

Hepatic involvement in children with diabetes: Pathophysiology, clinical manifestations, and current management

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ABSTRACT

Diabetes is a chronic disease characterized by hyperglycemia resulting from insulin deficiency or resistance to insulin action. Its onset may result from polygenic or monogenic mechanisms. The liver plays a central role in glucose metabolism and can be affected by various conditions. In poorly controlled type 1 diabetes, glycogenic liver disease presents with hepatomegaly and elevated liver enzymes, which is reversible with good metabolic control. Autoimmune hepatitis may coexist with type 1 diabetes due to shared immunological mechanisms or may develop during treatment with corticosteroids. In type 2 diabetes, metabolic dysfunction-associated steatotic liver disease (MASLD) is common and can progress to severe forms. Monogenic forms may be associated with structural abnormalities of the liver and biliary tract. Early recognition of liver involvement and a multidisciplinary approach are essential for preventing long-term complications.

Keywords: *diabetes mellitus; complications of diabetes; liver diseases; nonalcoholic fatty liver disease; diabetes mellitus with onset in adulthood.*

doi: <http://dx.doi.org/10.5546/aap.2026-11117.eng>

To cite: Lezama Elecharri C, Álvarez F. Hepatic involvement in children with diabetes: Pathophysiology, clinical manifestations, and current management. *Arch Argent Pediatr.* 2026;e202611117. Online ahead of print 8-OCT-2026.

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Funding: None.

Conflict of interest: None.

Received: 4-13-2026

Accepted: 8-10-2026



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INTRODUCTION

Diabetes is a chronic endocrine-metabolic disease characterized by elevated blood glucose levels resulting from decreased insulin production or inadequate insulin utilization.^{1,2} In cases of type 1 diabetes, an autoimmune disease that leads to the destruction of insulin-producing cells,³ and type 2 diabetes, which occurs as a result of a metabolic change known as insulin resistance,⁴ the inheritance pattern is polygenic.⁵⁻⁷ In other words, several genes contribute to the pathogenesis of these diseases, leading to genetic susceptibility.

Some forms of diabetes have a monogenic cause, known as MODY (maturity-onset diabetes of the young), which generally affects children or young adults and is inherited in an autosomal dominant manner.⁸ Some of the genes responsible for MODY are transcription factors, which are expressed not only during embryonic development in the pancreas but also in the liver and kidneys. In the liver, they play a role not only in the development and maturation of the intra- and extrahepatic bile ducts but also in the final formation of the organ's structure.⁹

In this review, we describe the characteristics of liver complications associated with different types of diabetes, which an interdisciplinary team must detect and treat. In some cases, these liver diseases can be severe and require appropriate treatment and rigorous follow-up due to their potential short-, medium-, and long-term effects on liver function.¹

POLYGENIC DIABETES AND LIVER DISEASE

Polygene-driven diabetes results from the interaction between multiple genetic variants—many of which are still under study—and environmental factors that lead to an imbalance in glycemic control.⁶ In this context, the liver emerges as a key organ not only in glucose homeostasis but also as a target for various clinical manifestations associated with metabolic and immunological imbalances.⁵

Diabetes in childhood is not a homogeneous condition, and liver involvement in children with diabetes poses a diagnostic and therapeutic challenge.⁵ It is essential to consider conditions with distinct—though potentially overlapping—pathophysiological mechanisms, such as glycogenic liver disease,¹⁰ autoimmune hepatitis¹¹ and metabolic dysfunction-associated steatotic liver disease (MASLD).¹²

Integrating the interplay between genetics,

immunity, and metabolism in childhood supports more precise diagnostic strategies and targeted treatments.

