

Traditional Chinese Medicine Chronobiological Pathogenesis of Type 2 Diabetes Mellitus and Time-Sequenced Prevention and Treatment Strategies

Chen Rui¹, Lu Bo^{2,*}

¹Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China

²Endocrinology Department, Shaanxi Provincial Hospital of Chinese Medicine, Xi'an 710003, Shaanxi, China

*Correspondence Author

Abstract: ***Objective:** To explore the central role of circadian rhythm disruption in the pathogenesis of type 2 diabetes mellitus (T2DM) from the perspective of Traditional Chinese Medicine (TCM) chronobiology, and to establish novel prevention and treatment strategies. **Methods:** We systematically integrated TCM theories—including “correspondence between heaven and man,” “fluctuations of yin and yang,” and “midday-midnight circulation”—with modern chronobiology research on circadian genes, gut microbiota, and the gut-brain axis to conduct interdisciplinary mechanism interpretation. **Results:** We propose that T2DM fundamentally stems from “desynchronization between endogenous biological rhythms and natural rhythms,” with the core pathogenesis being “disordered temporal sequencing of spleen and kidney functions.” Circadian genes (e.g., BMAL1/CLOCK) regulate insulin secretion rhythms, providing a molecular basis for the “yin-yang diurnal rhythm.” The circadian oscillations of gut microbiota reflect the microscopic manifestation of the “spleen-stomach transformation rhythm,” while the gut-brain axis provides a biological bridge for the “spleen-stomach-mind” theory. Based on this, a new temporal prevention and treatment paradigm—“timing-based, organ-differentiated, syndrome-regulated”—is refined. **Conclusion:** Strategies such as time-based daily routines, time-restricted eating, and meridian-based medication can restore rhythmic synchrony, offering new insights for integrated Chinese and Western medicine in preventing and treating T2DM.*

Keywords: Type 2 diabetes, Traditional Chinese Medicine chronobiology, Circadian rhythm, Circadian clock genes, Gut microbiota, Gut-brain axis, Prevention and treatment strategies.

1. Introduction

Type 2 diabetes (T2DM) falls under the category of “xiaoke disease” in Traditional Chinese Medicine. It is caused by a variety of factors, including constitutional predisposition, diet, emotional state, physical exhaustion, advanced age, and external pathogens, and is characterized by the “three excesses and one deficiency.” Formerly known as non-insulin-dependent diabetes or adult-onset diabetes, this condition is a chronic metabolic disease resulting from the combined effects of genetic and environmental factors, characterized primarily by hyperglycemia, insulin resistance, and insufficient insulin secretion. It accounts for more than 90% of all diabetes cases [1]. Modern medical research has found that circadian rhythm disruption can promote the onset and progression of T2DM [2]. Epidemiological data show that its incidence and prevalence have risen significantly over the past few decades, making it a major global public health challenge [3]. As one of the countries with the heaviest global burden of diabetes, China exhibits distinct local characteristics in the epidemiological trends of the disease [4], and it has become a major public health issue. T2DM accounts for the majority of diabetes cases; if detected and managed early in the disease course, it is largely preventable and, in some cases, reversible. China’s urbanization and modernization processes have profoundly altered residents’ lifestyles; factors such as unhealthy dietary patterns, insufficient physical activity, and increased psychological stress have collectively led to a significant rise in obesity and T2DM prevalence. Obesity or excessive weight gain is considered the most important and significant risk factor for

the development and progression of T2DM across all age groups, and it has reached epidemic proportions [4]. Research projections for T2DM in China over the next five years indicate that the prevalence, mortality, and DALYs (disability-adjusted life years) associated with T2DM will continue to rise between 2022 and 2026, suggesting that the burden of T2DM in China will continue to increase and that the situation regarding disease prevention and control remains severe [5].

