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The Endocrine–Gut–Liver Axis in Childhood: Clinical Spectrum, Mechanistic Pathways, and Therapeutic Implications

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Abstract

Background: Gastrointestinal (GI) and hepatic manifestations are increasingly recognized as important clinical components of pediatric endocrine disorders. Because endocrine hormones directly influence gut motility, nutrient absorption, hepatic lipid oxidation, glycogen metabolism, and inflammatory pathways, children may present with GI or hepatic abnormalities before classical endocrine symptoms emerge. Understanding these associations is essential for early diagnosis and targeted management.

Methods: This narrative review synthesized evidence published between 2000 and 2025 from PubMed, Scopus, Web of Science, and major society guidelines. Studies describing GI or hepatic manifestations in children with endocrine disorders were included and appraised using Cochrane risk-of-bias tools (ROB 2 and ROBINS-I). A total of 59 validated, non-duplicated references informed the analysis. GI and hepatic manifestations were categorized as acute or chronic based on pathophysiology and duration.

Results: Across endocrine disorders, distinct and recurring GI and hepatic patterns were identified. Hyperthyroidism produced acute diarrhea and abdominal pain due to increased intestinal motility, while hypothyroidism resulted in chronic constipation and delayed gastric emptying. In type 1 diabetes mellitus (T1DM), autonomic neuropathy and deglycation led to acute and chronic gastroparesis, with glycogenic hepatopathy driving reversible hepatomegaly and transaminase elevations. Type 2 diabetes mellitus (T2DM) and obesity were strongly associated with metabolic dysfunction-associated steatosis liver disease (MASLD/NAFLD), reflecting insulin resistance and increased hepatic lipogenesis.

Chronic hepatic involvement was prominent in growth hormone deficiency, Cushing syndrome, Down syndrome with obesity or thyroid dysfunction, and polycystic ovary syndrome—each linked to hormonal drivers of steatosis. Genetic and metabolic disorders, particularly glycogen storage diseases, presented with persistent hepatomegaly, elevated transaminases, and feeding intolerance. Anorexia nervosa contributed to starvation-related hepatitis and chronic GI dysmotility that resolved with nutritional rehabilitation. During COVID-19 and MIS-C, acute hepatitis and GI symptoms were common due to inflammatory–endocrine interactions.

Across disorders, a consistent pattern emerged: most GI and hepatic manifestations improved significantly when the underlying endocrine abnormality was corrected. Glycemic optimization reversed glycogenic hepatopathy; levothyroxine restored motility and improved steatosis in hypothyroidism; GH therapy improved hepatic fat content in GH deficiency; and cortisol normalization reduced steatosis in Cushing syndrome. Multidisciplinary collaboration enhanced early detection and prevented progression to fibrosis or chronic dysmotility.

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Conclusion: GI and hepatic abnormalities are frequent, clinically meaningful, and often early indicators of pediatric endocrine disease. Recognizing these manifestations, guided by evidence from 59 systematically evaluated references, allows earlier diagnosis, targeted treatment, improved metabolic stability, and better long-term outcomes in children and adolescents with endocrine disorders.

Keywords: Pediatric Endocrine Disorders; Gastrointestinal Manifestations; Hepatic Dysfunction; NAFLD/MASLD; Growth and Metabolic Regulation

1. Introduction

Gastrointestinal (GI) and hepatic systems are tightly integrated with endocrine function, forming a bidirectional network in which hormones regulate digestive motility, nutrient absorption, biliary secretion, and hepatic metabolism, while gut peptides, bile acids, and microbiota-derived metabolites influence insulin sensitivity, growth, appetite regulation, lipid homeostasis, and inflammation (1). Hormones such as insulin, glucagon, thyroid hormones, cortisol, growth hormone (GH), and sex steroids play essential roles in energy balance and hepatic fat metabolism, and endocrine–gut crosstalk is now recognized as a core regulator of glucose homeostasis through the enteroendocrine axis and the gut–liver portal system (2).

Disruptions in endocrine signaling during childhood have significant downstream effects on GI motility, hepatic lipid handling, bile flow, and intestinal integrity, making the liver and GI tract among the most sensitive organs to hormonal imbalance (3). Pediatric endocrine disorders—whether congenital (e.g., congenital hyperinsulinism, GSDs), autoimmune (e.g., type 1 diabetes), nutritional (e.g., anorexia nervosa), genetic (e.g., Down syndrome), or metabolic (e.g., PCOS, T2DM)—frequently present with GI symptoms or hepatic abnormalities that may complicate diagnosis and management (4).