Glycogenic liver disease

Glycogenic liver disease (GLD) is characterized by excessive glycogen storage in hepatocytes. It is primarily observed in children or adolescents with type 1 diabetes and poor metabolic control, although it has also been reported in patients with type 2 diabetes treated with insulin.¹³

It was first described by Paul Mauriac as part of a classic triad consisting of hepatomegaly, cushingoid features, and delayed puberty, which gave rise to what is known as Mauriac syndrome.¹⁴ Most reports are small case series, and since the introduction of intensive insulin regimens, continuous glucose monitoring, and routine glycated hemoglobin testing, this complication has become rare.¹⁵

Its pathophysiology involves marked fluctuations in blood glucose levels and exogenous insulin administration in the context of poor metabolic control.¹⁰ Sustained hyperglycemia facilitates the uptake of glucose into hepatocytes via GLUT-2 transporters, a process that is independent of insulin. Subsequent insulin administration stimulates glycogen synthase activity and promotes glycogen synthesis and accumulation.¹⁰ Hepatomegaly is a direct consequence of this intracellular storage.

Furthermore, chronic relative insulin deficiency—the anabolic hormone par excellence, stimulates peripheral lipolysis, generating substrates for hepatic lipogenesis and promoting dyslipidemia.¹⁰ Recurrent hypoglycemia, secondary to insulin administration, can activate counterregulatory mechanisms leading to increased cortisol. Sustained elevation of cortisol, along with decreased IGF-1 levels secondary to poor metabolic control, contributes to the classic manifestations of the syndrome, such as growth retardation, hypogonadism, and cushingoid features.¹⁵

Findings may resemble those in children with MASLD, although liver enzyme levels are generally higher, with aspartate aminotransferase (AST) predominating. Liver biopsy establishes a definitive diagnosis.¹⁶

Histologically, diffuse hepatocyte enlargement with pale cytoplasm and prominent cell membranes is observed. Periodic acid-Schiff (PAS) staining reveals glycogen deposits that

disappear after diastase treatment, which selectively digests them (*Figure 1*).

With proper metabolic control, liver involvement is reversible; in general, it is associated with a low risk of progression to advanced liver disease.¹³

Autoimmune hepatitis and diabetes

In pediatrics, the coexistence of autoimmune hepatitis (AIH) and diabetes is a rare clinical condition that can influence diagnostic and therapeutic decision-making.¹⁷

AIH is a chronic inflammatory liver disease characterized by IgG hypergammaglobulinemia, specific autoantibodies, and a favorable response to immunosuppressive therapy.¹⁷⁻¹⁹

Conventional treatment is based on a combination of immunosuppressive drugs, with corticosteroids serving as the first-line therapy.^{11,20}

Various pediatric series report the prevalence of AIH associated with another autoimmune disease ranging from 20% to 40%; among the most frequently described are autoimmune thyroiditis, type 1 diabetes, ulcerative colitis, Crohn's disease, and celiac disease.^{17,20}

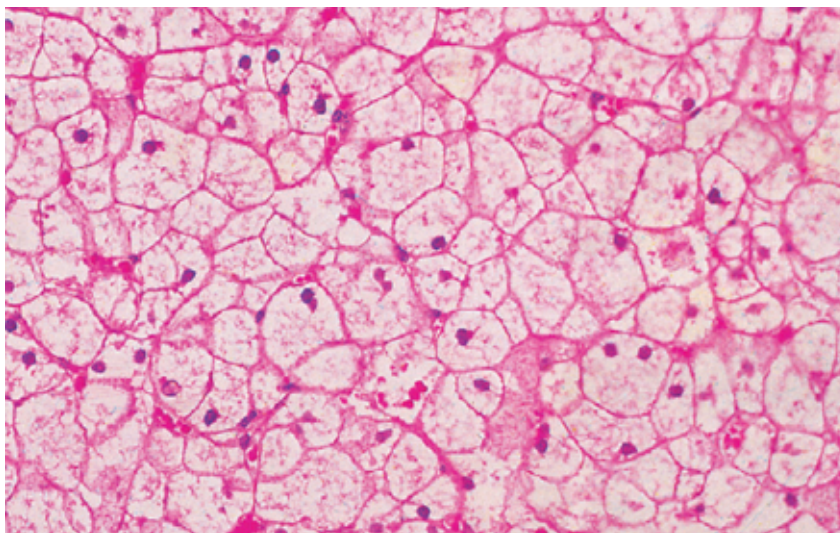
From a pathophysiological perspective, the coexistence of AIH and type 1 diabetes may reflect shared autoimmunity. Both conditions are strongly associated with certain class II major histocompatibility complex haplotypes, particularly HLA-DR3 and HLA-DR4, which promote the loss of immune tolerance, the production of

autoantibodies, and the activation of autoreactive T cells, reflecting a common susceptibility to organ-specific autoimmune phenomena.²¹