The circadian rhythm is one of the most important biological pathways in humans and other mammals. The primary function of this system is to optimally prepare and adapt the organism’s physiological state to current environmental conditions; it is controlled by complex cellular pathways involving feedback loops. Desynchronization of the circadian rhythm system can have serious implications for metabolic health; such changes alter certain metabolic pathways in the body’s cells and may affect treatment outcomes, particularly for metabolic diseases such as type 2 diabetes mellitus (T2DM) [6]. This desynchronization of the circadian timing system is also referred to as circadian desynchronization or circadian misalignment. Circadian rhythm disorders can act directly on the liver or indirectly through the gut-brain axis and the gut microbiota [7]; they can also directly affect glucose and lipid metabolism [8-9], playing a significant role in the onset and progression of T2DM. T2DM can be regarded as a “disease of circadian desynchronization,” the essence of which lies in the loss of synchronization between the body’s rhythms of yin, yang, qi, and blood and the natural rhythms of the four seasons and day-night cycles. In modern medicine,

disruptions in the circadian gene network and abnormal oscillations in the gut microbiota are specific manifestations of this desynchronization at the microscopic level. These perspectives align with the principles of Traditional Chinese Medicine's time-based medicine. TCM chronobiology elucidates human physiology and pathology from the perspective of changes in natural rhythms and guides the treatment and prevention of diseases at corresponding times. Based on the holistic concept of "correspondence between heaven and humanity," TCM chronobiology integrates yin and yang, the four seasons, the Five Elements, and meridians to explore their effects on human physiology and pathology and to guide disease treatment [10]. The rhythms of the four seasons, the Ying-Wei system, Yin-Yang, and the twelve-hour cycle bear a striking resemblance to the concepts of modern circadian rhythms. From the perspective of TCM chronobiology, this paper posits that the onset of type 2 diabetes is closely linked to disruptions in circadian clock genes, the rhythms of the four seasons, the rhythms of the twelve Earthly Branches, the daily rhythms of the Nutritive and Defensive Qi, and the daily rhythms of Yin and Yang. By analyzing the temporal rhythms of the onset and progression of T2DM, this study deepens our understanding of T2DM from the perspective of TCM chronobiology and provides new insights for clinical diagnosis and treatment.

2. Overview of Traditional Chinese Medicine's Theory of Chronobiology and Type 2 Diabetes Mellitus (T2DM)

2.1 Core Theories: The Fluctuations of Yin and Yang and the Zi-Wu Flow

The cornerstone of Traditional Chinese Medicine's theory of chronobiology is the holistic concept of "correspondence between Heaven and Man." The fluctuations of the two vital energies—Yin and Yang—in the natural world constitute the most fundamental rhythms. The "Su Wen: Treatise on the True Words of the Golden Chamber" offers a succinct explanation: "From dawn to noon, it is the Yang of Heaven, the Yang within Yang..." As an integral part of the natural world, the human body's physiological activities also follow this law: Yang energy emerges during the day, while Yin energy is retained internally at night, forming a daily Yin-Yang rhythm synchronized with Heaven and Earth. This is the fundamental guarantee for the coordinated and orderly functioning of the zang-fu organs.

The theory of "Zi-Wu Flow" further concretizes these temporal rhythms, elucidating the patterns by which qi and blood flourish, wane, open, and close within the Twelve Meridians according to the hours of the day. Specifically, qi and blood flow through one meridian every two hours (one "shi" or hour), causing its function to reach a physiologically peak state during the corresponding time period. Among these, the key hours closely related to glucose metabolism include: Chen Hour (7-9 a.m., Foot Yangming Stomach Meridian, governing reception and digestion), Si hour (9-11 a.m., Foot Taiyin Spleen Meridian, responsible for transformation and transportation), and You hour (5-7 p.m., Foot Shaoyin Kidney Meridian, responsible for storing essence and governing water). This provides a core theoretical basis for understanding the functions of the zang-fu organs from a

temporal perspective and for "timed treatment."

2.2 The Pathogenesis and Temporal Characteristics of T2DM in Traditional Chinese Medicine

T2DM falls under the category of "xiaoke" in Traditional Chinese Medicine. Its core pathogenesis is "yin deficiency with dry heat," often complicated by "qi deficiency" and "blood stasis" in later stages. From the perspective of chronobiology, its essence lies in the disruption of the yin-yang and circadian rhythms.

