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Exploring the Onset of Type 2 Diabetes Mellitus Based on the Theory of Liver-Spleen Harmonization

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Abstract: ***Type 2 Diabetes Mellitus (T2DM) is a clinical syndrome characterized primarily by chronic hyperglycemia, resulting from the combined effects of multiple factors. In traditional Chinese medicine (TCM), it falls under the category of "Xiaoke disease." The syndrome differentiation and treatment of Xiaoke disease often follow the "three types of Xiao" approach. Guided by the holistic concept of TCM, treatment transcends single-organ strategies by integrating both the holistic and differential perspectives of TCM, emphasizing coordination among multiple organs—particularly liver and spleen harmonization—to achieve unity between local and systemic regulation. This paper explores the pathogenesis of T2DM from multiple angles, including inflammatory responses, glucose and lipid metabolism, gut microbiota, bile acid metabolism, and pancreatic fat deposition, to elucidate the roles of the liver and spleen in the onset of T2DM. It provides a theoretical basis for the prevention and treatment of early-stage T2DM through liver-spleen harmonization. Aligned with the TCM principle of "preventive treatment of disease," this approach advocates for early detection and effective intervention of abnormal blood glucose levels. By soothing the liver and relieving stagnation, tonifying qi and strengthening the spleen, the harmony between wood and earth is restored, and blood glucose naturally stabilizes. This strategy holds significant value in improving patients' quality of life and delaying the progression of early-stage T2DM.***

Keywords: Liver-spleen harmonization, Newly diagnosed type 2 diabetes mellitus, Inflammatory response, Gut microbiota, Bile acid metabolism**.**

1. Introduction

Type 2 Diabetes Mellitus (T2DM) is a clinical syndrome characterized by chronic hyperglycemia resulting from the combined effects of multiple factors. According to the 10th edition of the Global Diabetes Atlas published by the International Diabetes Federation in 2021 [1], the number of people with diabetes in China increased from 90 million in 2011 to 140 million in 2021, marking a 56% rise over the past decade. T2DM often develops from a state of hyperglycemia, which itself indicates a significantly elevated risk of future diabetes onset [2]. Therefore, early detection and timely intervention are critical to reversing the upward trend in blood glucose and preventing disease progression [3].

In traditional Chinese medicine (TCM), T2DM corresponds to the category of "Xiaoke" (wasting-thirst disorder). Patients with newly diagnosed T2DM—defined as those with a disease duration of less than five years and without significant complications—can benefit greatly from early identification and effective management, which may slow disease progression and reduce the risk of complications. Studies have shown that in the syndrome element distribution of early-stage T2DM, the primary affected organs are the liver, spleen, and kidney, with the liver and spleen accounting for as much as 65.1% [4]. This highlights the pivotal role of both the liver and spleen in the pathogenesis of early T2DM.

In TCM theory, the liver favors free flow and governs dispersion, while the spleen prefers ascending movement and governs transformation and transportation. The liver belongs to the wood element, and the spleen to the earth element. Wood can restrain earth, but also facilitate its function. If the spleen becomes obstructed, it may counteract the liver in return. He Yajie et al. [5] proposed that both "wood restraining earth" and "earth achieving flow through wood" represent the dynamic relationship between these two elements. The latter concept originates from the Su Wen · Bao Ming Quan Xing Lun, which states: "Wood is felled by metal, fire is extinguished by water, earth is activated by wood…" Here, "activation" implies smooth flow or regulation. Thus, the liver's dispersing function promotes the spleen's transformation and transportation. The liver aids digestion by facilitating the spleen's function, while the spleen's ability to ascend and distribute clear qi depends on the rising nature of Shaoyang qi [6].

When the spleen is deficient, food essence becomes stagnant; when fluid distribution is impaired, dampness accumulates; and when liver qi fails to disperse, pathogenic factors stagnate, leading to internal heat, which over time contributes to the development of Xiaoke [7]. Therefore, the physiological functions of liver dispersion and spleen transformation are mutually supportive, while their pathological changes are interrelated and mutually reinforcing. The traditional "three Xiao differentiation" approach, which treats each organ individually, has limitations. Given that the liver and spleen together account for over 65% of syndrome elements in early-stage T2DM, treatment should not isolate organ systems but instead emphasize liver-spleen harmonization. This approach aligns with the holistic principles of TCM and aims to achieve a dynamic balance between local organ function and systemic regulation [8].