Corticosteroids can induce hyperglycemia, which may be explained by the interaction between an individual's metabolic predisposition and increased hepatic glucose production from stimulation of gluconeogenesis and increased expression of gluconeogenic enzymes, thereby promoting glucose release into circulation.^{22,23} Furthermore, they induce peripheral insulin resistance by reducing the glucose uptake in skeletal muscle and decrease GLUT-4 transporter translocation, while in adipose tissue they promote lipolysis and an increase in free fatty acids, exacerbating insulin resistance.^{22,23} In some patients, impaired pancreatic β -cell function may also be observed, which limits the compensatory response to hyperglycemia.²² The maximum hyperglycemic effect of corticosteroids usually occurs 4 to 8 hours after administration.^{22,23} The risk of developing steroid-induced diabetes is higher in individuals with a genetic predisposition to type 2 diabetes, obesity, metabolic syndrome, advanced age, or prolonged treatment and/or high doses. However, in the early stages, it is not always easy to distinguish between autoimmune diabetes and treatment-induced diabetes.

In patients with type 1 diabetes who present with persistent abnormal liver enzyme levels, a diagnosis of AIH should be considered.¹⁷ In the presence of hypergammaglobulinemia or specific

FIGURE 1. Liver biopsy section from a child with Mauriac syndrome



Section stained with hematoxylin and eosin. Hepatocyte distension due to glycogen deposition.

autoantibodies, a liver biopsy is recommended to determine the type of liver involvement.²⁴ Immunosuppressive therapy should avoid the use of corticosteroids.¹¹ It has been reported that the response to treatment for AIH is similar in patients with or without diabetes, although it has been associated with higher rates of death or liver transplantation.¹⁷

Type 2 diabetes and liver disease associated with metabolic dysfunction

Type 2 diabetes and metabolic dysfunction-associated steatotic liver disease (MASLD) represent two closely related manifestations of the spectrum of metabolic disorders linked to insulin resistance.^{25,26} In recent decades, the rise in childhood obesity has contributed to the increasingly frequent occurrence of both conditions in the pediatric population.²⁷

MASLD is characterized by fat accumulation in hepatocytes and the presence of one or more cardiometabolic risk factors, in the absence of other causes of liver disease, and develops through a complex interaction of genetic, environmental, and metabolic factors.^{25,28} In children and adolescents, obesity, a sedentary lifestyle, and high-calorie dietary patterns are significant environmental determinants that interact with an individual genetic predisposition.²⁷ Variants in genes involved in hepatic lipid metabolism, such as *PNPLA3*, *TM6SF2*, and other modulators of lipid transport and storage, have been associated with increased susceptibility to the development and progression of MASLD.^{28,29}

From a pathophysiological perspective, insulin resistance and compensatory hyperinsulinemia play a central role in the development of hepatic steatosis.^{25,26} Hyperinsulinemia promotes an increase in the flow of free fatty acids from adipose tissue to the liver, stimulates de novo lipogenesis, and reduces fatty acid oxidation, leading to the accumulation of triglycerides in hepatocytes.²⁶ In turn, hepatic insulin resistance contributes to increased hepatic glucose production, perpetuating the vicious cycle between disturbances in carbohydrate and lipid metabolism.²⁶ The progression from simple steatosis to more advanced forms of liver disease involves additional mechanisms of cellular damage.^{25,30} These include mitochondrial dysfunction, impaired fatty acid β -oxidation, and increased oxidative stress with the generation of reactive oxygen species.³⁰ These phenomena