2.2.1 Imbalance of Yin and Yang, Abnormal Wakefulness and Sleep—The Pathogenesis of Sleep Rhythm Disruption in Traditional Chinese Medicine

The alternation between wakefulness and sleep is the most direct manifestation of the smooth transformation of the body's Yin and Yang qi. The "Ling Shu: Chapter on the Convergence of Nutritive and Defensive Qi" states: "Defensive qi circulates through the Yang channels twenty-five times... and stops at the Yin." Patients with T2DM often experience sleep disturbances characterized by "inability to concentrate during the day and inability to sleep soundly at night," which results from an imbalance of yin and yang and disharmony between the nutritive and defensive qi. When yin fails to contain yang at night, insomnia occurs, and over time, this depletes yin fluids; when yang fails to rise during the day, mental lethargy and reduced activity ensue, further impeding the flow of yang qi. This vicious cycle can lead to dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system excitation, thereby exacerbating insulin resistance (IR) [11], which aligns with the TCM understanding that "yin deficiency generates internal heat," which in turn aggravates the pathogenesis of "xiao ke" (thirst and wasting syndrome). Zhang Naiwen [12] and colleagues also analyzed the mechanisms by which circadian clock genes regulate circadian rhythms and the relationship between these mechanisms, the theories of yin and yang and ying-wei, and circadian rhythms. They found that these concepts are interconnected and mutually reinforcing. This not only points the way toward an integrated understanding of circadian rhythms from both TCM and Western medicine perspectives but also provides important insights for TCM treatments that regulate sleep through circadian clock genes.

2.2.2 The Influence of Seasonal Rhythms on T2DM

The seasonal fluctuations in cold and warmth represent the annual cyclical rhythms of the growth and decline of yin and yang in nature. The "Su Wen: Treatise on the Eight Correct Principles and Divine Clarity" emphasizes that "the four seasons... should be regulated in accordance with their respective times." The "Wai Tai Mi Yao" also records that xiaoke "begins in the seventh and eighth months, peaks in the eleventh and twelfth months, and subsides in the second and third months." Modern research has found that the prevalence and control rates of type 2 diabetes (T2DM) exhibit seasonal variations. The control rate of T2DM tends to rise as temperatures increase, while it is lower during cold winters [13]. This is because winter cold can suppress the thermogenic activity of brown adipose tissue, leading to

impaired glucose utilization; consequently, blood glucose levels in T2DM patients are often higher in winter than in summer [14-16]. Furthermore, the incidence of various Traditional Chinese Medicine (TCM) syndrome patterns (such as “damp-heat oppressing the spleen” and “dry-heat injuring the lung”) also exhibits seasonal peaks [17], suggesting that climatic factors across the four seasons may contribute to the onset and progression of T2DM by influencing the body’s yin-yang, qi, and blood states.

Apart from general influences of cold and heat, the “Su Wen: Treatise on the Correspondence of Zang-Qi with the Seasons” states: “If the disease is in the kidney, recovery occurs in spring; if it does not recover in spring, it worsens in late summer; if the patient survives late summer, the condition persists into autumn and resurfaces in winter.” In the later stages of T2DM, the kidneys are often affected; therefore, the progression of the disease may be related to the Five Elements’ cycle of generation and restraint in the annual climate. For example, in years dominated by Damp Earth (Taiyin Ruling Heaven) or Ministerial Fire (Shaoyang Ruling Heaven), the pathogenic mechanisms of damp-heat or dry-heat in T2DM may be exacerbated. This represents a promising direction for future in-depth research that can be validated in conjunction with meteorological medicine.

2.2.3 Disruption of the Circadian Rhythm of Spleen and Stomach Function

The spleen’s function of transformation and transportation and the stomach’s function of receiving and holding food exhibit distinct circadian rhythms, as described by the saying “the stomach at Chen, the spleen at Si.” Irregular eating habits, such as skipping breakfast or eating late-night snacks, directly disrupt this physiological rhythm, leading to “the spleen failing to disperse essence.” This results in abnormal distribution of the essence derived from food and drink, causing stagnation in the middle jiao, which transforms into turbid pathogens (manifesting as hyperglycemia). From a modern medical perspective, this disrupts the synchrony of the biological clocks in peripheral metabolic organs such as the liver and pancreas, leading to impaired glucose tolerance and abnormal insulin secretion rhythms—providing a modern explanation for “the spleen’s failure to transport and transform.”

When the spleen fails to function properly, the rhythm of the stomach’s ability to receive and digest food is disrupted. Poor dietary habits—such as skipping breakfast or eating late-night snacks—directly violate the transformative principle of “the stomach at Chen, the spleen at Si,” leading to abnormal distribution of essential nutrients, which accumulate as turbid pathogens (hyperglycemia).

