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Type 1 diabetes mellitus: the liver's role, sex-specific outcomes, and advances in disease-modifying therapies - a literature review

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Abstract

Type 1 Diabetes Mellitus (T1DM) is a chronic autoimmune disease characterized by the destruction of pancreatic β -cells, leading to insulin deficiency. While insulin remains the cornerstone of treatment, achieving optimal disease control and preventing long-term complications remain significant challenges. This review synthesizes recent findings on the epidemiology, pathophysiology, and management of T1DM, with a particular focus on sex-based differences in disease presentation and outcomes, the role of the liver, and the emerging significance of C-peptide in understanding disease complications. Additionally, the involvement of T cells and B cells in the immune response and the potential of disease-modifying therapies, such as TNF-alpha inhibitors, anti-CD3 antibodies, abatacept, and cell-based therapies, are explored. The article highlights the need for further research into personalized and gender-specific treatment approaches and the development of novel therapeutic strategies. Addressing these critical areas may lead to improved disease management and quality of life for individuals with T1DM, paving the way for more effective and individualized therapeutic interventions.

Keywords: Type 1 diabetes mellitus, diabetic kidney disease, diabetic nephropathy, hyperglycemia, C-peptide, lymphocytes, therapies, treatments



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INTRODUCTION

Type 1 Diabetes Mellitus (T1DM) is a chronic autoimmune disease characterized by the destruction of insulin-producing β -cells in the pancreas, leading to absolute insulin deficiency. Unlike Type 2 Diabetes Mellitus, T1DM primarily manifests during childhood or adolescence, although it can occur at any age. Its etiology involves a complex interplay of genetic predisposition, environmental factors, and immune system dysregulation. Over the past few decades, significant advancements have been made in understanding the pathophysiology, genetic basis, and management of T1DM, yet many challenges remain in achieving optimal disease control and preventing long-term complications.

T1DM is distinct among common autoimmune diseases as it does not exhibit a female predominance^[1], and studies have highlighted significant sex-based differences in disease presentation, management, and outcomes, underscoring the need for gender-specific research and treatment approaches. Although insulin has remained the primary treatment for T1DM since its discovery, the disease is increasingly recognized as a complex condition with systemic implications, including associations with liver conditions such as metabolic-associated fatty liver disease (MAFLD)^[2-4] and metabolic dysfunction-associated steatotic liver disease (MASLD). C-peptide, a byproduct of insulin biosynthesis, is drawing renewed interest for its potential role in understanding and managing T1DM-related complications, suggesting a broader relevance beyond its traditional use as a marker of insulin secretion^[5,6]. Emerging disease-modifying therapies, such as tumor necrosis factor- α (TNF- α) inhibitors^[7-9], anti-CD3 antibodies^[9], abatacept, cell-based therapies, and vitamin D supplementation, show promise in slowing disease progression, preserving β -cell function, and improving glycemic control^[10].

This literature review aims to synthesize recent research on the epidemiology, sex differences, and risk factors of T1DM, the liver's role, the involvement of C-peptide, the contribution of T and B cells, and evolving therapeutic strategies, highlighting areas for future investigation and potential clinical applications.

DISCUSSION

Epidemiology and sex differences

T1DM is the only common autoimmune disease that does not exhibit a female predominance^[1]. In fact, in Caucasian communities, the prevalence of T1DM is higher among men compared to women^[1]. T1DM typically presents in young individuals, with most cases diagnosed before the age of 20^[1]. Globally, more than one million children and adolescents are estimated to be affected by T1DM [Table 1]^[11]. In recent years, the incidence of T1DM has been rising in the United States, particularly among Hispanic and non-Hispanic Black youth [Table 1]^[12,13].

Despite these trends, studies have reported inconsistent findings regarding sex-based differences in T1DM prevalence. For instance, the SEARCH for Diabetes in Youth study, initiated in 2000 by the Centers for Disease Control and Prevention and the National Institute of Diabetes and Digestive and Kidney Diseases, found no clear sex differences in T1DM prevalence between 2001 and 2009^[14]. However, multiple outcomes related to T1DM appear to be worse in females than in males, especially regarding body mass index (BMI), glycemic control, diabetic ketoacidosis, and quality of life^[13]. Additionally, women have been reported to show higher postprandial C-peptide and insulin levels following a meal test^[1]. It is also noteworthy that diabetic renal complications tend to manifest ten years later in women compared to men of the same age^[15].

Gender medicine emphasizes analyzing biological sex differences and their impact on disease pathophysiology, presentation, and outcomes^[16-19]. Many studies on T1DM complications have focused exclusively on one sex, often males, limiting the reliability of findings and complicating cross-sex

Table 1. Summary of epidemiological trends and sex-specific clinical outcomes in Type 1 diabetes mellitus

Aspect	Key findings	Sex-specific differences
Global prevalence ^[11]	> 1 million children and adolescents affected globally	Some studies report no sex-based difference; others indicate higher prevalence in males
Incidence trends ^[13]	Rising globally, particularly among Hispanic non-Hispanic Black youth in the U.S.	Postprandial C-peptide and insulin levels are notably higher in females
Glycemic control ^[30]	HbA1c targets (< 7%) often unmet	Females tend to have poorer glycemic control and are less likely to meet BP/lipid targets
Diabetic complications ^[25]	Includes CVD, DKD, MAFLD, and MASLD	Females are at higher risk of CVD and renal disease progression, with a delayed onset of DKD
Renal disease ^[15]	DKD affects 30% of patients with T1DM	CKD is more common in females, while ESRD rates are higher in males
Cardiovascular risk ^[24]	T1DM increases CVD risk by up to 30-fold and shortens life expectancy	Women experience greater excess mortality and worse treatment outcomes compared to men
Liver involvement (ALT levels) ^[1]	Elevated ALT observed in ~9.5% of T1DM patients; associated with MAFLD/MASLD	Poorer glycemic control in women may exacerbate liver-related complications
Sex hormones & insulin sensitivity ^[1]	Estrogens/androgens influence β -cell function and immune modulation	Females show higher insulin resistance, likely due to lower muscle mass and increased adiposity

T1DM: Type 1 diabetes mellitus; CVD: cardiovascular disease; DKD: diabetic kidney disease; MAFLD: metabolic-associated fatty liver disease; MASLD: metabolic dysfunction-associated steatotic liver disease; ESRD: end-stage renal disease; ALT: alanine aminotransferase.

comparisons^[20]. This historical bias has overlooked important sex-specific factors, including differences in renal glucose handling and disease progression^[15].

Women generally exhibit greater insulin resistance than age-matched men, which may be explained by lower skeletal muscle mass, higher adipose tissue mass, and increased levels of circulating free fatty acids^[1,21,22]. One study examining pregnancy-induced metabolic changes in mice highlighted dynamic alterations in body weight and fat deposition, as well as impaired glucose tolerance and insulin sensitivity during late pregnancy. Thermogenic activity in brown and inguinal white fat was reduced, while gonadal fat showed increased lipid mobilization. Mammary gland differentiation was observed in certain fat depots, and metabolic adaptations were also seen in the liver and pancreas. These findings reflect similar metabolic changes during human pregnancy and may help inform the prevention and treatment of maternal metabolic diseases^[20]. Moreover, young females with T1DM may be subject to treatment bias, which could affect the quality of their daily care and the management of risk factors^[11]. Thus, thorough analysis and comparison of sex differences are essential for a deeper understanding of T1DM and the optimization of its clinical management and care [Table 1].