This paper briefly reviews the pathogenesis of Xiaoke, drawing from classical Chinese medicine theory and integrating contemporary biomedical research on T2DM. It aims to explore the feasibility and necessity of applying the

theory of liver-spleen harmonization in the treatment of newly diagnosed T2DM.

2. Pathogenesis of Xiaoke

In classical Chinese medical texts such as the Huangdi Neijing, "Xiaoke" refers to what is now known in modern medicine as diabetes. The Lingshu · Five Transformations states: "Those with weak five zang organs are prone to Xiaoke," indicating that congenital deficiencies and weakened vital qi are foundational causes of the disease. In addition, the Neijing attributes the onset of Xiaoke to improper lifestyle habits, emotional excesses, and psychological stress, with the liver, spleen, and kidney being the key organs involved.

With rapid societal development, increasing pressures from study, work, and life have led to emotional disturbances such as anxiety and depression, as well as unhealthy dietary habits including excessive intake of rich and greasy foods. These factors adversely affect liver and spleen function. For example, anger injures the liver, leading to liver qi stagnation; excessive worry and overthinking impair the spleen. The Su Wen · Yin Yang Ying Xiang Da Lun notes: "Anger harms the liver… thinking harms the spleen." Overeating rich foods causes internal heat and fullness, disrupting dispersion and transformation, and eventually leading to fire from stagnation and metabolic dysfunction [9].

The Su Wen · Qi Bing Lun states: "The five flavors enter the stomach, the spleen distributes the fluids, and when the fluids are in the spleen, the mouth tastes sweet. This is caused by rich foods. Such individuals often consume sweet and fatty foods. Fat causes internal heat, sweetness causes fullness, and the rising qi transforms into Xiaoke." Liu Wansu's Three Xiao Treatise records: "Excessive emotions transform into fire, and intense heat damages yin, resulting in Xiaoke." The Su Wen · Ju Tong Lun says: "All diseases arise from qi." The Lingshu · Five Transformations further explains: "Why are some people prone to Xiaoke? Shaoyu replied… anger causes qi to rise and reverse, accumulating in the chest, blood and qi stagnate, skin becomes full, blood vessels are blocked, heat arises, and heat consumes the flesh, leading to Xiaoke." The Lingshu · Ben Zang Pian states: "A fragile liver is prone to Xiaoke and easily injured." Huang Yuanyu's Su Ling Wei Yun · Xiaoke Jie emphasizes: "The cause of Xiaoke lies in anger, specifically in liver wood." It explains that the liver is yin in substance and yang in function; excessive dispersion transforms into fire and damages yin. When yang function is overactive, it consumes the yin substance, leading to internal heat and the onset of Xiaoke [10].

These classical insights confirm that the pathogenesis of Xiaoke is closely related to liver and spleen dysfunction. The Treatise on Blood Disorders states: "Wood governs dispersion; food qi enters the stomach and relies on liver wood qi to disperse, allowing transformation." The Essentials of Diagnosis and Treatment · Food Injury Section notes: "Human digestion begins with the spleen and stomach; overeating injures the liver." These statements highlight the physiological interdependence between liver dispersion and spleen transformation.

The wood-earth relationship is one of mutual regulation. The liver corresponds to wood, and the spleen to earth. Wood can restrain and facilitate earth, but if the spleen is obstructed, its qi cannot be dispersed, and it may counteract the liver. If spleen qi is deficient due to poor diet and excessive consumption of rich foods, fullness occurs, and obstructed earth counteracts wood, impairing liver dispersion. Conversely, liver qi stagnation leads to wood failing to regulate, overwhelming the spleen, causing qi stagnation and worsening fullness. This creates a vicious cycle: liver fails to disperse and overwhelms the spleen, while spleen obstruction counteracts liver wood, showing their pathological interdependence.