The “Ling Shu: Ben Zang” states: “When the spleen is fragile, one is prone to wasting diseases and easily injured.” which indicates a close relationship between spleen-stomach deficiency and T2DM. Leng Yulin [18] et al. propose that “stagnation of spleen qi—impaired transformation and transportation” and “deficiency of spleen qi—inadequate transformation and transportation” lead to abnormalities in the ascending and descending functions, and the failure to distribute essential nutrients—constitute the fundamental

pathogenesis of pancreatic islet dysfunction in diabetes. These are closely related to the core mechanisms of β -cell “silencing” and “identity loss.” They propose therapeutic approaches such as tonifying spleen qi, nourishing spleen yin, unblocking spleen collaterals, and transforming spleen turbidity to comprehensively restore the spleen’s transport and transformation functions. This aims to reshape the fate of islet cells, maintain β -cell identity, improve pancreatic islet dysfunction, and restore blood glucose homeostasis. Li Chixiang et al. [19] found that the key pathogenesis of insulin resistance (IR) is “the spleen’s failure to disperse essence”; the function of insulin in breaking down glucose to release energy for cellular activity aligns closely with the spleen’s function of transporting and transforming the essence of food and drink.

As stated in “Treatise on the Spleen and Stomach”: “Deficiency of the spleen and stomach leads to lethargy, a tendency to lie down, and weakness in the limbs.” Since the spleen governs the muscles, weakness of the spleen and stomach impedes the smooth circulation of fluids and dampness, facilitating the accumulation of phlegm and fluid retention within the body. This manifests as excessive fat deposition in skeletal muscles, forming “fat toxicity,” which induces apoptosis of pancreatic β -cells, exacerbates IR, and thereby accelerates the onset and progression of T2DM [20]. This violation of the principle of “eating only at the proper times” directly disrupts the synchrony of peripheral circadian rhythms in the liver, pancreas, and intestines [21-22], leading to impaired glucose tolerance and abnormal insulin secretion rhythms. From a modern scientific perspective, this explains why “the spleen’s failure to transport and transform, resulting in the stagnation of essence and nutrients” manifests as uncontrolled postprandial blood glucose levels.

2.2.4 Disruption of the Daily Rhythm of Kidney Yin and Yang

According to the theory of “the circulation of qi and blood,” the Hour of You (5:00-7:00 p.m.) corresponds to the Kidney Meridian, during which Kidney Yin and Kidney Yang transition. If a patient suffers from deficiency of Kidney essence (particularly insufficiency of Kidney Yin), they lack the capacity to maintain stable blood glucose levels during this critical transition, resulting in peak blood glucose fluctuations. This aligns with the mechanism of the “twilight phenomenon” [23] observed in modern medicine—where basal insulin secretion begins to decline in the evening and glucose tolerance is impaired—suggesting that the approach of “tonifying the kidneys and consolidating the root” may help stabilize blood glucose levels at dusk.

The “Xiaopin Fang: Formulas for Treating Thirst and Promoting Diuresis” records: “In cases of xiaoke (thirst), tracing its origin reveals that it is caused by kidney deficiency.” Deficiency of kidney yin fails to restrain the “ministerial fire,” and the upward surge of “deficient fire” exacerbates “dry heat”; insufficiency of kidney yang fails to facilitate the transformation and transportation of qi, which can also lead to abnormalities in fluid metabolism. The kidneys are the “organ of water” and the “source of yin fluids”; when kidney yin is deficient, “deficient fire” arises internally. When this fire ascends to affect the heart and lungs, it causes restlessness,

thirst, and excessive drinking; when it scorches the spleen and stomach, it leads to rapid digestion and frequent hunger, manifesting as “thirst and wasting disease.” Sun Ding et al. [24] through a study of the dynamic blood glucose “Hurst index” and the characteristics of blood glucose fluctuations in T2DM at different times of the day, found that the “Kidney hour” is a critical juncture at which blood glucose fluctuations begin to become unstable. Zhang Cuiping et al. [25] also observed the patterns of dynamic blood glucose changes across the 12 traditional Chinese time periods and found that during the You hour (Kidney), both the mean blood glucose level (MBG) and the standard deviation of blood glucose fluctuations (SDBG) were most pronounced, indicating that blood glucose fluctuations were greatest at this time. This conclusion is consistent with the findings of Men Yu et al [26].

