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Review Article

Emerging Therapeutics Targeting Cellular Stress Pathways to Mitigate End-Organ Damage in Type 1 Diabetes

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Abstract
Type 1 diabetes (T1D) is an autoimmune disease characterized by insulin deficiency and impaired glucose regulation. While daily insulin therapy is life-saving, many patients struggle to achieve optimal glycemic control, leading to microvascular complications affecting various organs, including the kidneys and the liver. This review aims to summarize the current state of knowledge regarding the pathogenesis of hepatic and renal complications in T1D, highlight recent advances in potential therapeutic targets, and provide evidence-based recommendations for mitigating end-organ damage. Chronic hyperglycemia drives diabetic complications through several interrelated mechanisms, including increased polyol pathway flux, advanced glycation end-product (AGE) formation, protein kinase C activation, and mitochondrial reactive oxygen species overproduction. In the liver, these processes contribute to non-alcoholic fatty liver disease, with up to 50% of T1D patients developing hepatic steatosis. Diabetic nephropathy, affecting 25%–40% of long-term T1D patients, is characterized by glomerular basement membrane thickening, mesangial expansion, and tubulointerstitial fibrosis. Recent innovations in T1D management include genomics and precision medicine approaches, gut microbiome modulation, nanomedicine, and artificial intelligence-driven glucose monitoring systems. Emerging immunotherapies aim to fundamentally modify the autoimmune response in T1D. Mitigating T1D complications requires intensive glycemic control, targeted pharmacotherapy, and lifestyle modifications. Emerging therapies and precision medicine approaches offer promising avenues. Ongoing research into molecular mechanisms remains crucial for developing novel interventions and improving long-term outcomes in T1D patients.
Keywords: Type 1 diabetes, Diabetic nephropathy, Diabetic liver disease, Oxidative stress, Fibrosis

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Background

Type 1 diabetes (T1D) is an autoimmune disease characterized by T cell-mediated destruction of insulin-producing pancreatic beta cells, resulting in insulin deficiency and impaired glucose regulation. While daily insulin therapy is life-saving, various patients struggle to achieve optimal glycemic control. Hyperglycemia is associated with microvascular complications affecting the kidneys, eyes, nerves, and cardiovascular system. There is now recognition that the liver is also a target organ subject to injury in T1D (1-5).

Diabetic nephropathy, leading to progressive chronic kidney disease, is one of the most severe complications of T1D. It affects 25%–40% of patients with a diabetes duration over 20 years. Hyperglycemia triggers kidney damage through multiple pathways, including advanced glycation end-product (AGE) formation, polyol flux, oxidative stress (OS), and pro-inflammatory and profibrotic signal activation. This results in structural changes, including glomerular basement membrane thickening, hypertrophy, mesangial expansion, and tubulointerstitial fibrosis. Functionally, increased glomerular permeability and albuminuria occur early, followed by a declining glomerular filtration rate (6,7).

Diabetic liver disease refers to a spectrum of abnormalities, ranging from steatosis to steatohepatitis and cirrhosis. Up to 50% of T1D patients develop non-alcoholic fatty liver disease (NAFLD). Insulin deficiency promotes adipose lipolysis, increasing free fatty acid flux to the liver. Hyperglycemia also drives de novo lipogenesis while impairing mitochondrial fatty acid oxidation. This imbalance causes triglyceride accumulation in hepatocytes. A subset of patients progresses to non-alcoholic steatohepatitis (NASH) with inflammation

and fibrosis, which can advance to cirrhosis. Chronic hyperglycemia promotes OS, hepatocyte death, and dysregulated repair mechanisms that contribute to liver injury. The pathophysiology underlying hepatic and renal complications in T1D is complex and multifactorial (8,9).

Chronic hyperglycemia is implicated as a major driver of diabetic complications through several interrelated mechanisms (Table 1). First, increased flux through the polyol pathway is associated with deleterious osmotic stress and OS. Second, the generation and accumulation of advanced glycation end-products (AGEs) trigger inflammatory pathways and fibrosis through receptor-mediated signaling cascades, such as the receptor for AGE (RAGE). Third, the activation of various protein kinase C isoforms by hyperglycemia alters gene transcription in pathways that promote fibrotic changes. Fourth, the mitochondrial overproduction of reactive oxygen species (ROS), induced by excess glucose metabolism, can damage proteins, lipids, and DNA. Finally, the repeated cycles of glycogen accumulation and removal in tissues such as the liver and kidneys induced by a sustained excess glucose supply create cellular stress (10,11). Overall, these multiple downstream effects of chronic hyperglycemia are understood to drive the micro- and macro-vascular complications associated with poorly controlled diabetes. Hyperglycemia also dysregulates lipid metabolism, complement pathways, endothelial function, and gut microbial communities in ways that contribute to end-organ damage. Genetic and epigenetic factors influence individual predisposition and progression rate.