Glycemic and blood pressure control, dyslipidemia, sex hormones

Glycemic and blood pressure control

Sex differences play a critical role in glucose homeostasis, particularly in individuals with T1DM and prediabetic syndromes. Women with T1DM are less likely to achieve an HbA1c level < 7%, to be prescribed lipid-lowering medications [Table 1], and, when treated, to reach recommended blood pressure and lipid targets^[23]. A recent study demonstrated the impact of sexual dimorphism on mitochondrial bioenergetic adaptations in T1DM^[24]. These findings may help explain the sex-specific differences in glycemic control observed in boys but not girls, underscoring the need to develop sex-based therapies for diabetes^[1].

Dyslipidemia

Current literature emphasizes that the atherosclerosis process in individuals with T1DM often begins in early childhood at the endothelial level and progresses in an accelerated manner^[24]. A 2011 study comparing

sex differences in T1DM revealed that the protective effect of high-density lipoprotein (HDL) may be markedly decreased in women with T1DM compared to men, which may help explain the increased risk of complications in female patients^[25].

Sex hormones

Sex is increasingly recognized as a significant factor influencing T1DM and warrants greater clinical attention^[11]. Several hypotheses attempt to explain the biological and gender-related bases for these variations, although the mechanisms remain incompletely understood. Sexual dimorphism is thought to stem, at least in part, from the influence of sex hormones such as estrogens and androgens. During puberty, hormonal changes in women are associated with better-preserved residual β -cell function compared to men, suggesting a transient protective effect against T1DM^[11,26,27]. Furthermore, recent studies have identified an association between sex hormone-binding globulin (SHBG) and T1DM risk. Elevated levels of SHBG in women have been linked to a lower risk of developing diabetes^[14]. Therefore, imbalances in sex hormones may represent an important risk factor that merits further consideration.

Cardiovascular system

Cardiovascular complications are also a major determinant of prognosis and quality of life in patients with T1DM [Table 1]. Studies have shown that individuals with T1DM have a 30-fold increased risk of severe cardiovascular disease and a life expectancy that is 16 years shorter than those without T1DM^[24]. For instance, data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort revealed that for every 1% increase in mean HbA1c, the risk of developing any form of cardiovascular disease increased by 31%^[24].

Sex-specific analyses indicate a markedly higher risk of cardiovascular disease (CVD) in women with T1DM compared to men^[16]. Notably, in individuals with T1DM, the mortality rate from CVD before age 40 is 10 times higher in men, but strikingly 40 times higher in women^[24,28,29].

Although studies on T1DM and atrial fibrillation are limited, recent analyses have confirmed a higher incidence of atrial fibrillation in individuals with T1DM^[30]. The risk is only slightly elevated in men, but is significantly higher (~50%) in females of the same age group^[30].

A longitudinal study spanning 11 years and involving 774 individuals with T1DM found that the Fatty Liver Index (FLI), a non-invasive marker of liver steatosis, independently predicted all-cause mortality and major cardiovascular events. Patients with an FLI ≥ 60 had significantly higher risks of death and cardiovascular complications, highlighting the importance of liver health assessment in T1DM management to reduce adverse outcomes^[31].

Regarding heart failure, a meta-analysis of 47 cohort studies including over 12 million individuals found that T1DM and T2DM confer a higher risk of heart failure in women than in men, with women showing a 47% greater excess risk^[16]. Several factors may contribute to this disparity, including: (1) poorer glycemic control in women with T1DM; (2) undertreatment of women with diabetes, which may lead to diabetic cardiomyopathy; and (3) a longer duration of prediabetes in women, as they were found to have two additional years of hyperglycemia compared to men^[16].

Several narrative reviews have highlighted the critical link between liver dysfunction, particularly MASLD, and increased cardiovascular risk in patients with T1DM. These reviews emphasize the importance of early

detection and targeted management of liver abnormalities as essential strategies to improve cardiometabolic outcomes in this population^[32-34].

Renal failure and diabetic kidney disease

Diabetic Kidney Disease (DKD) is one of the most common complications of diabetes mellitus [Table 1], affecting approximately 30% of individuals with T1DM^[14]. An epidemiological study highlights the importance of achieving better glycemic control to reduce the incidence of DKD in patients with T1DM or T2DM, regardless of sex^[35]. While End-Stage Renal Disease (ESRD) is more prevalent in men, CKD appears to be more common in women^[15]. Research suggests that women with T1DM may be at increased risk of developing CKD, possibly due to greater susceptibility to changes in glomerular filtration rate (GFR)^[14].

Recent investigations into sex differences across renal transporters throughout the nephron have shown that sodium-glucose co-transporters 1 and 2 (SGLT1 and SGLT2) function in a sex-independent manner. This may explain why sex differences are not consistently reported in studies evaluating the efficacy of currently available SGLT2 inhibitors^[14]. However, several studies have reported a higher incidence of adverse effects in women with T1DM undergoing SGLT2 inhibitor therapy - such as increased rates of urinary tract infections (UTIs), genital infections, and diabetic ketoacidosis - compared to men^[14].

Sex hormones and immune regulation in T1DM

Sex differences play a significant role in the pathogenesis and progression of T1DM [Table 1]. Estrogens promote β -cell survival and modulate immune responses by influencing regulatory T cells and cytokine expression, while androgens have complex, dose-dependent effects on insulin sensitivity and inflammation^[1]. Estrogen surges during puberty are associated with better residual β -cell function in females than in males^[11]. Additionally, elevated SHBG levels in women have been inversely associated with T1DM risk, suggesting a protective endocrine profile^[14]. These hormonal factors may partially explain observed sex differences in insulin sensitivity, as females with T1DM often exhibit greater insulin resistance than males - likely due to lower muscle mass and higher adiposity^[1]. A deeper understanding of how hormonal modulation influences immune-mediated β -cell destruction may facilitate the development of sex-specific therapies or biomarkers for early risk stratification [Figure 1].

Type 1 diabetes mellitus and the role of the liver

Liver Involvement and MAFLD in T1DM

T1DM is characterized by autoimmune destruction of pancreatic β -cells [Figure 2], resulting in absolute insulin deficiency and lifelong dependency on exogenous insulin therapy. Insulin has remained the cornerstone of treatment for over a century since its discovery^[36]. Innovations such as hybrid closed-loop systems have significantly improved the quality of life for individuals with T1DM^[36]. However, despite these advancements, morbidity and mortality associated with the disease continue to rise globally^[31].