3. Chronobiology Provides Evidence for the Multi-Layered Mechanism of Traditional Chinese Medicine’s Theory of Temporal Sequences

Circadian genes, gut microbiota circadian oscillations, and the gut-brain axis do not simply correspond one-to-one with the concepts of yin and yang or the spleen and stomach in Traditional Chinese Medicine (TCM). Rather, they provide objective, material evidence for the TCM theory of organ rhythms at three levels—molecular, microbiome, and neuroendocrine—while also distinguishing between two independent pathways: primary circadian rhythm damage and circadian rhythm disruption secondary to hyperglycemia.

3.1 Circadian Gene Network: The Molecular Carrier of the Rhythmic Fluctuations of Yin and Yang in the Human Body

The mammalian circadian system consists of the central master clock in the hypothalamic SCN and peripheral clocks in the liver, islets, muscles, and adipose tissue. At the cellular level, 24-hour autonomous oscillations are maintained by the BMAL1/CLOCK-PER/CRY transcriptional and translational negative feedback loop [27]. In this loop, BMAL1 and CLOCK proteins form a heterodimer, acting as core activators to initiate the transcription of period genes (*Per1*, *Per2*) and cryptochrome genes (*Cry1*, *Cry2*), among others. Subsequently, PER and CRY proteins accumulate in the cytoplasm and form complexes; upon entering the nucleus, they inhibit the transcriptional activity of BMAL1/CLOCK, thereby completing an oscillatory cycle of approximately 24 hours [28-30]. This precise molecular oscillatory system, with its dynamic, self-sustaining, and mutually regulating characteristics, exhibits profound systemic isomorphism with the philosophical concepts of “the balance of the waxing and waning of yin and yang” and “the mutual containment of yin and yang” in Traditional Chinese Medicine. Peaks in BMAL1/CLOCK-driven gene expression typically occur during the day (the active phase), analogous to the “growth of yang,” while the accumulation of PER/CRY and the peak of their inhibitory activity typically occur at night (the resting phase), resembling the “growth of yin.” Pancreatic β -cells possess their own independent circadian clock; downregulation of the central clock gene BMAL1 and attenuation of rhythmic

oscillations directly reduce the ability to secrete insulin in response to glucose stimulation, inducing impaired glucose tolerance, which further disrupts secretory rhythms and peripheral circadian clocks, thereby inducing or exacerbating T2DM [31-33].

3.2 Circadian Oscillations in the Gut Microbiome: A Microecological Extension of the Transport and Metabolism Functions of the Spleen and Stomach

The gut microbiota is often referred to as the “forgotten organ,” and its composition and function exhibit significant circadian rhythmic fluctuations. These fluctuations are regulated, on the one hand, by the host’s central clock through mechanisms such as feeding behavior and hormone secretion; on the other hand, the microbiota itself possesses a relatively independent oscillator and can influence the host’s circadian rhythm through metabolic byproducts [34-35]. When the interaction between the gut microbiota and the circadian clock is disrupted, it leads to metabolic disorders such as obesity and insulin resistance (IR), thereby accelerating the onset of type 2 diabetes mellitus (T2DM) [36]. Reitmeier et al. [37] found that in individuals with T2DM, various bacterial genera—including *E. coli*, *Bacteroides*, *Bifidobacterium*, *Faecalibacterium*, *Prevotella*, *Ruminococcus*, and others—exhibited varying degrees of loss of rhythmicity. This is consistent with research findings showing that both high-fat diet (HFD)-induced obesity and circadian rhythm disruption can lead to dysbiosis of the gut microbiota and the disappearance or phase shift of circadian oscillations in its metabolites (such as short-chain fatty acids, SCFAs) [35-38]. Through its rhythmic fermentation, the gut microbiota produces beneficial metabolites such as SCFAs and participates in the host’s energy metabolism, regulation of insulin sensitivity, and maintenance of immune homeostasis; this can be regarded as an indispensable microecological link in the generation and transformation of “the essence of food and drink.”

The function of the “spleen governing transformation and transport” in Traditional Chinese Medicine refers not only to the host’s digestion and absorption of food and drink but should also encompass the synergistic metabolic processes with the gut microbiota. Therefore, abnormalities in microbial oscillations can lead to insufficient generation of “essence and subtleties” or impaired distribution, thereby triggering disorders in glucose and lipid metabolism. From a microecological perspective, this profoundly elucidates the modern scientific significance of the core pathogenesis of T2DM: “When the spleen fails to transport and transform, the ‘essence and subtleties’ become stagnant.”