promote lipid peroxidation, the activation of inflammatory pathways, and hepatocellular injury.³⁰ Finally, alterations in the gut microbiota and increased intestinal permeability may contribute to liver damage by allowing the passage of bacterial endotoxins and the activation of immuno-inflammatory mechanisms that promote fibrogenesis in liver tissue³¹ (Figure 2). The coexistence of type 2 diabetes and MASLD in childhood is associated with an increased risk of progression to more advanced forms of liver disease, such as steatohepatitis, fibrosis, and even cirrhosis.^{27,32} For this reason, in children and adolescents with type 2 diabetes who have persistently elevated aminotransferases or ultrasound findings consistent with hepatic steatosis, systematic evaluation for MASLD, as well as for other causes of liver disease, should be considered.³²

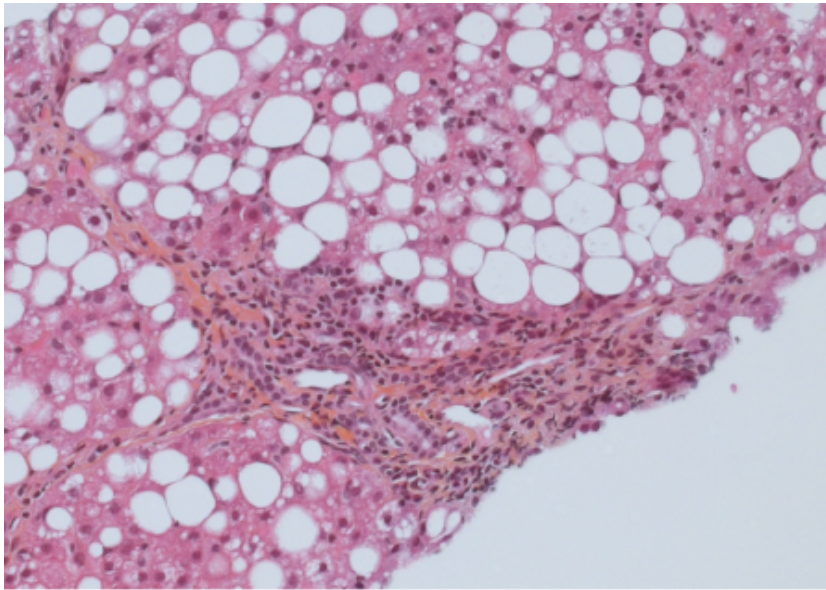
The therapeutic approach is primarily based on interventions aimed at improving insulin resistance and the metabolic profile, involving drastic lifestyle changes, weight control, and optimization of diabetes treatment.^{25,32}

MONOGENIC DIABETES AND LIVER DISEASE

Monogenic forms of diabetes are inherited in an autosomal dominant pattern and are known as MODY (maturity-onset diabetes of the young). This form of diabetes accounts for between 1% and 6.5% of children with diabetes; many of these cases are misdiagnosed as type 1 or type 2 diabetes. The diagnosis is usually made before the age of 25, and the course of the disease is relatively mild and asymptomatic.³³

The most common causes in the West involve mutations in the *GCK* (glucokinase), *HNF1A*, and *HNF4* (hepatocyte nuclear factor) genes; the latter two are transcription factors. Less common are mutations in *HNF1B*, *HNF6*, or *OC1* (*ONECUT 1*). Mutations in the various HNF genes may be associated with complications or liver disease.

