mentioned methods are generally safe and easy to implement, more large-sample, long-term follow-up clinical trials are still needed to determine the best intervention plan and the lasting efficacy.

6.2 Fecal microbiota transplantation and intestinal targeted anti-inflammatory and barrier recovery strategies

Fecal microbiota transplantation (FMT) restores microbial diversity and function by transplanting the intestinal

microbiota of a healthy donor into a PD patient. Preclinical and early clinical studies have shown that FMT can correct intestinal ecological imbalance in PD models, alleviate intestinal and central nervous system inflammation, and improve gastrointestinal and partial motor symptoms (Guo et al., 2025; Porwolik et al., 2025). Mechanism studies have shown that FMT can inhibit pro-inflammatory signaling pathways such as TLR4/NF-κB, repair the integrity of the intestinal and blood-brain barriers, and reduce the aggregation of α -synuclein in the intestinal and central nervous systems, thereby exerting neuroprotective effects (Zhao et al., 2021; Panaitescu et al., 2024). However, its exact mechanism of action and long-term safety still await further systematic assessment.

In addition to fecal microbiota transplantation, anti-inflammatory measures targeting the intestine and methods for repairing the intestinal barrier are also being intensively studied, including specific probiotics, prebiotics, nutritional supplements with anti-inflammatory effects, and intervention measures that can enhance the function of the intestinal mucosal barrier (Wang et al., 2021; Yao et al., 2024; Kumar et al., 2025). These methods can reduce intestinal permeability, that is, solve the problem of "leaky gut", and also alleviate the inflammatory response throughout the body. They are expected to sever the pathological link between abnormal intestinal function and neurodegeneration in patients with Parkinson's disease. Although these methods have promising prospects, they are still in the early stage of clinical application at present. Therefore, it is necessary to formulate standardized treatment procedures and comprehensively assess their safety and practical effects.

6.3 Vagus nerve regulation, combined DBS strategy and comprehensive management model for intestinal health

The vagus nerve is an important signaling channel on the gut-brain axis, responsible for transmitting various neural and immune signals between the intestine and the central nervous system. Regulating the activity of the vagus nerve by methods such as drugs, electrical stimulation or behavioral intervention is believed to affect the neuroinflammation of PD and the transmission process of α-synuclein (Wang et al., 2021). At present, vagus nerve stimulation (VNS) and related neuromodulation techniques are being studied for alleviating neuroinflammation, improving gastrointestinal peristalsis, and possibly even delaying disease progression. However, the relevant clinical research is still in its infancy (Yadav and Raj, 2025).

On this basis, incorporating intestinal health management into the PD care system has also attracted increasing attention. For example, combining deep brain stimulation (DBS) with intestinal-targeted therapy, dietary guidance, and regular examination of gastrointestinal symptoms, and jointly improving patients' motor and non-motor symptoms through multiple methods (Salim et al., 2022; Zhu et al., 2022). With the continuous deepening of research, personalized comprehensive management plans centered on gugut brain axis intervention and combined with existing neuromodulation therapies are expected to become an important way to improve the rehabilitation effect of PD patients (Wang et al., 2021; Alam et al., 2024; Kumar et al., 2025).

7 Conclusion

The gut-brain axis for Parkinson's disease (PD) offers promising approaches for disease improvement and enhancing the quality of life of patients. Interventions such as probiotics, prebiotics, dietary adjustments, and fecal microbiota transplantation (FMT) can, to a certain extent, regulate intestinal ecological imbalance, reduce neuroinflammation, and improve both motor and non-motor symptoms. At the same time, they partially act on potential pathogenic mechanisms such as abnormal intestinal permeability and α-synuclein aggregation. Therefore, integrating intestinal-directed therapy into PD management It is expected to achieve a transformation from simple symptom relief to more comprehensive disease improvement.

The microbiota in the gut can change due to factors such as genetics, environment, and diet, making it difficult to establish a universal treatment approach and biomarkers. There are currently no unified usage norms for intervention methods such as fecal microbiota transplantation (FMT), probiotic regulation, and dietary adjustment, which affects the comparability and consistency of research results. At present, the basis of related research mostly comes from animal experiments or small-scale human studies, and there is still a lack of large-scale, scientifically designed clinical trials to confirm the efficacy and safety of these methods for different patients. Therefore, we urgently need more rigorous clinical research and more targeted treatment plans to enhance the therapeutic effect.

Future research should focus on long-term follow-up studies and multi-omics joint research to clarify the causal relationship between intestinal microbiota disorders and the occurrence and development of Parkinson's disease. At the same time, reliable and non-invasive biomarkers should be identified for the early diagnosis and monitoring of the disease. The assessment of the gut microbiota should be integrated into the entire process of risk prediction, early intervention and personalized treatment of Parkinson's disease. The focus of the research should shift from "observing phenomena" to "active intervention", integrating the latest research achievements of artificial intelligence and systems biology. Relying on the collaboration of multiple disciplines such as neurology, gastroenterology, microbiology, and nutrition, more precise and effective targeted treatment methods for the gut-brain axis have been developed at present.

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Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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