The liver plays a central role in glucose and lipid metabolism and is significantly affected in T1DM due to insulin deficiency and chronic hyperglycemia [Figure 2]. Hepatocytes take up glucose via insulin-independent GLUT2 transporters [Figure 3]. Once inside the cell, glucose is phosphorylated by glucokinase to glucose-6-phosphate and enters metabolic pathways such as glycogenesis, glycolysis, or lipogenesis^[37-39]. In insulin-deficient states, this tightly regulated process becomes disrupted, leading to metabolic dysfunction.

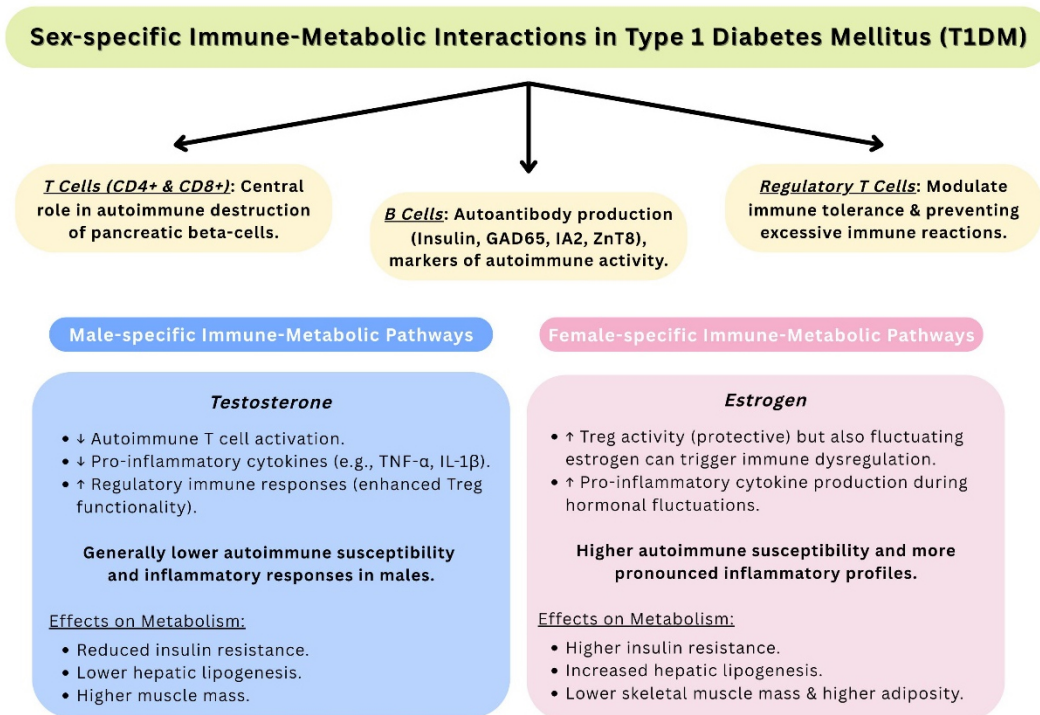


Figure 1. Summary of Sex-specific Immune-Metabolic Interactions in T1DM. T1DM: Type 1 diabetes mellitus.

Autoimmune Destruction of β -Cells	
Triggered by genetic and environmental factors.	Leads to insulin deficiency and loss of glycemic regulation.
Reduced Insulin Signaling to the Liver	
Impaired insulin delivery to hepatocytes.	Disrupted suppression of hepatic glucose production.
Hepatic Glucose Overproduction	
Liver increases gluconeogenesis and glycogenolysis.	Contributes to fasting and postprandial hyperglycemia.
Altered Lipid Metabolism	
Insulin deficiency promotes lipolysis.	Liver converts excess free fatty acids into triglycerides \rightarrow risk of MAFLD/MAFLD.
Inflammation and Immune Crosstalk	
The liver releases proinflammatory cytokines.	May contribute to systemic immune dysregulation and amplify autoimmunity.
Impaired Detoxification and Hormonal Processing	
Chronic hyperglycemia may alter hepatic enzyme activity.	Affects sex hormone metabolism and glucose counter-regulation.
Liver as a Target for Therapeutic Modulation	

Figure 2. Overview of the Liver's Role in the Pathophysiology and Progression of Type 1 Diabetes Mellitus.

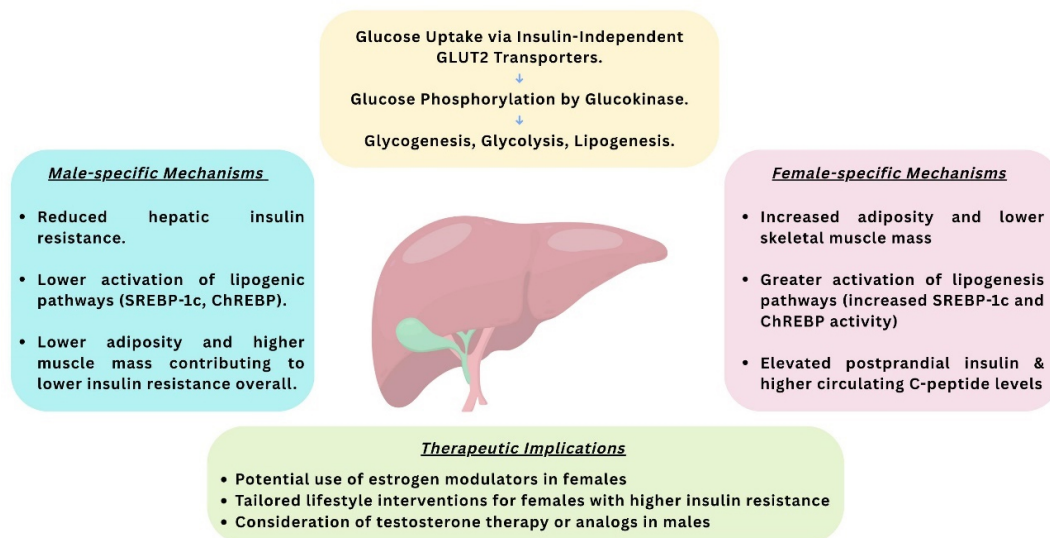


Figure 3. Schematic Illustration of the Metabolic Role of the Liver in Hepatic Insulin Resistance and Implications for Therapy.

Emerging evidence indicates early hepatic involvement in the pathogenesis of T1DM. A study analyzing cord serum samples found that reduced levels of major choline-containing phospholipids were associated with an increased risk of developing T1DM, suggesting early liver-based metabolic disruptions^[32].

In patients with poorly controlled T1DM, hepatic glycogen metabolism is markedly impaired [Figure 2]. Research has shown significant reductions in both hepatic glycogen synthesis and breakdown in these individuals. Although short-term insulin therapy improved these abnormalities, levels did not return to normal. Furthermore, glycogenic hepatopathy-characterized by excessive hepatic glycogen storage-has been observed in patients with T1DM, particularly in those with erratic glycemic control and frequent insulin fluctuations^[40-43]. Beyond glycogen storage, chronic hyperglycemia and exogenous insulin therapy contribute to hepatic steatosis. Mechanistically, this is linked to upregulated GLUT2 expression [Figure 3] and the activation of lipogenic transcription factors such as carbohydrate-responsive element-binding protein (ChREBP) and sterol regulatory element-binding protein 1c (SREBP-1c), which promote hepatic de novo lipogenesis and fat accumulation^[44].

