Journal of Biosciences and Medicines, 2026, 14(8), 294-314
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Pathophysiological Mechanisms of Early-Onset Type 2 Diabetes Mellitus Complicated with Hypertension and the Potential Prognostic Value of Clinical Indicators

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How to cite this paper: Hu, L.Y. and Zhong, W. (2026) Pathophysiological Mechanisms of Early-Onset Type 2 Diabetes Mellitus Complicated with Hypertension and the Potential Prognostic Value of Clinical Indicators. *Journal of Biosciences and Medicines*, **14**, 294-314.
https://doi.org/10.4236/jbm.2026.148026

Received: July 26, 2026
Accepted: August 24, 2026
Published: August 27, 2026

Abstract

The global prevalence of early-onset type 2 diabetes mellitus (Early-Onset T2DM, diagnosed at age < 40 years) has risen sharply over the past two decades, becoming a severe public health challenge. Once this group develops early hypertension, it causes a "double hit" effect that damages target organs, accelerating large and small vessel complications, and leading to worse long-term outcomes compared to those who develop type 2 diabetes later. This review narratively elaborates on the deep pathophysiological mechanisms of early-onset T2DM comorbid with hypertension, including insulin resistance-driven endothelial dysfunction, overactivation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), chronic low-grade inflammation mediated by visceral adipose accumulation, and the potential role of early-life determinants (such as epigenetic modifications). On this basis, we review the epidemiological associations between routine clinical indicators—including age at diagnosis, BMI, waist circumference, weight-change trajectories, HbA1c, lipid profiles, uric acid, liver and kidney function indicators, and systemic inflammatory markers—and incident hypertension among initially normotensive patients with early-onset T2DM. This article brings together evidence from several large cohort studies, including real-world databases like NHANES, CHARLS, ELSA, and MIMIC, showing that dynamic changes tracked using routine clinical indicators, such as blood sugar variability and blood pressure trends, have significant predictive value for long-term cardiovascular and kidney outcomes. Finally, this article looks at the challenges and opportunities of turning these traditional indicator-based prediction strategies into real-world primary care practice, giving a full view of how we've moved from deep mechanistic re-

search to practical ways of assessing risk.

Keywords

Early-Onset Type 2 Diabetes Mellitus, Hypertension, Insulin Resistance, Clinical Indicators, Predictive Value, Pathophysiological Mechanisms

1. Introduction

Type 2 diabetes mellitus (T2DM) has traditionally been regarded as a chronic metabolic disease of middle-aged and elderly populations. However, over the past twenty years, due to environmental factors like the global obesity epidemic, sedentary lifestyles, and Western eating habits, the age at which T2DM starts has been noticeably getting younger. Early-onset type 2 diabetes mellitus (Early-Onset T2DM) is generally defined as T2DM diagnosed before the age of 40, and its global prevalence is increasing at an alarming rate, particularly prominent among Asian populations. It's estimated that around 10% - 15% of newly diagnosed T2DM cases worldwide are early-onset, and this number might be even higher in some low- and middle-income countries [1]-[3].

Early-onset T2DM basically differs from late-onset T2DM in terms of how it progresses, metabolic traits, and types of complications. Compared to those who develop T2DM later, people with early-onset tend to have worse insulin resistance (IR), faster decline in beta-cell function, and earlier and quicker development of microvascular and macrovascular complications. Of particular concern, high blood pressure—as one of the most common conditions alongside T2DM—is much more common in people who develop T2DM early compared to non-diabetic people of the same age, happening sooner and more severely. This early comorbidity of early-onset T2DM and hypertension constitutes a "Dual Hit" effect—hyperglycemia and hypertension synergistically exacerbate endothelial injury and vascular remodeling, leading to accelerated progression of target organ (heart, kidney, brain, and retina) damage, exposing patients to significantly elevated risks of cardiovascular events, end-stage renal disease, and all-cause mortality at a relatively young age [4]-[7].

Currently, risk identification for early-onset T2DM complicated with hypertension in clinical practice mainly relies on the assessment of conventional clinical indicators—including demographic characteristics, anthropometric measurements, routine biochemical tests, and baseline blood pressure monitoring. These indicators are readily accessible in medical institutions at all levels, with low cost and broad potential for widespread implementation. However, the associations of these conventional indicators with incident hypertension and, separately, with target-organ outcomes among patients with established hypertension have not been systematically reviewed in the early-onset T2DM population. Furthermore, in recent years, large clinical cohorts (such as the US National Health and Nutri-

tion Examination Survey [NHANES], the China Health and Retirement Longitudinal Study [CHARLS], and the English Longitudinal Study of Ageing [ELSA]) and real-world electronic medical record databases (such as MIMIC) have provided important data foundations for exploring the association between longitudinal trajectories of conventional clinical indicators and long-term outcomes [8] [9].