Aggressive glycemic control and pharmaceutical management targeting downstream pathways can mitigate complications, but additional therapies are needed in this regard. Ongoing research into the molecular drivers of injury and potential areas for intervention, such as inflammation, OS, and the microbiome, continues to be essential for improving the long-term prognosis of T1D (12-14). This review attempts to summarize the current state of knowledge concerning the pathogenesis of these microvascular complications, highlight the most recent advances in potential remedial targets, and present evidence-based suggestions for mitigating end-organ damage in patients with T1D. It is noteworthy that the focus on emerging combination approaches makes this review unique.

Pathogenesis of Hepatic Effects in Type 1 Diabetes

While the renal complications of poorly controlled T1D are well established, there is growing recognition that the liver is also a target organ subject to injury. The mechanisms linking T1D to liver damage include hyperglycemia, inflammation, and OS. Hyperglycemia appears to be a key driver of hepatic complications in T1D. Elevated blood glucose causes increased glycolysis and mitochondrial overproduction of ROS. ROS activate profibrogenic pathways and impair hepatocyte function. Hyperglycemia also promotes the generation of AGEs. The binding of AGEs to RAGE triggers OS and inflammation. Additionally, hyperglycemia alters lipid metabolism, leading to hepatic steatosis (15,16).

Inflammation significantly contributes to hepatic pathology in T1D. Levels of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and IL-6 are elevated in T1D patients. Chronic low-grade inflammation activates Kupffer and hepatic stellate cells, promoting fibrosis. Hyperglycemia-induced mitochondrial dysfunction and endoplasmic reticulum stress further feed into inflammatory pathways (17-19). OS is both a consequence and a driver of high blood glucose and inflammation in T1D. ROS generation outpaces antioxidant defenses, modifying lipids, proteins, and DNA. This oxidative damage impairs hepatocyte function and activates hepatic stellate cells to deposit collagen. Nitric oxide bioavailability is also reduced, contributing to the vasoconstriction of hepatic sinusoids (20,21).

NAFLD is the most common hepatic manifestation of T1D. It encompasses a spectrum ranging from simple steatosis to NASH, with the risk of progression to cirrhosis. Up to 50% of T1D patients have NAFLD, with a higher prevalence in older individuals with longer disease duration. Insulin deficiency leads to upregulated lipolysis and increased free fatty acid delivery to the liver. Hyperglycemia also drives de novo lipogenesis through activating carbohydrate response element-binding proteins. Mitochondrial dysfunction impairs fatty acid oxidation. This imbalance between synthesis, uptake, and oxidation causes excessive triglyceride accumulation in hepatocytes (22-25).

NASH represents more advanced NAFLD with hepatocellular injury, inflammation, and fibrosis. The mechanisms linking T1D to NASH progression are multifactorial. Hyperglycemia induces OS and hepatocyte death. Proinflammatory cytokines activate Kupffer cells and recruit lymphocytes to the liver. The activation of hepatic stellate cells increases collagen deposition, while

Table 1. Mechanisms of Liver Injury in Type 1 Diabetes

Mechanism	Description
Hyperglycemia	Increased glycolysis and mitochondrial ROS production impair hepatocyte function; AGE generation triggers inflammation and fibrosis via RAGE.
Inflammation	Elevated cytokines, such as TNF-α, IL-1β, and IL-6, activate hepatic macrophages and stellate cells to drive fibrosis.
OS	ROS overproduction from hyperglycemia damages cellular components and impairs NO availability.
Dyslipidemia	Insulin deficiency → adipose lipolysis → hepatic FFA accumulation; de novo lipogenesis and impaired mitochondrial FA oxidation.

Note. ROS: Reactive oxygen species; AGE: Advanced glycation end-products; RAGE: Receptor for advanced glycation end-products; TNF-α: Tumor necrosis factor alpha; IL-1β: Interleukin-1 beta; NO: Nitric oxide; FFA: Free fatty acid; OS: Oxidative stress.

impaired matrix degradation leads to fibrosis. There is emerging evidence that the gut microbiome may contribute to NASH through the release of lipopolysaccharides and other pathogen-associated molecular patterns. Small intestinal bacterial overgrowth and increased gut permeability are the features of T1D that may drive hepatic inflammation (26-29).