MAFLD, more recently referred to as MASLD, is increasingly reported in T1DM. A systematic review and meta-analysis of 3,901 adults with T1DM reported a MAFLD prevalence of 22%^[2]. This high prevalence is attributed to factors such as elevated circulating free fatty acids, systemic inflammation, oxidative stress, and suboptimal glycemic control. Additionally, the total daily insulin dose has been positively correlated with MAFLD progression^[45].

T1DM-associated hyperglucagonemia, caused by the absence of intra-islet amylin secretion, further contributes to hepatic lipid accumulation and exacerbates metabolic dysregulation^[2]. Elevated levels of alanine aminotransferase (ALT) are observed in approximately 9.5% of individuals with T1DM. In pediatric patients with poor glycemic control, the odds of elevated liver enzymes are more than twice as high compared to well-controlled peers, even after adjusting for confounding factors^[46]. These markers serve as clinically relevant, non-invasive indicators of hepatic involvement in T1DM and may help identify high-risk patients^[45].

Finally, a Mendelian randomization study has established a causal relationship between T1DM and the progression of liver fibrosis and cirrhosis. It further showed that both acute and chronic complications, especially neurological and ocular, are independently associated with an increased risk of liver fibrosis. These findings underscore the importance of comprehensive T1DM management strategies that include routine monitoring of liver health^[47].

Metabolic dysfunction-associated steatotic liver disease and T1DM

A link between MASLD and T1DM has been recently established in novel published studies^[31]. These two conditions share common predisposing factors, including obesity and insulin resistance. Consequently, the rising prevalence of obesity among people with T1DM has made the need for intensive insulin therapy increasingly inevitable^[31]. Studies investigating the prevalence of MASLD in individuals with T1DM are limited, and existing findings are difficult to compare due to variations in study populations^[31].

Several factors in T1DM contribute to the consequent development of MASLD, including poor glycemic control, obesity, dyslipidemia, unhealthy dietary habits, and lipoprotein abnormalities^[31,48,49]. Notably, a cross-sectional study of 659 adults with T1DM reported an association between elevated HbA1c levels and MASLD, independent of obesity status^[50]. In this study, patients with HbA1c levels above 7.6% showed significantly higher liver enzyme levels. Chronic hyperglycemia in T1DM promotes hepatic glucose uptake via glucose transporter 2 (GLUT2), leading to activation of sterol regulatory element-binding proteins (SREBPs) and carbohydrate-responsive element-binding proteins (ChREBPs)^[36]. These pathways stimulate hepatic de novo lipogenesis^[31], thereby contributing to the development of MASLD in T1DM patients. Mechanistically, the literature highlights the role of advanced glycation end products (AGEs) in vascular complications. However, it often overlooks the significance of early glycation of Amadori-modified proteins, which have been found to be strongly associated with an increased risk of nephropathy in T1DM patients^[45]. Current evidence remains limited and inconclusive, highlighting the need for further research to clarify the liver's role in T1DM-related complications and its implications for prognosis and clinical management. Liver complications commonly observed in T1DM are illustrated in [Figure 4](#).

Involvement of c-peptide in type 1 diabetes mellitus

Mechanism of action of C-peptide in T1DM

C-peptide is a 31-amino-acid peptide that connects the A and B chains of proinsulin and has emerged as a potentially valuable factor in understanding the pathogenesis of T1DM-related complications. Following cleavage by endoproteases, C-peptide is secreted into the bloodstream in equimolar amounts with endogenous insulin, making it a reliable marker of insulin production^[51,52]. C-peptide binds to specific cellular receptors, such as G-protein coupled receptor 146 (GPR146), initiating intracellular signaling cascades that regulate essential endothelial functions, including nitric oxide production, thereby supporting vascular health. In T1DM, vascular damage is partly attributable to endothelial dysfunction; C-peptide's modulation of these signaling pathways helps mitigate such damage^[5,53-55]. Additionally, studies have shown that C-peptide restores sodium-potassium (Na⁺/K⁺)-ATPase activity in neurons and glomeruli, contributing to reduced nerve injury and decreased hyperfiltration-induced stress on the kidneys^[5,56,57]. In certain studies, an early C-peptide response to glucose challenges suggests better-preserved β -cell function in individuals with single autoantibody positivity. This highlights C-peptide's role in glucose-stimulated insulin secretion and supports its potential as a biomarker for residual β -cell activity in cases of less severe autoimmunity^[58,59].

Evidence linking C-peptide levels to T1DM complications

Diabetic nephropathy, also referred to as DKD, is a chronic microvascular complication of T1DM resulting from hyperglycemia-induced damage to the glomeruli. In the early stages, elevated blood glucose levels lead

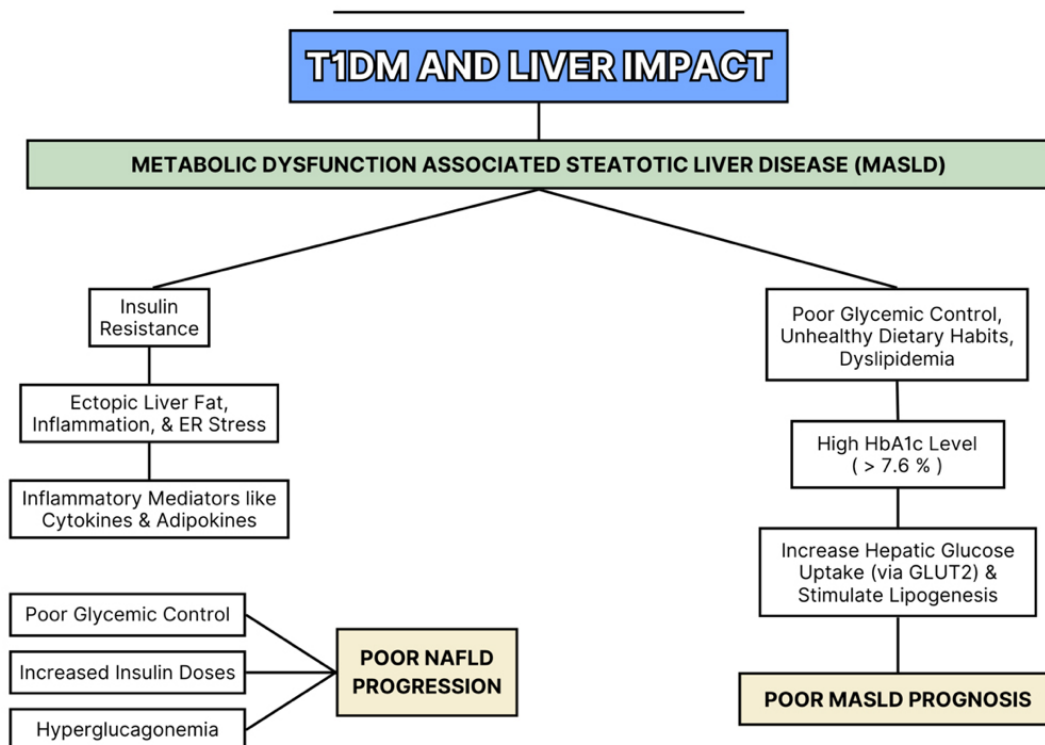


Figure 4. Liver Pathologies Associated with T1DM. T1DM: Type 1 diabetes mellitus.

to an increase in GFR. Over time, heightened intraglomerular and transcapillary pressures cause glomerulosclerosis. In addition, disruptions in renal hemodynamics promote interstitial fibrosis through the release of cytokines and growth factors. DKD is classified into five stages based on the patient's GFR, ranging from stage 1 (pre-nephropathy) to stage 5 (end-stage renal disease). Maintaining strict glycemic control remains essential in preventing the onset and progression of DKD, underscoring the need to explore therapeutic strategies such as C-peptide administration^[5].