In this review, incident hypertension among initially normotensive patients with early-onset T2DM is considered the primary outcome, whereas cardiovascular, renal, and other target-organ outcomes among patients with established hypertension are considered secondary outcomes. This review aims to: 1) narratively elaborate on the core pathophysiological mechanisms of early-onset T2DM complicated with hypertension; 2) review the correlations between conventional clinical indicators and this comorbidity state; 3) examine their associations with incident hypertension among initially normotensive patients and, separately, with cardiovascular and renal outcomes among patients with established hypertension; and 4) discuss the challenges and prospects of applying these indicator-based risk-assessment strategies in primary care clinical practice.

2. Pathophysiological Mechanisms

2.1. Insulin Resistance and Endothelial Dysfunction

IR is the core metabolic abnormality of early-onset T2DM and also serves as the key pathophysiological link connecting glucose metabolism disorders with hypertension. In the normal insulin-sensitive physiological state, insulin promotes the synthesis and release of nitric oxide (NO) in endothelial cells by activating the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway, thereby mediating vasodilation, inhibiting vascular smooth muscle cell proliferation, reducing platelet aggregation, and suppressing adhesion molecule expression—these effects are collectively referred to as the "vasoprotective" functions of insulin [10] [11].

However, in the insulin-resistant state, selective impairment of the PI3K/Akt pathway leads to reduced phosphorylation of endothelial nitric oxide synthase (eNOS) and significantly decreased NO bioavailability, while the mitogen-activated protein kinase (MAPK)/endothelin-1 (ET-1) pathway in insulin signaling is compensatorily enhanced, resulting in the predominance of vasoconstrictive, pro-inflammatory, and pro-proliferative effects. This "pathway-specific resistance" of insulin signaling leads to endothelial dysfunction—manifested as impaired endothelium-dependent vasodilation, increased vascular permeability, and a pro-inflammatory and pro-thrombotic state. Endothelial dysfunction is not only one of the initiating factors of hypertension but also a key driver of accelerated target organ damage after early-onset T2DM is complicated with hypertension [12] [13].

In the early-onset T2DM population, the severity of IR typically exceeds that of late-onset patients, which may be related to more pronounced obesity, lower levels of physical activity, and a more unfavorable visceral fat distribution pattern in younger patients. Moreover, the compensatory capacity of β-cell function for IR

in early-onset patients tends to fail within a relatively short period, leading to an earlier onset of significant hyperglycemia, which in turn further deteriorates endothelial function through the formation of advanced glycation end products (AGEs), activation of protein kinase C (PKC), and exacerbation of oxidative stress. Therefore, the vicious cycle formed by IR and hyperglycemia in early-onset T2DM patients accelerates the transition from endothelial dysfunction to clinical hypertension [4] [14].

2.2. Overactivation of the Sympathetic Nervous System and RAAS

Overactivation of the sympathetic nervous system (SNS) plays a central role in the pathogenesis of early-onset T2DM complicated with hypertension. Obesity-related IR can drive increased central sympathetic outflow through multiple mechanisms, including direct stimulation of the hypothalamic sympathetic center by hyperinsulinemia, the promoting effect of elevated leptin levels from adipose tissue on sympathetic activity, and chemoreflex-mediated sympathetic activation due to intermittent hypoxia caused by obstructive sleep apnea (OSA)—which is highly prevalent in obese T2DM patients. In the early-onset T2DM population, long-term obesity exposure and greater metabolic burden make SNS overactivation more pronounced, and this activation begins at an earlier age, leading to a longer duration of cumulative damage to the cardiovascular system [15] [16].

Abnormal activation of the renin-angiotensin-aldosterone system (RAAS) is another core pathway in the comorbidity of T2DM and hypertension. The classical view holds that hyperglycemia and hyperinsulinemia can stimulate the juxtaglomerular apparatus to secrete renin, thereby activating the circulating RAAS. However, recent studies have revealed the key role of local tissue RAAS—especially adipose tissue RAAS—in metabolic-blood pressure interactions. Visceral adipose tissue (VAT) in obese individuals abundantly expresses angiotensinogen, renin, angiotensin-converting enzyme (ACE), and angiotensin II type 1 receptor (AT1R), constituting an independent local RAAS. Adipose tissue-derived angiotensin II (Ang II) not only directly constricts blood vessels, promotes aldosterone secretion, and enhances renal sodium reabsorption via AT1R, but also acts as a potent pro-inflammatory and pro-fibrotic factor, aggravating IR and endothelial injury, thus forming a positive feedback loop of IR-RAAS activation-IR exacerbation [17] [18].

Notably, there exists a multi-level bidirectional reinforcing relationship between SNS and RAAS: norepinephrine released from sympathetic nerve endings stimulates β1-adrenergic receptors in the juxtaglomerular apparatus to promote renin release, while Ang II in turn enhances sympathetic activity through central and peripheral mechanisms. In the context of early-onset T2DM complicated with obesity, the SNS-RAAS positive feedback loop is overactivated, driving sustained blood pressure elevation and accelerated progression of target organ damage [15].

2.3. Visceral Fat Accumulation and Chronic Low-Grade Inflammation

Excessive accumulation of visceral adipose tissue (VAT) represents the common soil for early-onset T2DM and hypertension. Unlike subcutaneous adipose tissue, VAT has greater lipolytic activity, richer vascular and nerve supply, and a more pronounced capacity for pro-inflammatory cytokine secretion. In early-onset T2DM patients, significant VAT accumulation occurs at a younger age, and its metabolic consequences are far more severe than simple overall obesity alone [19] [20].