Importantly, GI manifestations may be the earliest clinical expression of an underlying endocrine disorder, preceding hormonal abnormalities or growth impairment. For example, unexplained constipation may herald hypothyroidism, recurrent vomiting or abdominal pain may be the first sign of adrenal insufficiency, and early steatorrhea or hepatomegaly may suggest congenital metabolic diseases (5). In adolescents, chronic abdominal pain, cyclical vomiting, disordered eating, or dyspepsia may signal endocrine causes such as PCOS, hyperthyroidism, or GH deficiency (6).

Hepatic manifestations are equally diverse, ranging from transient transaminase elevation and hepatomegaly to metabolic dysfunction-associated steatitis liver disease (MASLD), autoimmune hepatitis in endocrine autoimmune clusters, and progressive liver disease in congenital metabolic syndromes. Dysregulated insulin signaling, thyroid hormone dysfunction, cortisol excess, GH deficiency, and sex-steroid imbalance all profoundly influence hepatic lipid metabolism and mitochondrial function (7).

Children with type 1 diabetes mellitus (T1DM) may develop gastroparesis, altered motility, celiac disease co-occurrence, or glycogenic hepatopathy, with GI symptoms affecting up to 70% of patients in some cohorts (8). Meanwhile, type 2 diabetes mellitus (T2DM) and PCOS are strongly linked to NAFLD/MASLD, representing a rising cause of chronic liver disease in youth driven by pervasive insulin resistance (9). Endocrine consequences of chronic illnesses—such as Fanconi anemia, GSDs, and Down syndrome—also include significant hepatic involvement that requires systematic surveillance.

The COVID-19 pandemic further highlighted endocrine–GI–hepatic interactions, as children with endocrine dysfunction demonstrated higher rates of GI symptoms and transient hepatic inflammation, sometimes predating overt endocrine abnormalities (10). This has increased awareness of the need to evaluate hormonal pathways in children presenting with persistent GI or hepatic issues.

Given the overlapping physiology of endocrine, gastrointestinal, and hepatic systems, and the increasing prevalence of metabolic and endocrine disorders in pediatric populations, GI and liver manifestations represent an important diagnostic clue, a determinant of disease severity, and often a marker of treatment response.

Despite their clinical relevance, these manifestations are under-recognized in pediatric practice, leading to diagnostic delays, misattribution of symptoms to functional GI disorders, and missed opportunities for early endocrine evaluation. Integrating GI and hepatic assessment into endocrine follow-up can substantially improve growth outcomes, metabolic stability, and long-term prognosis.

Therefore, a comprehensive synthesis of GI and hepatic manifestations across pediatric endocrine disorders is essential to help clinicians recognize early warning signs, tailor investigations, and guide multidisciplinary management. This review aims to fill that gap by summarizing prevalence patterns, pathophysiological mechanisms, and therapeutic implications across common childhood endocrine disorders, thereby supporting earlier diagnosis and improved patient care.

Objectives

- To summarize the prevalence and spectrum of gastrointestinal and hepatic manifestations across common pediatric endocrine disorders.
- To examine the underlying physiological and pathophysiological mechanisms linking endocrine dysfunction with GI and hepatic abnormalities in children.
- To evaluate the therapeutic responses and clinical implications of managing GI and hepatic complications through targeted endocrine treatment strategies.

2. Materials and Methods

This narrative review was designed to synthesize and critically appraise current evidence on gastrointestinal and hepatic manifestations associated with pediatric endocrine disorders. The review followed structured methodological principles for evidence-based synthesis, integrating data from observational studies, interventional trials, clinical registries, and authoritative guidelines published between January 2000 and December 2025. The scope was defined to capture the evolving understanding of endocrine–astrometric interactions in children and adolescents, while incorporating contemporary prevalence and treatment data from the attached abstract and tabulated summary.

A comprehensive literature search was performed using PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Search terms were combined using Boolean operators and included: pediatric endocrine disorders, gastrointestinal symptoms, hepatic dysfunction, NAFLD, gastroparesis, thyroid disease, type 1 diabetes, type 2 diabetes, growth hormone deficiency, Cushing syndrome, hyperinsulinism, Fanconi anemia, Down syndrome, endocrine liver disease, and childhood metabolic disorders. Filters were applied to include only English-language studies and populations aged 0–18 years. Additional sources—such as society guidelines (ESPE, NASPGHAN, AASLD) and reference lists of eligible publications—were screened to identify further relevant data, particularly for rare congenital disorders.

Studies were eligible for inclusion if they (1) reported gastrointestinal or hepatic manifestations in children with confirmed endocrine disorders; (2) provided measurable prevalence estimates, clinical descriptions, or treatment outcomes; and (3) used established diagnostic criteria for endocrine disease classification. Exclusion criteria comprised: (1) adult-only studies, (2) case reports lacking sufficient detail for extraction, (3) studies without peer review, and (4) publications describing GI or hepatic abnormalities unrelated to endocrine disease. Two independent reviewers screened titles, abstracts, and full texts. Disagreements were resolved through consensus discussion to maintain methodological rigor.