In individuals with adult-onset T1DM, measurable levels of C-peptide may persist even after long disease duration, and are associated with improved glycemic control^[60]. Furthermore, adults with T1DM typically present with higher C-peptide levels at diagnosis, which may contribute to a reduced incidence of diabetic ketoacidosis and a lower risk of hypoglycemia^[60]. C-peptide also exerts anti-inflammatory effects by inhibiting nuclear factor kappa B (NF-κB) - a key pro-inflammatory pathway - and promoting the production of anti-inflammatory cytokines (e.g., IL-10). This anti-inflammatory environment reduces vascular inflammation and oxidative stress, helping to protect against complications like diabetic nephropathy^[5]. Beyond renal protection, C-peptide influences critical physiological processes including vascular function, neural integrity, and systemic inflammation in T1DM. These actions have significant implications for understanding disease progression and the development of complications^[61-65]. Higher circulating levels of C-peptide may protect against microvascular damage and inflammatory responses, offering a potential therapeutic target in T1DM management^[61].

Therapeutic potential of C-peptide in T1DM

Research indicates that C-peptide administration has shown beneficial, albeit clinically limited, effects on kidney-associated dysfunctions. However, the DCCT study provides strong evidence that even residual

levels of C-peptide are associated with improved clinical outcomes in patients. Specifically, C-peptide has been shown to alleviate diabetic nephropathy by reducing glomerular hyperfiltration and albuminuria. It modulates endothelial function, enhances nitric oxide production, and inhibits pro-inflammatory pathways, thereby offering renal protection^[66-69]. In T1DM models, C-peptide therapy has also improved nerve conduction velocity and reduced neuropathic symptoms. These effects are attributed to its ability to restore Na^+/K^+ -ATPase activity and improve endoneurial blood flow^[70,71]. Regarding its vascular effects, C-peptide exerts anti-inflammatory effects by downregulating adhesion molecules such as P-selectin and intracellular adhesion molecule-1 (ICAM-1) on endothelial cells, thereby decreasing leukocyte adhesion and vascular inflammation. However, some studies suggest that C-peptide may also have pro-atherogenic effects by stimulating vascular smooth muscle cell proliferation through Src kinase and MAPK pathways^[70]. These findings reinforce the notion that C-peptide is not just a biomarker but may also play an active role in mitigating diabetic complications^[72,73]. Importantly, these therapeutic utilities must be supported by investigations into C-peptide's biological activity in both *in vitro* and *in vivo* models^[5]. In studies on combination therapies, fluctuations in C-peptide levels observed in placebo groups - compared with those receiving combination therapy - suggest that these changes are not solely due to the "honeymoon phase" (a period following T1DM diagnosis during which the pancreas retains some insulin-producing capability) but reflect a real therapeutic effect^[74-76]. C-peptide also has potential utility in guiding therapeutic strategies. Insulin monotherapy is generally recommended for individuals with random C-peptide levels below 300 pmol/L. For those with levels above 300 pmol/L, insulin may be combined with other diabetes therapies^[60]. Patients with levels exceeding 600 pmol/L can often be managed similarly to those with T2DM^[60]. Moreover, therapies aimed at preserving β -cell function have shown promise in improving glycemic control. For example, a 20% preservation in C-peptide levels has been associated with a clinically meaningful 0.5% reduction in HbA1c^[77]. However, long-term studies are needed to evaluate the durability of these therapeutic benefits, highlighting the importance of more robust trial designs to assess sustained metabolic outcomes beyond the initial treatment phase^[77].

Despite these promising findings, the utility of C-peptide in predicting therapeutic responses remains limited. One key challenge is its temporal variability-C-peptide levels fluctuate based on disease duration, age, and metabolic state, making cross-patient comparisons difficult. Additionally, C-peptide exhibits delayed responsiveness; its levels may not immediately reflect ongoing β -cell destruction or the effects of immunomodulatory therapy. In early-stage disease or in individuals with a single autoantibody, C-peptide concentrations may remain within normal range despite active immune-mediated β -cell injury, limiting its usefulness in identifying therapeutic targets or predicting disease progression^[59].

Finally, researchers are exploring the use of C-peptide in combination with other therapies, which may enhance treatment efficacy and improve the management of T1DM and its complications^[61].

Role of T cells and B cells in T1DM

Overview of immune-mediated mechanisms in T1DM

T1DM is a T cell-mediated autoimmune disease characterized by the selective destruction of pancreatic insulin-secreting β -cells, principally by islet-reactive T cells^[78-80]. This autoimmune response arises from a complex interplay among genetic susceptibility, environmental factors, and the gastrointestinal (GI) microbiome^[74]. For example, viral infections are thought to contribute to β -cell damage, while molecular mimicry - a mechanism associated with the GI microbiome - can trigger T cell responses that lead to T1DM^[78]. In addition to T cells, B cells have been detected infiltrating pancreatic islets in humans, where they contribute to disease progression^[78]. Studies have shown that B cell-deficient mice do not develop spontaneous T1DM, suggesting a critical role for B cells in disease onset. Similar to T cells, some B cells that develop in the bone marrow can randomly acquire autoreactive breakpoint cluster region (BCR)

proteins^[81]. Moreover, the activation of self-reactive T cells in T1DM is probably driven by antigen-presenting cells (APCs) - such as dendritic cells (DCs), macrophages, B cells, and islet β -cells - through the presentation of self-antigens via MHC class I or II molecules^[78]. Notably, exposure to insulin in the diet during infancy has been shown to trigger both B and T cell responses^[82].

Contribution of T cells to T1DM progression

In T1DM, the immune system erroneously identifies pancreatic β -cells as foreign and initiates an autoimmune attack, leading to their destruction. This impairs insulin secretion and disrupts blood glucose regulation, driving disease onset and progression. Antigen-specific immune cells, particularly CD4⁺ and CD8⁺ T cells, along with other immune cells such as natural killer cells and macrophages, are activated and recruited to target β -cells^[82]. Various types of islet autoantigen-specific T cells have been identified. These include: preproinsulin-specific T cells, which initiate islet destruction; glutamic acid decarboxylase 65 (GAD65)-specific T cells, which trigger inflammation and amplify the autoimmune response; zinc transporter 8 (ZnT8)-specific T cells, which play a critical role in diabetes onset under immune-compromised pancreatic conditions; insulin-specific T cells, involved directly in β -cell destruction; and islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP)-specific T cells, which also contribute to insulinitis and β -cell damage^[82]. Cytokines play a pivotal role in these mechanisms. For example, interferon gamma (IFN- γ) may modulate the autoimmune response by sustaining T cell activation^[82].