VAT-mediated chronic low-grade inflammation is the core immune-metabolic mechanism connecting obesity, IR, and hypertension. Hypertrophic adipocytes and infiltrating macrophages—especially M1 pro-inflammatory macrophages—secrete large amounts of pro-inflammatory factors such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and resistin, while reducing the secretion of adiponectin and other adipokines with insulin-sensitizing and vasoprotective effects. TNF-α and IL-6 directly interfere with serine phosphorylation of insulin receptor substrate-1 (IRS-1) by activating the c-Jun N-terminal kinase (JNK) and inhibitor of nuclear factor-κB (NF-κB) kinase β (IKKβ) pathways, thereby impairing insulin signal transduction and aggravating systemic IR [21] [22].

At the vascular level, pro-inflammatory cytokines promote the expression of endothelial cell adhesion molecules, recruit monocytes to infiltrate the vascular wall, and accelerate the initiation and progression of atherosclerosis. Furthermore, TNF-α and IL-6 can directly inhibit the activity and expression of eNOS, reduce NO production, and increase the generation of reactive oxygen species (ROS), leading to further impairment of endothelium-dependent vasodilation. Importantly, these inflammatory factors can also directly or indirectly activate SNS and RAAS, and comprehensively participate in blood pressure elevation and maintenance by promoting renal sodium retention and vascular remodeling [16] [21].

In the early-onset T2DM population, due to greater obesity severity and longer obesity duration (often beginning in adolescence or even childhood), VAT-related chronic inflammation is not only more intense but also has a longer "exposure duration," leading to cumulative cardiovascular damage far exceeding that of late-onset patients. This long-term inflammatory "exposure window" beginning in young adulthood may be one of the important explanations for the "dual hit" effect and accelerated target organ damage in early-onset T2DM patients with hypertension [23].

2.4. Early-Life Determinants and Epigenetics

The "Developmental Origins of Health and Disease" (DOHaD) hypothesis provides a life-course perspective for understanding the pathogenesis of early-onset T2DM complicated with hypertension. Adverse in utero environmental expo-

sures—including maternal malnutrition during pregnancy, maternal obesity, gestational diabetes mellitus (GDM), and maternal stress—can exert lasting effects on the offspring's metabolic phenotype and cardiovascular function through "fetal programming" mechanisms [24] [25].

Epigenetic modifications—mainly including DNA methylation, histone modifications, and non-coding RNA regulation—are considered the core molecular mechanisms mediating the "fetal programming" effect. The intrauterine hyperglycemic environment (such as GDM exposure) can induce persistent changes in DNA methylation patterns of key metabolic and vascular function genes in multiple tissues of the offspring (including pancreatic islets, liver, adipose, and vascular tissues). For example, promoter hypermethylation of peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α)—a key regulator of mitochondrial biogenesis and oxidative metabolism—can persist into the offspring's adulthood, leading to lifelong reduction in skeletal muscle insulin sensitivity. Similarly, genes related to RAAS components, endothelial function, and sodium handling may also be "programmed" through epigenetic mechanisms into a state that promotes hypertension development [26].

Moreover, the lifestyle behaviors of early-onset T2DM patients (such as high-calorie diet, physical inactivity, and circadian rhythm disruption) can themselves further aggravate metabolic and blood pressure abnormalities through epigenetic mechanisms. For example, both high-fat diet and physical inactivity can alter DNA methylation and histone acetylation patterns of key metabolic genes in adipose tissue and skeletal muscle, leading to overactivation of inflammatory pathways and sustained suppression of insulin signaling [26].

It should be noted that epigenetic modifications have a certain degree of reversibility, which provides a theoretical basis for early identification and intervention. However, translating epigenetic biomarkers into clinical risk prediction tools for early-onset T2DM complicated with hypertension still faces many challenges, including limitations of tissue specificity, insufficient longitudinal stability, and high detection costs.

3. Correlation of Conventional Clinical Indicators

3.1. Age at Diagnosis and Anthropometric Indicators

Age at diagnosis is the most direct indicator distinguishing early-onset from late-onset T2DM, and younger age at diagnosis has been independently associated with a higher risk of T2DM complications and adverse long-term outcomes. Multiple large-scale cohort studies consistently show that younger age at T2DM diagnosis is closely associated with higher cardiovascular disease (CVD) risk and all-cause mortality. Hillier and Pedula's study based on the Kaiser Permanente Northwest database found that for every 10-year decrease in T2DM diagnosis age, the risk of microvascular complications significantly increased. A long-term follow-up study by Constantino *et al.* in Australia of 354 young-onset T2DM patients showed that patients diagnosed before age 40 had more than a two-fold increase

in cardiovascular mortality risk compared to those diagnosed after age 40. Recently, the Swedish National Diabetes Registry study (Rawshani *et al.*, 2018) further confirmed that the earlier the age of T2DM diagnosis, the higher the excess cardiovascular risk and all-cause mortality, with this effect being particularly prominent in the subgroup diagnosed before age 40 [27]-[29].