Uncontrolled T1D accelerates the progression of chronic liver injury to cirrhosis. The repeated cycles of necroinflammation lead to disruption of the normal hepatic architecture and collagen scarring. Patients with T1D have a 3–4-fold higher risk of cirrhosis compared to those without diabetes. Cirrhosis, in turn, increases the risk of liver failure and hepatocellular carcinoma. The duration of diabetes and the degree of glycemic control are major determinants of fibrosis progression. Additional factors such as obesity, hypertension, and genetic polymorphisms likely modify susceptibility to advanced fibrosis in T1D (30-37).

Relationship Between Type 1 Diabetes and Glomerulonephritis

Diabetic nephropathy leading to chronic kidney disease is a major complication of poorly controlled T1D. While diabetic nephropathy classically manifests as nodular glomerulosclerosis on biopsy, some patients develop other patterns of injury resembling primary GN. T1D can be complicated by or contribute to multiple histological forms of GN through mechanisms linked to the metabolic and immune effects of hyperglycemia.

At a molecular level, hyperglycemia induces kidney damage through several interconnected pathways. Increased glucose flux through the polyol pathway accumulates sorbitol in cells, causing osmotic stress. The accumulation of AGEs triggers inflammation and fibrosis through receptors such as RAGE. Protein kinase C activation and hexosamine pathway flux alter gene expression profiles. The mitochondrial overproduction of ROS is both a consequence and a driver of high glucose levels (38-41). In general, these mechanisms promote glomerular damage in diabetic nephropathy. Several types of GN are associated with T1D, including some that may be secondary to hyperglycemia-induced injury (Table 2). Membranous nephropathy is characterized by glomerular basement membrane thickening and is one of the most common findings in T1D patients biopsied for proteinuria. Hyperglycemia may directly induce changes in podocytes and alter basement membrane components through non-enzymatic glycation. Increased vascular endothelial growth factor levels can disrupt the filtration barrier. Autoantibodies against podocyte antigens such as M-type phospholipase A2 receptor are also described in T1D (42, 43).

Post-infectious glomerulonephritis (GN) follows bacterial infections such as streptococcal pharyngitis and manifests with proliferation, crescents, and deposits. T1D patients have increased susceptibility to certain infections, which may predispose them to this immune-mediated complication. Episodes of poor glycemic control also impair neutrophil function, leading to dysfunctional immune responses to pathogens. Immunoglobulin A (IgA) nephropathy demonstrates mesangial IgA deposition with variable proliferation and scarring. The association with T1D is likely multifactorial. Hyperglycemia may directly impact IgA production and glycosylation. Increased mucosal permeability in T1D could enable food or bacterial antigens to trigger nephritogenic IgA. Shared immunogenetic risks, such as IL-10 polymorphisms, may predispose to both diseases (44).

Rapidly progressive GN has features of necrosis, crescents, and a rapid decline in kidney function. The causes include anti-neutrophil cytoplasmic antibody vasculitis, anti-glomerular basement membrane disease, and immune complex deposition. The role of T1D is controversial, though shared genetic and environmental risk factors are proposed. Hyperglycemia directly causes OS and endothelial dysfunction that could contribute to vascular inflammation (45,46).

Recent Innovations in Treating Type 1 Diabetes

The treatment of T1D requires lifelong insulin replacement therapy and careful blood glucose monitoring. However, the complex pathophysiology of T1D offers opportunities for innovative therapies beyond insulin aimed at preserving beta cell function, modulating autoimmunity, and improving glycemic control. Ongoing research is leveraging new tools in genomics, gut microbiota modulation, nanomedicine, herbal medicine, artificial intelligence (AI), and immunotherapy (47,48).

Genome, omics, and precision medicine approaches are uncovering new molecular pathways and treatment targets for T1D (Table 3). Large-scale genetic studies have identified over 60 genomic loci associated with T1D risk. Many of them contain immune-related genes, highlighting

Table 2. Types of GN Associated With Type 1 Diabetes

Type	Key Features	Potential Role of T1D
Membranous nephropathy	Glomerular basement membrane thickening	Direct effects of hyperglycemia on podocytes, the glomerular basement membrane
Mesangiocapillary GN	Mesangial expansion, complement deposition	Hyperglycemia-induced mesangial matrix expansion, complement activation
Post-infectious GN	Proliferation, crescents, and immune deposits	Increased infections in T1D; hyperglycemia impairs immune responses
IgA nephropathy	Mesangial IgA deposits	Impact of hyperglycemia on IgA; gut permeability driving autoimmunity
Rapidly progressive GN	Necrosis, crescents, and rapid functional decline	Unclear; potential contributions from hyperglycemia, shared genetic risks

Note. GN: Glomerulonephritis; IgA: Immunoglobulin A.