In summary, liver and spleen influence each other physiologically and interact pathologically. Spleen deficiency and earth obstruction impair transformation, while liver stagnation and fire disrupt dispersion. Internally, this leads to food essence stagnation; externally, it manifests as elevated blood glucose. Therefore, liver-spleen disharmony is a key pathogenic mechanism in Xiaoke [6]. Treatment should focus on soothing the liver, relieving stagnation, tonifying qi, and strengthening the spleen—harmonizing wood and earth through liver-spleen regulation.

3. Exploring the Pathogenesis of T2DM from the Perspective of Integrated Traditional Chinese and Western Medicine

3.1 The Relationship Between "Excessive Internal Heat" (Zhuanghuo) and Inflammation

In the context of Xiaoke disease (diabetes) in traditional Chinese medicine (TCM), improper diet and emotional disturbances can lead to internal heat syndromes such as fire-heat, damp-heat, and stagnated heat. Pathological factors like liver qi stagnation transforming into fire and food accumulation generating heat are collectively referred to as "Zhuanghuo" (excessive internal heat). This internal fire not only damages yin fluids but also consumes vital qi, a phenomenon described in TCM as "Zhuanghuo consumes qi" [11]. The depletion of vital qi results in dysfunction of the five zang organs. Combined with impaired dispersion and stagnation of qi and blood, pathological products such as blood stasis and phlegm become difficult to resolve, further aggravating internal heat and forming a vicious cycle of "Zhuanghuo–qi deficiency–phlegm and stasis" [11].

Yu Wenqian et al. [11] proposed that the concept of "Zhuanghuo" in TCM is closely related to inflammation in Western medicine. Xiong Hang et al. [12] also suggested that during the transformation of internal heat, the body enters a stress state, triggering inflammatory mechanisms and releasing pro-inflammatory cytokines. This leads to dysregulation of the neuro-endocrine-immune network and exacerbates inflammatory responses. If this pathological state is not promptly resolved, it may cause irreversible organic damage and contribute to the development of chronic degenerative diseases. Oxidative stress and inflammation are recognized as key contributors to the onset and progression of T2DM.

Among the five zang organs, the liver is associated with the wood element and governs dispersion. It favors smooth flow and is particularly sensitive to emotional constraint. Emotional disturbances can easily impair liver dispersion, leading to liver qi stagnation, which over time transforms into internal heat. This heat induces a stress response, activates inflammatory pathways, and promotes the release of inflammatory mediators. Chronic low-grade inflammation is a critical factor in the development of insulin resistance. Inflammatory cytokines interfere with insulin signaling, impairing glucose uptake and utilization by cells, ultimately resulting in hyperglycemia [13]. Furthermore, inflammation can cause mitochondrial dysfunction [14], which is closely linked to T2DM pathogenesis [15,16]. Mitochondrial damage further intensifies inflammation, creating a negative feedback loop that exacerbates insulin resistance and impairs insulin secretion.

The spleen and stomach are central to the regulation of qi movement. When spleen function is normal, digestion and nutrient absorption are coordinated, nourishing the entire body. However, dietary irregularities can disrupt spleen function, leading to internal heat and fire transformation. This fire triggers a stress response and activates inflammatory mechanisms, including adaptive immune responses and macrophage-mediated inflammation, which promote insulin resistance [17]. Internal heat increases the expression of inflammatory cytokines and activates signaling pathways such as nuclear factor kappa B (NF-κB), resulting in chronic low-grade inflammation. This interferes with insulin signal transduction and reduces insulin sensitivity [18]. Additionally, spleen dysfunction-induced obesity and lipid metabolism disorders can activate Toll-like receptor (TLR) pathways, further promoting inflammation [14]. Fat accumulation elevates levels of free fatty acids (FFA), which enhance oxidative stress and inflammatory responses. Inflammatory cytokines attack pancreatic β-cells, triggering immune responses and increasing the production of pro-inflammatory mediators. Ectopic fat deposition exacerbates lipolysis and FFA release, perpetuating a vicious cycle of inflammation and insulin resistance [19].