Role of B cells in T1DM pathophysiology

During development, B cells expressing autoreactive BCRs may undergo deletion or BCR editing to avoid autoimmunity. In T1DM, however, autoreactive B cells are thought to receive help from activated CD4⁺ T cells, leading to the production of autoantibodies - primarily targeting insulin, GAD65, IA2, and ZnT8. Although these autoantibodies are not themselves pathogenic, they serve as critical biomarkers for disease prediction and assessment of immune profiles based on the specificity of the targeted antigens. The functional role of autoreactive B cells in human T1DM remains poorly understood, although insulin-reactive B cells have been shown to lose their anergic state. Defects in the negative selection of autoreactive B cells have also been observed in individuals with T1DM^[81]. Furthermore, B cells are found within inflamed pancreatic islets, suggesting a pathogenic role in autoimmune diabetes. This is supported by studies in non-obese diabetic (NOD) mice, where B cell depletion prevents spontaneous disease onset. Co-transfer experiments have shown that the introduction of BCR-stimulated B cells along with diabetic NOD splenocytes induces disease, whereas pre-treatment of B cells with anti-CD80 and anti-CD86 antibodies nearly abolishes disease development. These findings highlight the essential role of B cells in antigen presentation to CD4⁺ T cells. B cells may also contribute to CD8⁺ T cell activation, as suggested by data from B cell-deficient mice^[78].

Despite their diagnostic utility, autoantibody biomarkers have several limitations. First, they lack pathogenicity - autoantibodies are not directly cytotoxic and do not reliably reflect active β -cell destruction. Second, they offer limited predictive value regarding therapeutic response. For instance, in the Abatacept prevention trial, the drug demonstrated immunomodulatory effects, but did not significantly delay disease progression in antibody-positive individuals^[83]. Third, antibody status does not always correlate with disease trajectory; some individuals progress to clinical T1DM even after seroreversion, emphasizing the role of non-humoral mechanisms in pathogenesis.

Type 1 diabetes and the role of inflammation

T1DM is fundamentally an autoimmune disorder characterized by the selective destruction of pancreatic β -cells by autoreactive T cells, resulting in persistent hyperglycemia^[84]. Increasing evidence suggests that

inflammation plays a central role in T1DM pathogenesis, with both innate and adaptive immune responses contributing to β -cell destruction. Mitochondrial dysfunction - particularly impaired mitophagy - has been identified as a key driver of inflammation in T1DM. The accumulation of damaged mitochondria leads to the release of mitochondrial reactive oxygen species (mtROS) and mitochondrial DNA (mtDNA), both of which act as damage-associated molecular patterns (DAMPs)^[84]. These DAMPs activate innate immune receptors, such as toll-like receptors (TLRs) and the NOD-like receptor NLRP3 inflammasome, leading to the production of pro-inflammatory cytokines such as interleukin-1 β (IL-1 β) and interleukin-18 (IL-18)^[84].

The resulting inflammatory environment promotes polarization of macrophages to the pro-inflammatory M1 phenotype and facilitates the recruitment and activation of autoreactive CD4⁺ and CD8⁺ T cells, which mediate β -cell destruction through both cytokine release and direct cytotoxicity^[84]. Chronic inflammation perpetuates β -cell apoptosis and loss of insulin production - hallmark features of T1DM^[84]. Genetic factors further modulate this process; for example, polymorphisms in genes like C-type lectin domain family 16 member A (Clec16a), which regulate mitophagy, have been shown to impair mitochondrial quality control and amplify inflammation^[84,85]. These insights have spurred the development of novel therapeutic strategies aimed at controlling inflammation and restoring mitophagy. Several pharmacological agents targeting the NLRP3 inflammasome and other inflammatory pathways are currently under investigation^[86].

Disease modifying therapies

Approved and near-approval therapies

TNF- α inhibitors

TNF- α has been implicated in the progression of T1DM [Table 2], both by enhancing antigen presentation and through its direct cytotoxic effects^[10]. As such, TNF- α represents a potential therapeutic target for T1D. TNF- α inhibitors function by binding to TNF- α and its receptors, thereby interfering with its pathological activity. Common TNF- α inhibitors include adalimumab, certolizumab, etanercept, and infliximab. Clinical trials investigating TNF- α inhibitors such as etanercept and golimumab in T1DM have shown reductions in HbA1c and increases in C-peptide levels, indicating their therapeutic efficacy^[10]. Adalimumab has also been associated with improved glycemic control and reduced hypoglycemia; however, case reports have documented hypoglycemic episodes in some patients^[10,87]. These adverse effects underscore the need for close monitoring and further investigation to determine which TNF- α inhibitors provide optimal glycemic control without inducing hypoglycemia [Table 3].

Anti-CD3 antibodies

Muromonab and Teplizumab are examples of anti-CD3 monoclonal antibodies [Table 2]. Muromonab-CD3 has been used in various transplantation settings and has shown potential in T1DM treatment. However, its use is limited by adverse effects such as fever, chills, headache, and pulmonary edema - typically occurring within hours of administration due to cytokine release by T cell receptor (TCR) and CD3 cross-linking, as well as Fc receptor interactions. Teplizumab is a humanized version of muromonab-CD3 with reduced Fc binding, specifically designed to reduce insulin dependence^[88]. A pooled analysis of five clinical trials evaluating teplizumab found that it significantly preserved C-peptide levels for over 2 years, indicating sustained β -cell function compared to placebo or standard care^[89]. In that same study, approximately 80% of patients developed lymphopenia, which resolved with continued treatment, while 50% experienced leukopenia - though infection rates were comparable between the teplizumab and control groups. Other transient adverse events included rash and decreased blood bicarbonate levels, which resolved within 4 weeks alongside the leukopenia. In a separate study involving high-risk individuals -

relatives of T1DM patients with at least two positive autoantibodies 6 months prior to enrollment - teplizumab significantly delayed disease onset. The median time to T1DM diagnosis was 48.4 months in the treatment group compared to 24.4 months in the placebo group^[88]. These findings suggest that teplizumab holds promise both for delaying the onset and for treating T1DM [Table 3].