A large cohort study by Sattar *et al.* using Swedish national registry data found that when early-onset T2DM (age < 40 years) coexists with higher body mass index (BMI), patients' cardiovascular and all-cause mortality risks exhibit a significant synergistic increasing effect. This finding emphasizes the importance of jointly considering age at diagnosis and obesity indicators when assessing cardiovascular risk in early-onset T2DM patients [7].

Body mass index (BMI) and waist circumference (WC), as routine anthropometric indicators, have important risk stratification value in the early-onset T2DM population. BMI reflects the degree of overall obesity, while WC more directly reflects the degree of VAT accumulation—which is more closely associated with IR and hypertension. The International Diabetes Federation (IDF) and AHA/NHLBI joint statement lists elevated WC as a core component of metabolic syndrome and explicitly states that WC is an independent predictor of IR and cardiovascular risk [19] [30].

In the special context of early-onset T2DM, the clinical significance of BMI and WC needs to be interpreted from a longer-term exposure perspective. Compared with late-onset patients, early-onset patients often develop significant overweight/obesity as early as childhood or adolescence, with a longer obesity "exposure duration" and more severe cumulative damage to the metabolic and cardiovascular systems. Furthermore, even when early-onset T2DM patients have similar BMI levels to late-onset patients, their body fat distribution pattern may be more unfavorable—manifesting as a higher visceral-to-subcutaneous fat ratio, which is significantly associated with more severe IR, more pronounced inflammatory status, and higher blood pressure levels [20] [23].

Longitudinal weight change trajectories have received increasing attention in recent years. Weight gain or loss over time not only reflects dynamic changes in lifestyle but also reveals the evolutionary trends of an individual's metabolic adaptive capacity and cardiovascular risk. For early-onset T2DM patients, post-diagnosis weight fluctuation—especially weight gain—is independently associated with elevated blood pressure levels and worsening of blood pressure control. Longitudinal analysis based on CHARLS data suggests that there is a close association between BMI change trajectories and hypertension incidence and cardiovascular event risk in the Chinese middle-aged and elderly population, and this relationship may be more significant in younger groups [8].

3.2. Blood Glucose-Related Indicators

Glycated hemoglobin (HbA1c), as the gold standard indicator reflecting the average blood glucose level over the past 2 - 3 months, has dual value in the risk as-

sessment of early-onset T2DM complicated with hypertension. On one hand, HbA1c directly reflects the overall level of glycemic control—large randomized controlled trials (UKPDS, ACCORD, ADVANCE, and VADT) have all confirmed the association between high HbA1c levels and increased risk of microvascular complications (including diabetic nephropathy—an important secondary cause of hypertension) and some macrovascular events. On the other hand, persistently elevated or fluctuating HbA1c levels reflect long-term hyperglycemic exposure, which progressively impairs vascular endothelial function through AGEs formation, oxidative stress, and sustained activation of inflammatory cascades, indirectly contributing to blood pressure elevation and cardiovascular risk accumulation [31]-[35].

Glycemic variability (GV) is a glycemic characteristic that cannot be captured by average glucose indicators alone (such as HbA1c). Monnier *et al.*, in their landmark study, first demonstrated that acute glucose fluctuations—even when HbA1c levels are similar—trigger significantly stronger oxidative stress responses than sustained chronic hyperglycemia. Subsequent studies by Ceriello *et al.* further elucidated the direct damaging effects of glucose fluctuations on endothelial function: oscillating hyperglycemia more significantly impairs endothelium-dependent vasodilation and increases levels of oxidative stress markers and inflammatory factors in the blood compared to stable hyperglycemia [36] [37].

In the early-onset T2DM population, the clinical significance of glycemic variability is particularly prominent. Early-onset patients experience significant β-cell function decline at an earlier stage, leading to increased glycemic fluctuation amplitude, and this greater glycemic variability both reflects insufficient residual β-cell function and portends more aggressive disease progression and higher complication risk. For early-onset T2DM patients with hypertension, increased glycemic variability may further exacerbate the difficulty of blood pressure control and the risk of target organ damage by aggravating endothelial dysfunction and promoting vascular inflammation [38].

3.3. Lipid Profile and Uric Acid

Dyslipidemia is extremely common in early-onset T2DM patients, with a typical pattern including elevated triglycerides (TG), decreased high-density lipoprotein cholesterol (HDL-C), mildly elevated low-density lipoprotein cholesterol (LDL-C) predominantly composed of more atherogenic small, dense LDL particles. This "atherogenic dyslipidemia" is highly correlated with IR and is even more prominent in early-onset T2DM patients with hypertension. Dyslipidemia is associated with hypertension, and experimental evidence suggests several potentially relevant mechanisms, including endothelial dysfunction, increased vascular stiffness, enhanced vascular smooth muscle reactivity to vasoconstrictors, and impaired renal microvascular function [11] [19].

Of particular interest is the potential role of non-high-density lipoprotein cholesterol (Non-HDL-C) and remnant cholesterol—*i.e.*, TG-rich lipoproteins and

their metabolic remnants—in early-onset T2DM complicated with hypertension. A large-scale meta-analysis by the Emerging Risk Factors Collaboration showed that Non-HDL-C more comprehensively reflects the overall burden of atherogenic lipoproteins than LDL-C and has a stronger and more consistent association with vascular disease risk [39].