3.3 The Gut-Brain Axis: A Neuroendocrine Bridge Linking the “Spleen and Stomach” to “Mental State”

The gut and the brain share a unique connection, including endocrine signals released by gut hormones, signaling molecules secreted and released by gut microbiota to the brain, and neural information transmitted via the vagus nerve and spinal afferent neurons in the gastrointestinal tract [39-40]; for this reason, the gut is also referred to as the “second brain.” Research has shown that the brain, by modulating neuronal activity, can regulate metabolic functions such as heat

production and glucose utilization in tissues [41], while lipids [42] and glucose [43] can activate afferent nerves in the intestinal wall. Pheromones facilitate communication between the brain and the gut, forming the microbiome-gut-brain axis (MGB).

The gut-brain axis is a complex bidirectional communication system that encompasses neural, endocrine, and immune pathways. As the largest peripheral endocrine organ, the gastrointestinal tract's epithelial endocrine cells respond to nutritional stimuli by rhythmically secreting various gut-derived hormones, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These hormones not only regulate insulin secretion peripherally through the "enteroinsulin effect" but also transmit signals to the central nervous system via pathways such as the vagus nerve, thereby modulating appetite, energy metabolism, and even mood [44].

This mechanism provides a modern scientific interpretation of the Traditional Chinese Medicine (TCM) theory that "the spleen and stomach are related to mental states." According to TCM, the spleen is associated with the mental state of "thought," and "excessive worry damages the spleen"; conversely, "if the stomach is not harmonious, sleep is disturbed." The brain is considered the "residence of the primordial spirit," but its functional activities depend on the "pure yang qi" generated by the spleen and stomach's transformation and transportation of food and drink, which ascends to nourish it. From the perspective of meridians, both the Hand Yangming Large Intestine Meridian and the Hand Taiyang Small Intestine Meridian ascend to connect with the head and face; functionally, the heart and small intestine are paired as exterior-interior organs and jointly govern mental states. The bidirectional communication along the gut-brain axis provides a complete neuroendocrine biological pathway that substantiates the classical understanding that "the state of the spleen and stomach (intestines) influences the mind (brain)," and "emotional fluctuations (brain) affect the function of the spleen and stomach."

4. Prospects for T2DM Strategies Based on Traditional Chinese Medicine's Chronobiology

Based on the aforementioned pathogenesis theory of "rhythmic desynchronization," this paper proposes a new paradigm for the prevention and treatment of T2DM centered on "adapting to the time of day—differentiating organ functions—regulating symptoms." The core of this paradigm lies in restoring the synchrony between endogenous rhythms and the external environment through comprehensive chronobiological interventions, thereby restoring metabolic homeostasis. Its specific strategies encompass the following aspects:

4.1 Adapting Daily Routines to the Time of Day, in Accordance with Yin and Yang—Consolidating Fundamental Rhythms

The primary strategy is to regulate daily routines by strictly adhering to nature's cycles of light and darkness. Adequate, high-quality sleep at night should be ensured, and exposure to

blue light at night (especially before bedtime) should be minimized as much as possible. This measure aims to strengthen the rhythmic output of the suprachiasmatic nucleus (SCN) in the hypothalamus—the master clock that serves as the "framework" for regulating the physiological rhythms of all bodily systems—and is highly consistent with the supreme principles of TCM health preservation: "regulating the spirit" and "harmonizing with Yin and Yang."

4.2 Timed Eating to Align with the Flow of Qi — Coordinating Metabolic Rhythms

Dietary interventions should align closely with the principles of the "Zi-Wu Flow of Qi." The core principle is "eat heartily during the Chen hour and lightly after the You hour." That is, in the morning (7-11 a.m.) when the Stomach and Spleen meridians are dominant—particularly during the Chen hour (7-9 a.m.)—consume a nutritionally balanced breakfast to activate and optimize the daytime metabolic engine. This aligns with findings from modern "time-restricted eating" studies, which show that shifting the eating window to daytime improves blood glucose levels. Conversely, one should avoid heavy meals after You hour (5-7 p.m.), when the Kidney Meridian is dominant and yang energy is contracting, to reduce the burden on metabolic organs such as the liver and pancreas during the night. This creates a rhythmic window for their repair and detoxification, helping to stabilize fasting blood glucose levels.