Table 3. Emerging Therapeutics for Type 1 Diabetes Complications

Approach	Examples	Mechanisms
Genomics and precision medicine	- Gene association studies, next-generation sequencing, and omics technologies	- Identifying molecular pathways, defining disease subtypes, and enabling customized treatment
Gut microbiome modulation	- Probiotics, prebiotics, antibiotics, and fecal microbiota transplantation	- Correcting dysbiosis, modulating immunity, and repairing barrier defects
Nanomedicine	- Encapsulate insulin, immunosuppressants, glucose-responsive release, and targeted delivery	- Improving oral bioavailability, enhancing cell/tissue specificity, and reducing off-target effects

the importance of pancreatic autoimmunity. Other implicated genes regulate beta-cell function and survival. Next-generation sequencing enables high-resolution examination of the genetic and epigenetic heterogeneity in T1D. Omics technologies, including transcriptomics, proteomics, and metabolomics, provide additional layers of molecular data. For example, circulating microRNAs show promise as biomarkers of beta-cell stress and early islet autoimmunity. The goal is to precisely define disease subtypes and match individuals with customized treatment regimens (49,50).

Modulating the gut microbiome is an active area of research for preventing and managing T1D. Alterations in the intestinal microbiota are detectable years before the onset of autoimmunity. The transfer of gut microbes from humans with T1D can trigger autoimmune diabetes in mice. Probiotics, prebiotics, antibiotics, and dietary changes are being studied to correct dysbiosis and support immune regulation. Fecal microbiota transplantation may hold potential. Additionally, strategies to repair intestinal barrier defects may limit the translocation of inflammatory bacterial products. Minimizing microbiome disruptions early in life could lower the risk of autoimmunity. Ongoing research is defining optimal therapeutic approaches (51-53).

Nanomedicine utilizes nanoparticles (NPs) for targeted drug delivery in T1D. Encapsulating insulin or immunosuppressants in NPs helps overcome barriers to oral administration and protects payloads from degradation. NPs can be engineered to selectively release insulin in response to glucose. Coating NPs with ligands targets them to inflamed islets or immune cells, improving bioavailability while reducing off-target effects. Additionally, NPs are being developed for the intracellular delivery of immunomodulatory genes or RNA interference constructs. Further innovation in nanotechnology could enable cell-specific therapies (54-60). Traditional herbal medicines and Chinese formulations are also being studied for T1D. Compounds such as curcumin and berberine exhibit anti-inflammatory, antioxidant, and immunomodulatory bioactivities with preclinical efficacy in diabetes models. Other natural products, such as resveratrol and epigallocatechin gallate, found in green tea (EGCG), protect beta cells from cytokine-induced apoptosis in vitro. Clinical trials are ongoing, but high-quality evidence in humans remains limited. Safety considerations regarding drug interactions exist. Nevertheless, certain herbs and supplements may emerge as useful adjuvants (61-64).

AI and machine learning tools are transforming glucose monitoring and insulin dosing for T1D patients. Closed-loop systems integrate continuous glucose monitors with insulin pumps by using algorithms to automate insulin delivery. Data analytics identify personalized patterns and tailor therapy. Machine learning can even forecast eventual glycemic deterioration and enable earlier intervention. Beyond automation, AI may gain the ability to replicate clinician decision-making for fully autonomous care. With further refinement, AI-driven platforms could revolutionize diabetes self-management (65,67). Novel immunotherapies aim to fundamentally modify the autoimmune response in T1D. Agents targeting T cells, B cells, dendritic cells, and immune signaling pathways are under development. For example, teplizumab delays T1D onset by impairing pathogenic T cells. Abatacept inhibits T cell activation, and rituximab depletes autoantibody-producing B cells. Antigen-specific immunotherapy utilizes peptides or modified autoantigens to induce tolerance. Combination approaches are also being tested to synergistically rebalance immunity. Though challenges exist, immunotherapy holds hope for durable remission (68-70).

Recommendations for Protecting the Liver and Kidneys in Patients With Type 1 Diabetes

T1D confers an increased risk for liver disease and diabetic nephropathy, leading to chronic kidney disease. While complete prevention of these complications is difficult, optimizing glycemic control and using specific pharmaceuticals and lifestyle approaches can help protect organ function (71,72). Intensive glycemic control is foundational for minimizing liver and kidney damage in T1D. The Diabetes Control and Complications Trial clearly demonstrated that maintaining hemoglobin A1c levels < 7% greatly reduced microvascular complications (73).