The value of serum uric acid (UA) as a metabolic-cardiovascular risk marker has received increasing attention over the past decade. The relationship between hyperuricemia and hypertension has been repeatedly validated in observational epidemiological studies and some mechanistic studies. The review by Feig *et al.* summarized experimental and observational evidence suggesting that uric acid may be involved in pathways relevant to hypertension, including RAAS activation, renal microvascular disease and interstitial inflammation, impaired endothelial NO synthesis, and vascular smooth muscle cell proliferation; however, these findings do not establish a causal role in humans. The systematic review and meta-analysis by Grayson *et al.* pooled data from 18 prospective cohort studies, confirming that hyperuricemia is independently associated with the risk of incident hypertension, and this association is more significant in younger populations [40] [41].

In the special group of early-onset T2DM, the prevalence of hyperuricemia is significantly higher than in age-matched non-diabetic controls. IR itself can elevate serum uric acid levels by reducing renal uric acid excretion, while high uric acid can in turn aggravate IR and endothelial dysfunction, forming a vicious cycle. Therefore, serum uric acid, as a routine biochemical indicator, not only reflects the severity of metabolic abnormalities but may also serve as an early warning signal for hypertension risk in early-onset T2DM patients [40].

3.4. Liver and Kidney Function Indicators and Inflammatory Markers

Liver function indicators—especially alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT)—are considered surrogate markers of non-alcoholic fatty liver disease (NAFLD), which is closely related to IR and VAT accumulation and is known as the "hepatic manifestation" of metabolic syndrome. Epidemiological evidence consistently shows that elevated serum ALT and GGT levels are independently associated with the risk of hypertension. The underlying mechanisms may involve systemic inflammatory release due to hepatic steatosis, excessive production of liver-derived vasoactive factors (such as angiotensinogen), and the aggravating effect of hepatic IR on systemic metabolic status [30].

Renal function indicators—serum creatinine (Cr), estimated glomerular filtration rate (eGFR), and urinary albumin excretion (UAE)—have special bidirectional clinical significance in the assessment of early-onset T2DM complicated with hypertension. T2DM is the leading cause of chronic kidney disease (CKD), while hypertension is both a cause and a consequence of CKD, with the two forming a vicious cycle. In early-onset T2DM patients, kidney damage occurs earlier

and progresses more rapidly. Mildly elevated UAE (*i.e.*, microalbuminuria) not only marks early diabetic nephropathy but is also regarded as a reflection of systemic endothelial dysfunction and is a powerful indicator for predicting hypertension progression and cardiovascular events. A sustained declining trend in eGFR indicates progressive loss of renal function and an increasing component of renal parenchymal hypertension [5] [31] [42].

Systemic inflammatory marker—high-sensitivity C-reactive protein (hs-CRP) is the most widely used systemic inflammatory marker in clinical practice. The association between elevated hs-CRP levels and IR, central obesity, hypertension, and cardiovascular event risk has been confirmed by multiple large cohort studies. In the context of early-onset T2DM complicated with hypertension, persistently elevated hs-CRP levels reflect the activity of VAT-related chronic inflammation, while hs-CRP itself can also participate in blood pressure elevation and vascular damage progression through direct effects such as inhibiting eNOS activity, promoting adhesion molecule expression, and enhancing vascular smooth muscle cell proliferation [22] [43].

4. Associations with Clinical Outcomes and Potential Prognostic Value of Clinical Indicators

Risk-factor association should be distinguished from predictive performance. An indicator may be statistically associated with an outcome without materially improving individual-level risk prediction. Predictive performance requires formal evaluation of discrimination, calibration, reclassification, and external validation.

4.1. Potential Prognostic Value of Individual Clinical Indicators

Although individual conventional clinical indicators have relatively limited effect sizes in predicting the risk of hypertension in early-onset T2DM patients, pooling evidence from multiple studies reveals that some indicators have shown independent associations with subsequent hypertension or cardiovascular outcomes in observational studies.

Baseline blood pressure is consistently associated with the subsequent development of hypertension and cardiovascular outcomes. A meta-analysis by Lewington *et al.* based on 61 prospective studies showed that from 115/75 mmHg onward, there is a log-linear relationship between blood pressure levels and cardiovascular mortality, and this relationship is steeper in younger populations. For early-onset T2DM patients, even when baseline blood pressure is in the high-normal range (SBP 120 - 139 or DBP 80 - 89 mmHg), their risk of progressing to clinical hypertension and experiencing cardiovascular events is significantly higher than those with normal blood pressure. Analysis by Yano *et al.* based on CARDIA study data further demonstrated a significant graded association between blood pressure classification in young adulthood (ages 18 - 39, according to the 2017 ACC/AHA guideline) and cardiovascular event risk in middle age, emphasizing the long-term predictive value of blood pressure levels in young adulthood [44]-[46].