4.3 Timed Medication and Acupuncture—Precision Targeting of Circadian Rhythms

Chrono pharmacology can be combined with the theory of the Twelve Meridians' Circulation to explore "timed therapy." For example, for patients with T2DM presenting with the pattern of spleen deficiency with dampness obstruction, consider administering formulas to strengthen the spleen and transform dampness during the Si hour (9:00-11:00 a.m.), when qi and blood in the Spleen Meridian are at their peak; for patients with the pattern of liver and kidney yin deficiency, choose to administer herbs that nourish water and support wood during the You hour (5:00-7:00 p.m.), when the Kidney Meridian is dominant. In acupuncture treatment, methods such as the "Na Zi Fa" (timing-based needling) can also be employed to select acupoints on the corresponding meridians at specific times (e.g., needling Zusanli and Sanyinjiao on the Spleen Meridian during the Spleen Meridian's active period) [45] to enhance therapeutic efficacy. This embodies the therapeutic principle of "going with the flow" and holds promise for improving the precision and efficiency of interventions. However, the efficacy of such therapies still needs to be validated through rigorously designed, large-scale randomized controlled trials (RCTs).

4.4 Time-Series Microbiome Interventions—Regulating Microbiome Rhythms

Future research could explore new intervention approaches based on microbiota rhythms. For example, supplementing specific probiotics or prebiotics at specific times (such as before meals) may produce synergistic effects with the host's inherent dietary rhythms and circadian clock, more effectively reshaping the beneficial diurnal oscillations of the gut

microbiota and thereby indirectly improving the host's glucose metabolism. This represents a deepening and expansion of the "Treatment Based on the Spleen" approach at the microbiome level.

5. Conclusion and Outlook

Based on the holistic and dynamic perspectives of Traditional Chinese Medicine (TCM) chronobiology, this paper systematically integrates the latest advances in modern chronobiology—including research on circadian clock genes, the gut microbiota, and the gut-brain axis—to construct a "multi-level rhythmic dysregulation" model for understanding type 2 diabetes (T2DM). This model attributes the essence of T2DM to the desynchronization of endogenous biological rhythms with natural and social rhythms, with the core pathogenesis in TCM lying in the "disruption of the temporal sequence of spleen and kidney functions." This framework not only provides a profound modern scientific interpretation of classical TCM theories such as "harmony between heaven and man" and "Yin-Yang rhythms," but more importantly, it has given rise to a highly promising new paradigm for prevention and treatment—"timing-based organ differentiation and syndrome regulation"—thereby advancing the approach to T2DM prevention and treatment from a static "differentiation of syndromes and treatment" to a dynamic "differentiation of time and treatment."

Future research could be further developed in the following areas: First, advancing research on the objectification and quantification of "temporal syndromes." By comprehensively utilizing wearable devices such as continuous glucose monitoring (CGM) and activity trackers, combined with biological sample collection at multiple time points, researchers can quantitatively analyze differences in rhythmic parameters (such as amplitude, peak phase, and rhythmic stability) among patients with different TCM syndrome patterns of T2DM, thereby introducing objective temporal-dimension indicators into TCM syndrome differentiation. Second, conduct high-level clinical evidence-based research. There is an urgent need to design and implement a series of high-quality, large-sample randomized controlled trials (RCTs) to rigorously evaluate the efficacy and safety of temporal therapies—such as time-specific medication administration and acupuncture based on the "Zi-Wu Flow" theory—thereby providing robust evidence-based medical support for their clinical application. Third, construct a multi-omics integrated circadian network model. Using systems biology methods, we will integrate multi-omics data—including genomic, transcriptomic, metabolomic, and metagenomic data—to construct a dynamic, cross-scale network model spanning "macro (environment) - holistic (human systems) - micro (molecular/microbial)" levels, thereby more systematically elucidating the complex mechanisms by which circadian rhythm disruption contributes to the onset and progression of T2DM.

Through these efforts, we hope to ultimately advance the prevention and treatment of T2DM into a new phase of "precision chronobiological medicine," opening up broader prospects for the integrated prevention and treatment of metabolic diseases using both traditional Chinese and Western medicine.

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