β-cell dysfunction and insulin resistance are hallmark features of T2DM, both of which are closely associated with inflammation. Inflammatory signals disrupt insulin action and metabolic homeostasis [11]. Pancreatic inflammation, glucolipotoxicity, and oxidative stress contribute to structural and functional deterioration of β-cells, accompanied by elevated levels of inflammatory cytokines [20]. T2DM is characterized by a persistent state of low-grade inflammation, which serves as a pathogenic link between obesity and insulin resistance, playing a direct or indirect role in disease onset and progression.

Therefore, in the treatment of newly diagnosed T2DM patients, controlling disease progression requires a dual approach: on one hand, lipid regulation and weight reduction are essential to minimize FFA release and mitigate inflammation; on the other hand, therapeutic strategies should focus on clearing internal heat, soothing the liver, and tonifying qi. These interventions target the "Zhuanghuo" state, which is closely related to inflammation, and may help alleviate chronic low-grade inflammation in early-stage T2DM patients.

3.2 The Relationship Between Liver-Spleen Disharmony and Insulin Resistance

The theory of liver-spleen interaction originates from classical Chinese medical texts such as the *Huangdi Neijing and Nanjing*, and constitutes a core component of the five-zang organ theory in traditional Chinese medicine (TCM). The smooth dispersion of liver qi and the robust transportation and transformation functions of the spleen are essential for the regulation of qi dynamics, distribution of qi, blood, and essence, fluid metabolism, blood storage, and digestion [5]. When liver-spleen harmony is disrupted, various pathological changes may occur, leading to metabolic disorders such as obesity, hyperlipidemia, diabetes, hypertension, and insulin resistance. In modern clinical observations of obese T2DM patients, a significant proportion present with liver-stomach damp-heat syndromes [21]. The symptoms and pathogenesis of "pi dan" (spleen exhaustion) described in the *Neijing*, characterized by damp-heat accumulation in the spleen and stomach, closely resemble those of many obese T2DM patients [22]. Furthermore, the *Lingshu · Ben Zang* states: "When the liver and spleen are fragile, one is prone to Xiaoke and injury," highlighting the inseparable relationship between Xiaoke (diabetes) and liver-spleen dysfunction.

In modern medicine, the development of diabetes is closely linked to pancreatic function. The term "pancreas" first appeared in Chinese medical literature in the Ming dynasty text *Compendium of Materia Medica* by Li Shizhen. In TCM, the spleen is conceptually associated with the pancreas, and the pancreas is often considered part of the spleen system [23]. Insulin secreted by the pancreas plays a vital role in maintaining blood glucose homeostasis. Its biological function is to transport glucose—the refined essence of food—to target tissues and organs, where it is metabolized to provide energy for cellular activity [24]. Studies have shown that pancreatic fat deposition can lead to β-cell damage and apoptosis, impairing insulin synthesis and secretion, thereby exacerbating insulin resistance [25,26]. From a TCM perspective, β-cell damage or apoptosis, resulting in impaired glucose transport, aligns with the concept of spleen deficiency and failure to distribute essence.

The *Suwen · Jingmai Bie Lun* states, "Fluids enter the stomach, overflow as essence, and are transported upward to the spleen… water essence is distributed throughout the body." Similarly, the *Suwen · Yuji Zhenzang Lun* describes the spleen as "the solitary organ, the central earth that nourishes the four directions." When spleen function is impaired, internal stagnation transforms into heat, damp-heat accumulates, qi movement is obstructed [27], and turbid toxins are generated internally. The failure to distribute refined essence leads to internal stasis, accumulation of "sugar turbidity," and ultimately the development of Xiaoke [28,29]. This supports the view that liver qi stagnation and spleen deficiency are central to the pathogenesis of diabetes. Internally generated dampness, phlegm, and blood stasis are closely associated with the onset of insulin resistance [30], which, if persistent, may progress to full-blown T2DM. Intervening in pancreatic fat deposition can improve islet function and reduce insulin resistance, thereby helping to correct impaired glucose

tolerance and slow the progression of T2DM [31].