Mutations in the *HNF1A* gene result in symptomatic diabetes. This transcription factor is essential for pancreatic development and maturation. In humans, this transcription factor is expressed in the pancreas, the kidney, and—during embryonic development—in the liver primordia, along with *HNF1B*. In families with *HNF1A* mutations, patients with hepatic adenomatosis have been identified when the gene is biallelically inactivated, when the second allele is inactivated. In patient cohorts, *HNF1A*

FIGURE 2. Liver biopsy section from a child with liver disease associated with metabolic dysfunction

Hematoxylin and eosin stain. Macro- and microvesicular steatosis, portal space fibrosis, and moderate inflammation.

mutations were found in 35-40% of hepatic adenomas.³⁴

The *HNF1B* gene is expressed early in the foregut, which gives rise to the liver, bile ducts, and pancreas; it is also expressed in the liver primordia, which are responsible for the organ's maturation. Mutations in the *HNF1B* gene have been associated, in a 10-year-old patient, with the development of a variant of giant syncytial cell hepatocellular carcinoma.³⁵

Considering the diseases associated with mutations in *HNF1* genes, we can conclude that they act as tumor suppressors.

Because both *HNF1B* and *OC1* (*HNF6*) factors are expressed in the foregut, we can conclude that they play a role in the development and maturation of the intra- and extrahepatic bile ducts.³⁶ Ductal plate malformations have been described in children with mutations in each of these genes. Conditions described in these cases include neonatal cholestasis and a low number of interlobular bile ducts, abnormal extrahepatic bile ducts, gallbladder agenesis, liver necrosis and fibrosis, and pancreatic agenesis. These conditions manifest clinically as cirrhosis with signs of portal hypertension, persistent abnormalities in serum liver enzymes, and, in some cases, associated renal failure. The *OC1*

(*HNF6*) gene product interacts with the NOTCH receptor in intrahepatic bile duct development, as does *Jagged1*, whose mutation reduces the number of interlobular ducts, as observed in patients with Alagille syndrome.³⁶

ONECUT 1 plays an important role in the development of the endogenous pancreas and the bile ducts. In this regard, we recently reported a case of a patient with a deletion in the regulatory sequences of this gene's expression.³⁷ This child presented with intrauterine growth restriction and developed diabetes during the neonatal period. In addition, he exhibited exocrine pancreatic insufficiency and required enzyme replacement therapy. Ultrasound revealed a hypoplastic pancreas and an absence (agenesis) of the gallbladder. Furthermore, the patient had syndactyly of the 2nd and 3rd toes on each foot. At age 13, gastrointestinal bleeding was the first manifestation of cirrhosis and portal hypertension. A liver biopsy revealed non-inflammatory cirrhosis with signs of ductal plate malformation. The renal biopsy, performed because of nephrocalcinosis and signs of decreased glomerular filtration, revealed partial atrophy of the renal tubules, interstitial nephropathy, and cystic glomerulopathy. This patient perfectly illustrates the organs affected by the absence of *HNF6*

transcription factor expression.

Syndromic monogenic causes include neonatal-onset diabetes accompanied by multiple other clinical manifestations, as in mutations in the *EIF2AK3* gene (eukaryotic translation initiation factor 2a kinase 3), which, in homozygous or compound heterozygous forms, cause Wolcott-Rallison syndrome. This autosomal recessive disorder is characterized by persistent neonatal diabetes, hepatic manifestations (a significant elevation in transaminases and, in some patients, signs of acute liver failure), epiphyseal dysplasia, and renal dysfunction.

CONCLUSION

The most common causes of diabetes in pediatrics are type 1 diabetes, which is autoimmune in origin, and—with an increasing incidence in recent years—type 2 diabetes, which is associated with poor nutrition and a sedentary lifestyle, leading to obesity and the development of MASLD. Hepatic complications in type 1 diabetes include autoimmune hepatitis and glycogenic liver disease, the latter of which is related to poor control of hyperglycemia. In type 2 diabetes, significant accumulation of triglycerides in the liver leads to an increased risk of progression to cirrhosis, liver failure, and, eventually, hepatocellular carcinoma.

In patients with monogenic diabetes, abnormalities in the development of the biliary tract and, in some cases, in the maturation and function of hepatocytes can lead to chronic cholestasis and contribute to the development of secondary biliary cirrhosis.

These institutions highlight, once again, the importance of interdisciplinary work, both for establishing a timely differential diagnosis and for implementing individualized treatment that considers each patient's characteristics and the potential adverse effects of various therapeutic strategies. ■

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