Table 2. Summary of C-peptide's role in type 1 diabetes mellitus

Focus area	Scientific insights	Implications for T1DM
Cellular mechanisms	<ul style="list-style-type: none"> - Activates GPR146 receptors - Stimulates nitric oxide production - Restores Na⁺/K⁺-ATPase in neurons 	<ul style="list-style-type: none"> - Enhances vascular function - Provides neuro- and reno-protection - Counters endothelial dysfunction
Diagnostic utility	<ul style="list-style-type: none"> - Secreted in a 1:1 ratio with insulin - Reflects endogenous insulin secretion - Sensitive in mild autoimmunity 	<ul style="list-style-type: none"> - Assesses β-cell reserve - Helps stratify disease severity - Guides early intervention
Microvascular complications	<ul style="list-style-type: none"> - Reduces inflammation & oxidative stress - Improves glomerular dynamics - Suppresses NF-κB, promotes IL-10 	<ul style="list-style-type: none"> - May slow progression of nephropathy & neuropathy - Fewer DKA & hypoglycemia episodes - Correlates with better glycemic control
Therapeutic modulation	<ul style="list-style-type: none"> - Supports endothelial/immune function - Lowers ICAM-1 and P-selectin - Promotes smooth muscle proliferation 	<ul style="list-style-type: none"> - Potential as adjunctive therapy - Improves renal & neurological outcomes - Requires monitoring for pro-atherogenic risk
Limitations in clinical Application	<ul style="list-style-type: none"> - Varies with age, disease stage, and metabolic state - Lags behind β-cell destruction - Normal levels may mask early damage 	<ul style="list-style-type: none"> - Not ideal as a standalone biomarker - Best interpreted in clinical context alongside other markers
Research & therapeutic outlook	<ul style="list-style-type: none"> - Preservation of C-peptide (e.g., 20%) lowers HbA1c by 0.5% - Demonstrates utility beyond the honeymoon phase - Supported by placebo-controlled studies 	<ul style="list-style-type: none"> - Encourages personalized therapy thresholds - Supports long-term trials for evaluating sustained benefits

T1DM: Type 1 diabetes mellitus; NF- κ B: nuclear factor kappa B; DKA: diabetic ketoacidosis.

Table 3. Summary of emerging disease-modifying therapies in type 1 diabetes mellitus: mechanisms, effects, and sex-based considerations

Therapy	Mechanism	Effects	Considerations
TNF- α inhibitors ^[89]	Suppress inflammatory cytokines	Lower HbA1c, increase C-peptide	Risk of hypoglycemia; sex-stratified trials needed
Anti-CD3 (Teplizumab)	Blocks T cell activation, preserves β -cells	Delays T1DM onset, maintains C-peptide for over 2 years	Females may exhibit differential immune responses
Abatacept (CTLA-4 fusion) ^[90]	Inhibits T cell co-stimulation (CD80/CD86)	Slows β -cell decline in early disease	More effective if initiated early; sex-specific response unclear
Treg cell therapy ^[92]	Restores immune tolerance	Temporarily delays T1DM progression	Irisin may enhance efficacy; lack of sex-specific data
MSC therapy ^[91]	Immunomodulatory; reduces β -cell apoptosis	Reduces HbA1c, increases C-peptide, lowers insulin needs	Some sex-specific adverse events reported (e.g., UTIs in women)
Vitamin D supplementation ^[95]	Enhances immune regulation and β -cell preservation	Mixed results; may reduce insulin autoantibodies	Deficiency more common in females with T1DM
C-Peptide therapies ^[70]	Improves endothelial function, reduces oxidative stress	Lowers risk of nephropathy and neuropathy	Promising adjunct; long-term benefits and sex-specific dosing need validation

T1DM: Type 1 diabetes mellitus; TNF- α : tumor necrosis factor-alpha; UTIs: urinary tract infections.

Investigational clinical-stage therapies

Abatacept

Abatacept [Table 2] is a cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) immunoglobulin that consists of the Fc portion of an antibody fused to CTLA-4. CTLA-4 is an immune checkpoint protein expressed on T cells, which can interact with CD80 and CD86 on antigen-presenting cells, leading to reduced T cell activity. In a study involving patients diagnosed with T1DM for less than 100 days,

continuous treatment with abatacept for over two years delayed β -cell function decline by 9.6 months. However, the overall rate of decline remained parallel to that observed in the placebo group^[90]. In another study involving siblings of individuals with T1DM or participants positive for GAD antibodies, one year of abatacept treatment did not significantly delay progression from stage 1 to stage 2 or 3 T1DM, despite achieving the anticipated immunologic effects. This suggests that after the development of two or more autoantibodies, blockade of CD80 and CD86 co-stimulation may no longer be effective at that stage of disease^[83]. Although further studies are required to determine its efficacy, current evidence indicates that abatacept may be most effective when administered early in the disease course [Table 3].

Mesenchymal stem cell therapy

Mesenchymal stem cells (MSCs) [Table 2] are fibroblast-like, spindle-shaped cells found in the umbilical cord, Wharton's jelly, bone marrow, and other tissues. They can be cultured *in vitro* and are capable of differentiating into multiple cell lineages following implantation. MSCs have immunomodulatory properties and interact with the immune system by modulating T lymphocytes, regulatory T cells (Tregs), and TNF- α all of which are implicated in certain autoimmune diseases^[91]. These properties make MSCs a promising candidate for clinical studies in autoimmune diseases such as T1DM. Several studies using MSCs derived from umbilical cord, adipose tissue, or Wharton's jelly have demonstrated increased C-peptide levels, reduced HbA1c, and decreased daily insulin requirements^[91]. Regarding safety, one study using allogeneic adipose tissue-derived stromal/stem cells combined with cholecalciferol reported adverse events, including headache, abdominal cramps, scotoma, thrombophlebitis, and mild localized reactions. However, other studies reported that MSC therapy was overall safe, with no serious adverse effects^[91].

Preclinical and translational research

Treg therapy for B cell preservation

Tregs [Table 2] play a role in modulating immune responses by suppressing autoreactive cells. Dysfunction of Tregs has been implicated in the pathophysiology of T1DM^[92]. Supporting this, studies have shown that patients with T1DM exhibit reduced expression of key Treg-associated mRNAs required for immunomodulation, including cytotoxic T lymphocyte-associated protein 4 (CTLA-4), interleukin-10 (IL-10) receptor alpha, and transforming growth factor beta 1 and 2 (TGF- β 1 and TGF- β 2)^[93]. Treg cell therapy involves isolating polyclonal Tregs from patients' peripheral blood, expanding them *ex vivo*, and reinfusing them into the patient. Although this therapy has been associated with improved glycemic control, C-peptide levels continued to decline progressively^[92]. Importantly, the therapy was shown to temporarily delay T1DM progression, with greater efficacy observed when administered during the earlier stages of the disease^[92]. Irisin, a myokine released through the proteolytic cleavage of fibronectin type III domain-containing protein 5 (FNDC5), has been found to support Treg function and immune modulation. It appears to reduce autoimmune activity targeting the pancreas and enhance Treg-mediated immune regulation^[93]. These findings suggest that combining irisin with Treg therapy may improve treatment outcomes [Table 3].