The *Gezhi Yulun* states, "The liver governs dispersion." While the spleen and stomach are the pivot of qi movement, the overall circulation of qi in the body depends on the ascending function of liver qi. When qi flows, blood and fluids follow. Liver dispersion promotes spleen-stomach transformation and bile secretion. When spleen function is normal, digestion and nutrient absorption are coordinated, nourishing the entire body. However, when the spleen is deficient, the generation of qi and blood is insufficient, the liver lacks nourishment, and its dispersing function is impaired [5]. This leads to qi stagnation, internal accumulation of food essence, and elevated blood glucose levels. Liver qi stagnation is thus a major pathogenic factor in T2DM [32].

From a modern biomedical perspective, the liver is responsible for approximately 90% of endogenous glucose production through gluconeogenesis and glycogenolysis [33]. Hepatocytes absorb glucose and convert it into glycogen. Both glucose uptake and endogenous glucose production are essential for maintaining stable blood glucose levels [34]. Gluconeogenesis is the primary pathway for endogenous glucose production. Insulin enters the liver via the bloodstream, promoting glycogen synthesis and inhibiting gluconeogenesis [35]. When excessive fat accumulates in the liver and other organs, glycogen storage decreases, blood glucose gradually rises, and the burden on pancreatic β-cells increases [30]. When insulin signaling is impaired, either directly or indirectly, glucagon activity is enhanced, leading to increased glycogen breakdown and gluconeogenesis, resulting in hyperglycemia and ultimately triggering T2DM [36].

3.3 The Relationship Between Liver-Spleen Function and the Gut Microbiota–Bile Acid Axis

In TCM, the spleen is regarded as the "sea of qi and blood" and the foundation of acquired constitution. Modern research shows that the TCM concept of the spleen encompasses functions related to digestion, metabolism, immunity, and neuroendocrine regulation, with the closest association being with the digestive system. The spleen is also closely linked to the gut microbiota. The role of gut microbiota in food digestion and nutrient absorption aligns with the physiological functions attributed to the spleen in TCM [37]. Spleen dysfunction can lead to gut microbial imbalance, and conversely, dysbiosis of the gut microbiota can manifest as symptoms of spleen deficiency [38,39].

In recent years, accumulating evidence has demonstrated a strong association between gut microbiota and T2DM [40–42]. Dysbiosis can promote fat storage, leading to obesity and insulin resistance, both of which are key contributors to T2DM pathogenesis [43]. Alterations in gut microbiota can compromise the intestinal mucosal barrier, increasing permeability and allowing bacterial lipopolysaccharides (LPS) to enter the bloodstream, triggering inflammatory responses [41]. Inflammation is a well-established factor in the development and progression of T2DM. Moreover, certain bacteria can accelerate β-cell apoptosis, reducing insulin secretion [42]. Therefore, changes in gut microbiota in patients with spleen deficiency may significantly influence the development of T2DM [38,43,44].

The *Donguibogam* states, "The surplus qi of the liver is discharged into the gallbladder, where it accumulates and becomes essence," indicating that bile production and excretion are regulated by liver dispersion. The liver's dispersing function influences gastrointestinal motility, with smooth muscle contraction and relaxation serving as its physiological effectors [45]. Disruption of gut microbiota can damage the intestinal barrier, increase permeability, and allow bacterial translocation into the bloodstream, leading to inflammation [41]. Inflammatory mediators can damage the liver, disrupt bile acid metabolism, and increase the risk of inflammation and microbial translocation, thereby disturbing intestinal homeostasis [46,47]. Gut microbiota can regulate bile acid metabolism [48], and bile acids possess antimicrobial properties that help maintain microbial balance and intestinal barrier integrity. Thus, a bidirectional regulatory relationship exists between gut microbiota and bile acids [37], and disturbances in bile acid homeostasis are closely associated with T2DM development [37].