For the liver, improved glycemic control reduces the risk of progression from simple steatosis to steatohepatitis and fibrosis. In the kidneys, tight glucose control significantly decreases proteinuria and slows a decline in the glomerular filtration rate. Real-time continuous glucose monitoring enables patients to spend more time in the target glycemic range. Islet transplantation and advanced insulin delivery systems, such as closed-loop pumps, also improve control (74-79).

Pharmaceutical management is multifaceted. Firstly, angiotensin-converting enzyme inhibitors and

angiotensin receptor blockers are critical. By blocking the renin-angiotensin-aldosterone system (RAAS), they reduce proteinuria, blood pressure, inflammation, and fibrosis. Developed RAAS inhibitors are recommended for both renal and hepatic protection in diabetes. Recently, sodium-glucose cotransporter-2 (SGLT2) inhibitors, such as empagliflozin, have emerged as novel agents to reduce complications. These inhibitors lower glucose by increasing urinary excretion, thereby reducing glomerular hyperfiltration and tubular stress. They may also have direct anti-inflammatory and antifibrotic effects. Dual RAAS and SGLT2 blockades demonstrate synergy in slowing diabetic kidney disease. The benefits for liver outcomes are being investigated (80-83).

Additionally, dyslipidemia management with statins and triglyceride-lowering agents is important. Statins reduce cardiovascular risk and may attenuate fatty liver disease. Fibrates such as gemfibrozil primarily lower triglycerides, which likely contributes to their efficacy in diabetic kidney disease trials. Omega-3 fatty acids show potential for NAFLD and diabetic nephropathy, based on small studies. Multidrug regimens are often needed for optimal treatment (84).

Lifestyle measures are crucial adjuvants in diabetes care. Weight loss in obesity provides benefits, as a higher body mass index is an independent risk factor for complications (Table 4). Smoking cessation is critical, given the synergistic adverse effects of smoking and diabetes on vessels. A Mediterranean-style diet high in polyunsaturated fats, fiber, and antioxidants such as flavonoids reduces inflammation and dyslipidemia. Aerobic and resistance exercise improves glycemic control, insulin sensitivity, and cardiovascular health. Stress management techniques such as yoga lower blood pressure and cortisol levels. Such lifestyle modifications synergize with pharmaceutical management (85-87).

Conclusion

Poor glycemic control promotes oxidative damage, inflammation, and fibrosis through interconnected mechanisms, including the accumulation of sorbitol and AGEs, protein kinase C activation, and mitochondrial ROS generation. In the liver, this manifests as NAFLD and a risk for progression to cirrhosis. In the kidneys, injury to glomerular structures leads to proteinuria and declining filtration. Emerging omics, nanotechnology, microbiome, AI, and immunotherapy approaches offer opportunities for earlier diagnosis, improved monitoring, and treatments that target root molecular pathways. However, intensive glycemic control remains the foundation for minimizing end-organ damage. Further research into the complex pathophysiology underlying diabetic microvascular complications is critical for developing combination therapies that preserve hepatic and renal function in T1D.

Recommendations

To protect the liver and kidneys in patients with T1D, clinicians should focus on optimizing glycemic control through continuous glucose monitoring, insulin pumps, and islet transplantation when feasible. Angiotensin system inhibitors, SGLT2 inhibitors, statins, and triglyceride-lowering agents should be utilized for pharmaceutical management. Lifestyle measures, such as weight loss, smoking cessation, a Mediterranean diet, and exercise, have synergistic benefits. Future research should continue to uncover disease subtypes and personalized therapy approaches through omics while also exploring the potential of emerging nanotechnology, microbiome modulation, natural products, and immunotherapy. Using these evidence-based combination strategies can help mitigate diabetic nephropathy and liver disease.

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Competing Interests

None declared.

Ethical Approval

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Table 4. Recommendations for Hepatorenal Protection in Type 1 Diabetes

Modality	Specific Examples	Benefits
Glycemic control	- Intensive insulin therapy, continuous glucose monitors, insulin pumps, and islet transplants	- Reducing microvascular complications
Pharmaceuticals	- ACEi/ARBs, SGLT2 inhibitors, statins, and fibrates	- Decreasing proteinuria and fibrosis - Improving lipid profile
Lifestyle	- Weight loss, smoking cessation, Mediterranean diet, and exercise	- Reducing inflammation - Improving insulin sensitivity - Lowering cardiovascular risk

Note. ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; SGLT2: Sodium-glucose cotransporter-2

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