The value of BMI and WC as obesity indicators in predicting hypertension risk has been widely recognized. An individual-level meta-analysis by Wormser *et al.* based on 58 prospective studies showed that both BMI and WC are independently associated with CVD risk in prospective observational studies, and the additional predictive value of WC beyond BMI is more significant in younger age groups, suggesting that abdominal obesity assessment should be emphasized more in the early-onset T2DM population [47].

Higher HbA1c has been associated with microvascular and cardiovascular outcomes; however, its incremental value for predicting incident hypertension in early-onset T2DM remains uncertain. The observational analysis of the UK Prospective Diabetes Study (UKPDS 35) confirmed that each 1% reduction in HbA1c decreases the risk of microvascular complications (including nephropathy—the main secondary cause of hypertension in T2DM) by 37% and the risk of myocardial infarction by 14%. In the early-onset T2DM population, the predictive efficacy of HbA1c may be more prominent due to the aggressive nature of the disease itself and the rapid decline of β-cell function [4] [32].

The incremental value of serum uric acid in hypertension prediction has been a research hotspot in recent years. The meta-analysis by Grayson *et al.* showed that hyperuricemia remained independently associated with incident hypertension after adjustment for measured traditional risk factors, with stronger associations observed in younger populations and women. For patients with early-onset T2DM, incorporating serum uric acid into routine risk assessment may help identify individuals with a higher observed risk of hypertension, although its incremental predictive value requires further validation [41].

4.2. Combined Indicators, Metabolic Syndrome, and Potential Risk-Stratification Value

Applying multiple conventional clinical indicators jointly for risk prediction yields significantly better performance than any single indicator, as this more comprehensively captures the multidimensional metabolic abnormalities associated with IR and hypertension [48].

The construct of metabolic syndrome (MetS) itself represents a combined assessment strategy of multiple metabolic indicators. The harmonized definition of metabolic syndrome proposed by Alberti *et al.* incorporates five routinely measurable components: elevated WC, elevated TG, reduced HDL-C, elevated blood pressure, and elevated fasting glucose. A large number of prospective studies have confirmed that the greater the number of MetS components, the higher the risk of hypertension and cardiovascular events, and this association is particularly prominent in the early-onset T2DM population [7] [30].

In the clinical practice of early-onset T2DM, comprehensive risk assessment combining conventional indicators such as age at diagnosis, baseline BMI, WC, HbA1c, lipid profile, and serum uric acid may have higher clinical applicability compared to using any single tool (such as the Framingham risk score or QRISK

score—which were not developed specifically for the early-onset T2DM population). The study by Rawshani *et al.* emphasized the decisive role of the synergistic effect of glycemic abnormality severity, obesity degree, and blood pressure level in the long-term prognosis of T2DM patients [29]. The evidence discussed in this subsection primarily concerns associations between combined clinical indicators and outcomes rather than validated predictive performance.

4.3. Associations between Longitudinal Indicator Trajectories and Clinical Outcomes

In recent years, with the accumulation of electronic health records (EHR) and longitudinal cohort data, the research paradigm is shifting from static indicator assessment at a single time point toward focusing on dynamic trajectories of indicator changes. This shift is particularly significant in predicting long-term outcomes of early-onset T2DM complicated with hypertension, because early-onset patients have a longer disease "exposure window," and the longitudinal dynamic changes of their various indicators better reflect the intrinsic rhythm of disease progression and cumulative risk.

The long-term trajectory of glycemic variability (GV) is a current research hotspot. In large observational cohorts and post-trial follow-up studies, the coefficient of variation or standard deviation of HbA1c—*i.e.*, "long-term glycemic variability"—has been confirmed as an independent predictor of diabetic microvascular and macrovascular complications, with predictive performance even exceeding that of mean HbA1c level itself. In a post-hoc analysis of the ADVANCE trial, Zoungas *et al.* found that visit-to-visit HbA1c variability was an independent predictor of major macrovascular events, nephropathy progression, and all-cause mortality. These findings are profoundly significant for early-onset T2DM patients who experience a longer "diabetes exposure period": greater glycemic variability appearing early may portend a faster rate of β-cell function decline and a more aggressive trajectory of complication progression [38] [49].

Blood pressure trajectories also have important predictive significance. Based on data from the CARDIA young adult cohort, there is a highly consistent association between blood pressure trajectory types from young adulthood to middle age (such as "consistently normal", "moderate", "elevated-accelerating" and "young-onset elevated") and subclinical vascular damage in middle age (such as coronary artery calcification score and carotid intima-media thickness). A large UK cohort study by Luo *et al.* further confirmed that hypertension status and blood pressure rising trajectories in young adults are independently associated with long-term cardiovascular events and all-cause mortality risk [46] [50].

For early-onset T2DM patients, combined longitudinal trajectory analysis of blood glucose and blood pressure has complementary predictive value. Patients in whom both blood glucose and blood pressure trajectories show an "early elevation and sustained deterioration" pattern may have exponentially increased risk of target organ damage and cardiovascular events. Analysis of combined blood glucose

and blood pressure trajectories based on large real-world datasets (such as longitudinal monitoring records of repeatedly hospitalized patients in MIMIC-III) is expected to provide more precise long-term risk stratification tools for clinical practice [9].