In TCM, the spleen is closely related to the normal gut microbiota, and dysbiosis is a hallmark of spleen deficiency. Meanwhile, bile acid metabolism disorders are indicative of liver qi stagnation. The bidirectional regulation between gut microbiota and bile acids, and their close association with T2DM, reflect the interdependence of the liver (wood) and spleen (earth) in TCM theory. When liver qi fails to disperse, it overacts on the spleen; conversely, spleen deficiency impairs liver dispersion. From a modern medical perspective, the gut microbiota–bile acid axis aligns with the TCM pathogenesis of liver depression and spleen deficiency [37]. Regulating this state may alleviate oxidative stress and inflammation in some diabetic patients [49]. The liver and gut microbiota interact through the "gut-liver axis," jointly participating in immune regulation, bile acid synthesis, and glucose-lipid metabolism, thereby influencing systemic homeostasis [5]. Changes in gut microbial composition and the dynamic bile acid pool offer new insights into the pathophysiology of metabolic diseases [48]. Chen Bingting et al. [50] proposed that alterations in bile acid composition in T2DM patients may serve as potential diagnostic biomarkers, aiding in early diagnosis and treatment. Therapeutically, liver-spleen harmonization targeting the bile acid–gut microbiota axis may help treat T2DM by increasing beneficial gut bacteria, promoting bile acid metabolism, reducing intestinal permeability, mitigating inflammation, stimulating gut hormone secretion, and improving insulin sensitivity [44]. This approach may effectively intervene in impaired glucose tolerance and help control disease progression in early-stage T2DM.

4. Treatment of Early-Stage T2DM Based on Liver-Spleen Harmonization

The *Huangdi Neijing* (Yellow Emperor's Inner Canon) states that Xiaoke (diabetes) is associated with congenital deficiencies, improper diet, emotional disturbances, and physical exhaustion [22]. In TCM, the liver governs dispersion and the spleen governs transformation and transportation. Based on the multidimensional analysis above, liver-spleen disharmony is closely related to the onset and

progression of T2DM.

Both animal experiments and clinical studies have demonstrated the efficacy of liver-spleen harmonization in treating Xiaoke. *Si Ni San* (Frigid Extremities Powder) is considered the foundational formula for harmonizing the liver and spleen. It regulates qi and blood, balances yin and yang, and harmonizes organ function. Jia Xiaolei et al. [51] used a combination of *Si Ni San and Tong Xie Yao Fang* in diabetic mice and found that liver-spleen harmonization significantly reduced blood glucose levels, improved glucose tolerance, enhanced insulin sensitivity, and alleviated insulin resistance. Clinical studies by Cai Shaona [52] and Zhao Zhai [53] also confirmed that the liver-spleen harmonization approach is effective in treating T2DM. It helps regulate blood glucose and lipids, improves immune function, enhances resistance to external pathogens, and improves patients' quality of life.

Further clinical evidence from Wang Guozhen [54] and Luo Qing [55] shows that harmonizing liver and spleen function can improve insulin resistance, increase insulin sensitivity, promote recovery of pancreatic β-cell function, improve lipid metabolism, and support weight reduction. These findings suggest that liver-spleen harmonization is a promising therapeutic strategy for managing early-stage T2DM.

5. Conclusion

With rapid societal development and increasing psychological and lifestyle pressures, many individuals experience emotional disturbances and poor dietary habits. These factors disrupt liver dispersion and spleen transformation, leading to metabolic imbalances in qi, blood, and body fluids—recognized as the core pathogenesis of early-stage T2DM.

Modern medical research has demonstrated that integrating traditional Chinese medicine with conventional Western treatments offers distinct advantages. The liver and spleen influence each other physiologically and interact pathologically. Therefore, treatment should adhere to the holistic principles of TCM, emphasizing liver-spleen harmonization. Therapeutic strategies such as soothing the liver to relieve stagnation and tonifying qi to strengthen the spleen can restore the balance between wood and earth elements, improve systemic regulation, and enhance patients' quality of life. This paper aims to provide a theoretical basis for early intervention and precision treatment of T2DM, with the goal of delaying disease progression and improving long-term outcomes.

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