Vitamin D and phenolipid jambone E

Preclinical studies have suggested a role for vitamin D in the pathogenesis and management of T1DM [Table 2]. Vitamin D has been shown to protect B cells from cytokine-induced apoptosis and regulate immune responses, indicating that supplementation could potentially slow T1DM progression, as demonstrated in experimental models^[94]. Moreover, patients with T1DM tend to have lower vitamin D levels than healthy individuals, and vitamin D deficiency has been associated with poorer glycemic

control^[94]. One study found that combining saxagliptin with vitamin D resulted in a smaller decline in the 2-hour mixed meal tolerance test C-peptide area under the curve (AUC) over 24 months compared to Saxagliptin alone. However, there was no significant difference in fasting C-peptide levels between the groups^[95]. Other interventional studies have yielded conflicting results: one reported a reduction in insulin autoantibodies after 6 months of calcitriol supplementation, while another found no significant effects on C-peptide or hemoglobin A1c (HbA1c) levels^[94]. Given the limited sample sizes, further studies are needed to better assess the potential of vitamin D as an adjunct therapy in T1DM [Table 3]. Jambone E (JE), a novel phenolipid compound, has shown promising antidiabetic properties. Preclinical studies have demonstrated that JE improves glucose metabolism, reduces hyperglycemia and hyperlipidemia, and enhances insulin signaling through protein kinase B (AKT) activation in both cell and mouse models. Metabolomic analyses have also identified relevant biomarkers supporting JE's therapeutic potential in diabetes management^[96]. In accordance with the findings summarized in Table 4, both clinical and preclinical studies have extensively quantified treatment outcomes in T1DM.

Table 4. Summary of clinical and preclinical studies quantifying treatment outcomes in T1DM

Therapy	Type of study	Sample size	Mean C-peptide preservation	HbA1c reduction (%)	Adverse events	Reference
Teplizumab	Phase 3 RCT	328	Preserved at 2 years	~0.5%	Rash, lymphopenia	[89]
Anti-TNF (Golimumab)	Phase 2 RCT	84	+0.2 nmol/L over 52 weeks	~0.3%	GI symptoms	[10]
Abatacept	Phase 2 RCT	112	N/A	~0.2%	Mild infections	[90]
MSC therapy	Pilot clinical trial	40	+0.15 nmol/L	~0.6%	None serious	[91]
Treg therapy	Phase 1	14	Transient effect	N/A	Well-tolerated	[92]

T1DM: Type 1 diabetes mellitus; MSC: mesenchymal stem cell; GI: gastrointestinal, RCT: randomized controlled trial.

Contrasting preclinical and clinical immunological findings in T1DM

In NOD mouse models, B-cell depletion has shown marked efficacy in preventing or halting the progression of T1DM. Specifically, B-cell-deficient NOD mice do not develop spontaneous diabetes. Furthermore, disease transfer experiments demonstrate that co-transfer of diabetic splenocytes with activated B cells restores disease, whereas B cells pre-treated with anti-CD80/86 antibodies fail to induce diabetes. These findings underscore the role of B cells as APS in activating autoreactive T cells and propagating the disease^[81].

In contrast, translating these findings into human clinical trials has proven challenging. Although B cells are found within human islet infiltrates and are responsible for producing disease-associated autoantibodies {e.g., anti-insulin, glutamic acid decarboxylase 65 [GAD65], insulinoma-associated antigen 2 [IA2], and zinc transporter 8 [ZnT8]}, clinical strategies targeting B cells remain limited. This is partly due to the functional heterogeneity of human B cells and the unclear pathogenic significance of autoantibodies. While anti-CD20 therapies, such as rituximab, have shown promise in delaying disease progression when administered early, they do not prevent T1DM onset and are associated with increased risks of infection and impaired immune surveillance^[89].

LIMITATIONS & FUTURE DIRECTIONS

Managing T1DM in children requires maintaining stable blood glucose levels to support normal growth and development and to prevent long-term complications. Core management strategies include insulin therapy and dietary modifications, with increasing attention to the glycemic index of carbohydrates. Research shows

that low-glycemic index diets can significantly improve glycemic control by reducing blood glucose fluctuations, lowering HbA_{1c} levels, and decreasing insulin needs, likely through their impact on weight and obesity. However, adherence to dietary recommendations remains a challenge, especially due to the need to restrict certain foods, which may inadvertently lead to increased fat consumption. A well-balanced diet that limits high-glycemic index foods while maintaining adequate carbohydrate intake for growth may effectively complement insulin therapy in achieving better glycemic control in children with T1DM^[97].

Despite the promise of newer diabetes technologies such as continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM), several limitations persist, involving healthcare professionals, patients, and the technology itself. Healthcare providers must be well-trained and supportive of these technologies to facilitate their adoption. However, biases in patient selection and limited provider

experience with advanced tools can hinder successful implementation. From the user's perspective, challenges include frequent sensor calibrations, infusion site changes, and interpreting real-time data, which may be overwhelming. Although structured education on flexible insulin regimens has been shown to reduce hypoglycemia, many patients still struggle with optimal glucose control. Treatment adherence remains a major obstacle, as not all patients are willing or able to consistently use these technologies. Common reasons for discontinuation include discomfort, inconvenience, and concerns about device accuracy - despite notable advances that have improved user compliance. Accuracy concerns persist, particularly due to sensor lag during rapid glucose changes, which may result in misinterpretations. Alarm fatigue is another frequent complaint, where repeated alerts can become disruptive, sometimes leading to device abandonment. Enhanced training and support systems may help mitigate these challenges and improve the effectiveness of diabetes technologies^[98].

This article builds upon recent literature by providing a comprehensive synthesis of emerging insights into T1DM, specifically focusing on the roles of sex differences, the liver, and C-peptide in disease progression and management. Unlike previous reviews that primarily emphasized Treg cell-based therapies as promising but still investigational, this article expands the scope to include broader immunological mechanisms involving both T cells and B cells. It also evaluates the therapeutic potential of novel disease-modifying interventions, including TNF- α inhibitors, anti-CD3 antibodies, and cell-based therapies beyond Tregs.

Moreover, the article emphasizes the importance of personalized and gender-specific treatment strategies, advocating for more targeted research in these areas. By integrating the latest evidence and addressing current knowledge gaps, this article sets the stage for advancing clinical practice and improving patient outcomes in T1DM, while also recognizing the ongoing challenges and opportunities associated with Treg-based therapies.

Future progress in diabetes technology, alongside improved understanding and psychological support, may help overcome existing barriers to adoption. Addressing concerns such as the fear of hypoglycemia and enhancing patient education will be crucial for optimizing both conventional and novel treatment approaches. These developments, grounded in evidence-based strategies, hold promise for improving disease management and quality of life for individuals with T1DM^[98].

CONCLUSION

In conclusion, T1DM remains a complex and multifaceted disease, with ongoing advancements in understanding its pathophysiology and clinical management. Despite significant progress in areas such as

disease-modifying therapies, liver involvement, and the emerging relevance of C-peptide, challenges persist in achieving optimal disease control and preventing long-term complications. The exploration of sex-based differences in disease presentation, along with the development of novel therapeutic strategies, presents new avenues for improving patient outcomes. Future research should continue to address these gaps, particularly in the context of personalized and gender-specific treatments. By building upon these insights, there is hope for advancing the management and potential modification of T1DM, ultimately improving the quality of life for individuals living with this chronic condition.

DECLARATIONS

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