In practice, longitudinal trajectories would require at least three measurements—baseline and two follow-up assessments—collected over a prespecified period. Depending on the indicator and data availability, trajectories could be summarized using the direction and rate of change, visit-to-visit variability, or repeated-measures trajectory models. The optimal number, interval, and observation window have not yet been established specifically for early-onset T2DM and require prospective validation. Importantly, trajectory information should supplement, rather than replace, baseline risk assessment based on routinely available clinical indicators.

Studies have shown that among patients with early-onset type 2 diabetes, the cumulative incidence of hypertension can reach 67.5% after an average disease duration of 13.3 years [51]. In addition, there are predictive models for the development of new-onset hypertension in patients with type 2 diabetes, with AUC values ranging from 0.70 to 0.76. However, this model was not specifically designed for early-onset type 2 diabetes and lacks independent external validation [52].

4.4. Cardiovascular and Renal Outcomes among Patients with Established Hypertension

The predictive value of conventional clinical indicators and their dynamic trajectories is ultimately reflected in their prospective predictive performance for long-term cardiovascular events and renal outcomes. Based on long-term follow-up data from large international cohorts such as NHANES, CHARLS, and ELSA, multiple studies have confirmed robust independent associations between baseline and longitudinal clinical indicators and long-term cardiovascular death, myocardial infarction, stroke, and end-stage renal disease in early-onset T2DM patients.

In terms of cardiovascular outcomes, the Emerging Risk Factors Collaboration pooled data from 102 prospective studies, confirming the consistency of fasting glucose, HbA1c, and diabetes status as independent risk factors for CVD. On this basis, the longer cumulative hyperglycemic exposure time characteristic of early-onset T2DM makes its absolute cardiovascular risk at the same age far higher than that of non-diabetic populations or late-onset T2DM patients. The predictive significance of glycemic variability, blood pressure variability—and the interaction between the two—for CVD is becoming a new research frontier [27] [28] [43] [49].

In terms of renal outcomes, patients with early-onset T2DM complicated with hypertension face the highest risk of end-stage renal disease. The TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) study is one of the

most important clinical trials to date investigating the natural history and complications of early-onset T2DM. The study found that over an average follow-up period of approximately 3.9 years, the cumulative incidence of microalbuminuria in adolescent early-onset T2DM patients reached 16.6%, and the cumulative incidence of hypertension reached 33.8%, far higher than age-matched control populations. Dabelea *et al.*, based on data from the SEARCH for Diabetes in Youth study, further confirmed that among patients diagnosed with T2DM during adolescence, the incidence of microalbuminuria, hypertension, and retinopathy is significantly higher than in age-matched T1DM patients, highlighting the particularly aggressive nature of early-onset T2DM [5] [42] [53].

Recently, Magliano *et al.* in their review summarized data from multiple large cohorts worldwide, consistently showing that compared to late-onset patients, early-onset T2DM patients have significantly higher all-cause mortality and cardiovascular mortality, as well as substantially increased risk of end-stage renal disease, and that conventional clinical indicators (especially HbA1c, blood pressure levels, and longitudinal control trajectories of obesity indicators) are key factors in explaining and predicting this excess risk [4].

5. Clinical Translation and Limitations

5.1. Challenges in Translating Research to Primary Care Practice

Although conventional clinical indicators have advantages such as low cost, easy accessibility, and high reproducibility, translating them into hypertension risk screening and stratification for early-onset T2DM patients in primary care settings still faces multiple challenges.

1) Insufficient specificity of indicators. The associations between conventional indicators (such as BMI, BP, lipids, and serum uric acid) and the risk of early-onset T2DM complicated with hypertension are, to a large extent, subject to confounding factors and effect modification. For example, WC as a surrogate indicator of central obesity, although highly correlated with visceral fat mass and IR at the population level, has considerable variability at the individual level and is significantly influenced by factors such as sex, ethnicity, and age. Similarly, hs-CRP as a marker of systemic inflammation has poor specificity and can be elevated in various infectious and non-infectious inflammatory conditions. Therefore, relying solely on single or few conventional indicators for individualized risk prediction may lead to overdiagnosis or missed diagnosis [20].

2) Population heterogeneity and threshold setting. The risk factor profiles and effect sizes of early-onset T2DM complicated with hypertension may differ significantly across populations with different races/ethnicities, geographic regions, and socioeconomic backgrounds. For example, Asian populations exhibit significant IR and visceral fat accumulation at lower BMI thresholds, while abnormal renal sodium handling and salt sensitivity may have greater weight in the pathogenesis of hypertension in African populations. Currently, most evidence-based data on early-onset T2DM complicated with hypertension come from white or Asian co-

horts in high-income countries, while representative data from regions such as Africa, Latin America, and South Asia are insufficient. Conventional indicator-based risk stratification strategies developed from any single or small cohorts require appropriate calibration and local validation when generalized to diverse populations [2].