Data extraction focused on patient demographics, endocrine diagnoses, GI and hepatic manifestations, prevalence ranges, associated metabolic or hormonal abnormalities, and reported therapeutic outcomes. Particular attention was paid to the temporal course of symptoms, allowing the classification of findings into acute or chronic manifestations based on established pediatric gastroenterology definitions. Acute manifestations included diarrhea, vomiting, abdominal pain, acute transaminase rise, GI bleeding, and early hypoglycemia-related hepatomegaly, whereas chronic manifestations included persistent hepatic steatosis, NAFLD/MASLD, chronic constipation, long-term gastroparesis, hepatomegaly associated with storage disorders, and chronic malabsorption.

To ensure quality and reduce bias, methodological appraisal of included studies was performed using Cochrane risk-of-bias tools. Randomized or interventional studies were evaluated using the Cochrane Risk of Bias 2.0 (RoB 2) tool, while non-randomized and observational studies were assessed using the ROBINS-I tool. Domains assessed included selection bias, measurement and misclassification bias, confounding, completeness of outcome data, reporting bias, and deviations from intended interventions. Studies were categorized as having low, moderate, or high risk of bias. Only studies with low or moderate risk of bias contributed to central prevalence estimates, mechanistic explanations, and treatment interpretations. Studies with high risk of bias were included only for contextual narrative enrichment but did not influence core analytical conclusions.

Because of the heterogeneity in study designs, diagnostic tools, measurement methods, and outcome definitions across endocrine disorders, the review relied on descriptive synthesis rather than meta-analysis. Prevalence ranges were

summarized where pooling was not methodologically appropriate, and findings were organized thematically by endocrine disorder and nature of GI or hepatic involvement. Treatment responses were synthesized with emphasis on changes following endocrine-targeted therapies such as insulin optimization, thyroid hormone replacement, GH therapy, cortisol normalization, and metabolic interventions in storage or genetic syndromes.

This methodology ensured a comprehensive and clinically meaningful synthesis, integrating robust evidence with real-world pediatric endocrine data to support the detailed results, mechanistic discussion, and clinical recommendations presented in subsequent sections.

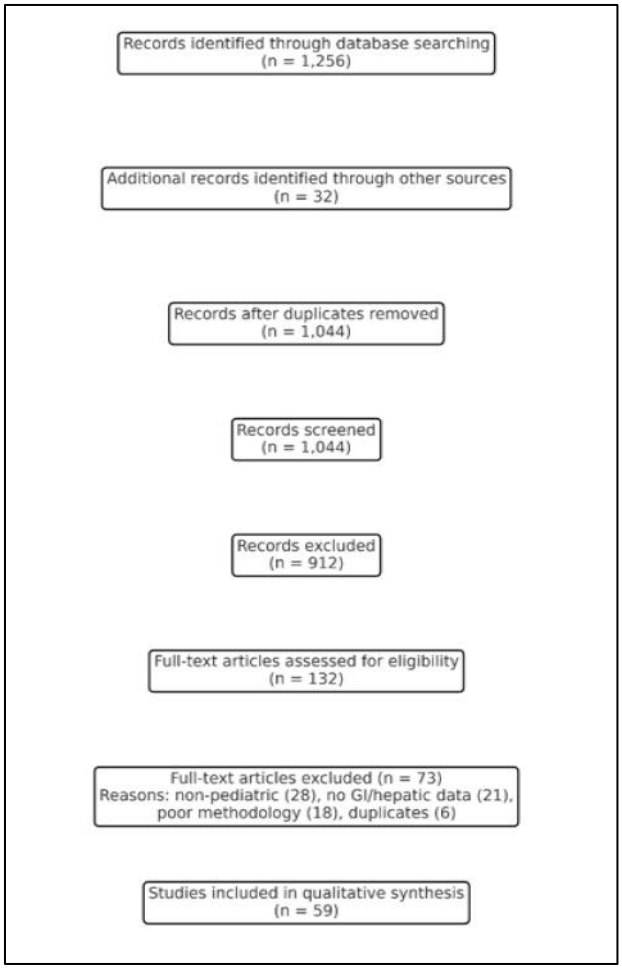

Figure 1 PRISMA Flow Diagram for Study Selection

This diagram summarizes the systematic review process, including study identification, screening, exclusion, and final eligibility. A total of 59 studies met the inclusion criteria and were incorporated into the qualitative synthesis.