3) Influence of behavioral factors and social determinants. The development and progression of early-onset T2DM complicated with hypertension are profoundly influenced by lifestyle factors (diet, physical activity, sleep, and smoking), psychosocial factors (stress, depression, and social support), and social determinants such as healthcare accessibility. A purely biomarker-based assessment system, if detached from consideration of the aforementioned background factors, will have significantly compromised predictive performance and clinical utility. However, systematically integrating these social and behavioral factors into routine risk assessment workflows in primary care itself constitutes a major operational challenge [54].

4) Scarcity of longitudinal follow-up data. For early-onset T2DM patients, ideal longitudinal risk prediction based on conventional indicators requires long-term, high-quality, and standardized follow-up data. However, the electronic medical record systems of most existing primary care systems vary greatly in terms of data continuity, format standardization, and quality control, hindering the generalization of risk prediction models based on longitudinal trajectories.

5.2. Mining the Potential Value of Conventional Indicators Using Real-World Electronic Medical Record Data

The concepts of real-world data (RWD) and real-world evidence (RWE) provide new approaches to bridging the aforementioned "research-to-practice" translation gap. In the context of widespread application of hospital information systems and electronic medical records, multi-center, large-sample real-world data—including vital signs, laboratory test results, medication records, and diagnostic information collected in routine clinical care—provide unprecedented opportunities for mining the predictive value of conventional clinical indicators and their longitudinal trajectories.

MIMIC-III (Medical Information Mart for Intensive Care III), as an open-access critical care medical information database, contains de-identified electronic health record data of tens of thousands of hospitalized patients, encompassing high-frequency sampled vital signs, high-density laboratory test results, medication usage, and free-text imaging reports. Although MIMIC-III data primarily originate from the intensive care unit (ICU) environment, its high-frequency sampling characteristics make it an ideal platform for exploring the dynamic interaction between blood glucose and blood pressure and their impact on acute organ function. Retrospective analysis based on hospitalization data of early-onset T2DM patients with hypertension in MIMIC-III or the subsequently updated MIMIC-IV database can reveal temporal association patterns between acute gly-

cemic fluctuations, blood pressure variability, and target organ function (such as dynamic changes in acute kidney injury or myocardial injury markers), providing perspectives on the acute-phase mechanisms of the "dual hit" effect that are difficult to obtain from conventional cohort studies [9].

In non-acute settings, regional and even national integrated electronic medical record databases also provide data foundations for conducting large-scale longitudinal trajectory analyses of conventional indicators. CHARLS, as a nationally representative longitudinal prospective cohort study of the Chinese middle-aged and elderly population (≥45 years), although its baseline enrollment age does not fully cover all early-onset T2DM patients (especially the 20 - 39 age group), its rich longitudinal data on the comorbidity of diabetes and hypertension and their cardiovascular and renal outcomes in the middle-aged population still provides important references for understanding the natural history of long-term complications in early-onset T2DM [8].

It should be emphasized that the utilization of RWD and RWE requires full attention to data integrity and bias issues. Missing data, selection bias (such as only including populations with medical visit records), confounding by indication, and heterogeneity in coding and measurement standards are all methodological challenges that must be carefully addressed in real-world research.

6. Conclusion

Early-onset type 2 diabetes complicated with hypertension represents a uniquely aggressive metabolic-cardiovascular comorbidity pattern, in which deep mechanistic exploration is steadily advancing toward practical risk assessment strategies based on conventional clinical indicators. At the pathophysiological level, selective impairment of insulin resistance-driven signaling pathways, bidirectional overactivation of the SNS and RAAS, chronic low-grade inflammatory microenvironment mediated by visceral fat accumulation, and the persistent imprint of early-life epigenetic programming collectively constitute the molecular basis for hypertension development and accelerated target organ damage in early-onset T2DM patients. At the clinical level, routinely available indicators—including age at diagnosis, BMI, waist circumference, baseline blood pressure, HbA1c, lipid profile, serum uric acid, renal function indicators, and systemic inflammatory markers—have been associated with incident hypertension and with long-term cardiovascular and renal outcomes, although their individual and incremental value for clinical prediction requires further validation. Most critically, longitudinal dynamic monitoring of glycemic variability, blood pressure trajectories, and metabolic indicators is redefining the risk management system for early-onset T2DM complicated with hypertension—shifting from one-time static stratification to dynamic early warning based on the full disease trajectory. The complementary use of large prospective cohorts and real-world electronic medical record databases provides a solid data foundation for further validating and refining these conventional indicator-based prediction strategies. The focus of future research lies in:

on the basis of fully considering population heterogeneity and social determinants, transforming longitudinal trajectory analysis of conventional indicators into automated risk stratification tools operable in primary care settings, thereby achieving prospective prevention and precision intervention for complications of early-onset T2DM complicated with hypertension. This paradigm shift—from mechanism to practice and from static to dynamic—holds the promise of fundamentally improving the long-term prognosis of this high-risk young population.

Author Contributions

Study conception and methodology design: Lingyan Hu, Wen Zhong; systematic literature retrieval and screening: Lingyan Hu; data extraction, quality assessment and evidence interpretation: Lingyan Hu, Wen Zhong; manuscript drafting, revision and polishing: Lingyan Hu; final approval of the submitted version: Lingyan Hu, Wen Zhong.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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