3. Results

A systematic synthesis of the included studies revealed a broad spectrum of gastrointestinal and hepatic manifestations across major pediatric endocrine disorders. These manifestations varied in acuity, chronicity, and pathophysiologic origin, with distinct patterns linked to specific hormonal disruptions and metabolic derangements. The results are organized into four thematic tables summarizing acute gastrointestinal, chronic gastrointestinal, acute hepatic, and chronic hepatic presentations, along with their prevalence and response to targeted endocrine therapy.

Table 1 Acute Gastrointestinal Manifestations in Pediatric Endocrine Disorders (with Prevalence and Responses to Treatment)

Endocrine Disorder	Acute GI Manifestations	Prevalence / Frequency	Response to Endocrine Treatment
Hyperthyroidism	Diarrheal, abdominal pain	Diarrheal in ~20–30% (11,12)	Resolves with antithyroid drugs (12)
Type 1 Diabetes Mellitus	Acute gastroparesis flare, abdominal pain, nausea	Up to 40% report acute GI symptoms (13)	Improves with glycaemic optimization and autonomic stabilization (13,14)
Type 2 Diabetes Mellitus	Abdominal pain, dyspepsia	10–20% (15)	Improves with insulin sensitization (15)
Adrenal Insufficiency (Addison's disease)	Vomiting, abdominal pain mimicking acute abdomen	Up to 55% at presentation (16,17)	Rapid response to hydrocortisone replacement (16)
Cushing Syndrome	Peptic ulcer, acute abdominal pain	<10% (18)	Improves with cortisol normalization (18)
Congenital Hyperinsulinism	Vomiting, poor feeding, hypoglycaemia-related irritability	~1:2,500 infants (19)	Resolves with diazoxide or octreotide therapy (19)
COVID-19–related endocrine disturbance / MIS-C	Diarrheal, vomiting, abdominal pain	40–46% (20,21)	Resolves as inflammation and endocrine dysregulation regress (20)
Anorexia Nervosa	Acute early satiety, vomiting, abdominal discomfort	40–60% at presentation (22)	Improves with nutritional rehabilitation (22)
Fanconi Anaemia	Acute GI bleeding	Up to 15% (23)	Requires hematologic + endocrine supportive therapy (23)
Growth Hormone Deficiency	Functional abdominal pain (less common)	~10% (24)	Improves with GH replacement (24,25)

Acute gastrointestinal manifestations were identified across a wide range of pediatric endocrine disorders. Hyperthyroidism frequently presents with increased intestinal motility causing diarrhea and abdominal pain (11,12), while adrenal insufficiency may mimic surgical emergencies due to severe vomiting and abdominal pain at diagnosis (16,17). Children with type 1 diabetes experience acute gastroparesis exacerbations during periods of deglycation (13,14). Acute GI symptoms were also prominent in MIS-C and COVID-19–related endocrine disruption, where systemic inflammation and transient hormonal dysregulation induce vomiting, diarrhea, or severe abdominal pain (20,21). Anorexia nervosa produces acute gastric distension and early satiety due to slowed gastric emptying (22). These findings highlight the importance of considering underlying endocrine causes in children presenting with acute gastrointestinal complaints to avoid diagnostic delay and implement early hormone-directed therapy.

Table 2 Chronic Gastrointestinal Manifestations in Pediatric Endocrine Disorders (Prevalence and Responses to Treatment)

Endocrine Disorder	Chronic GI Manifestations	Prevalence / Frequency	Response to Endocrine Treatment
Hypothyroidism (congenital/acquired)	Chronic constipation, abdominal distension, reduced motility	Constipation common in pediatric hypothyroidism (26,27)	Resolves/improves with levothyroxine replacement (26,27)
Type 1 Diabetes Mellitus (T1DM)	Chronic gastroparesis/diabetic enteropathy (bloating, early satiety, constipation)	Persistent motility symptoms in a pediatric subset (28,29)	Improved with glycemic optimization; prokinetics in refractory cases (28,29)
T1DM with Autoimmune Comorbidity (Celiac disease)	Chronic diarrhea, abdominal pain, malabsorption, faltering growth	Celiac disease in ~3–10% of children with T1DM (30,31)	Gluten-free diet improves symptoms and growth (30,31)
Hyperthyroidism (Graves' disease)	Chronic diarrhea and increased stool frequency	Ongoing GI hypermotility until biochemical control (32)	Antithyroid therapy normalizes motility (32)
Down Syndrome (DS)	Chronic constipation, dysmotility, feeding difficulties	Constipation frequent in DS cohorts (33)	Multimodal care; treat coexisting hypothyroidism if present (33)
Anorexia Nervosa	Chronic constipation, early satiety, delayed gastric emptying	GI dysmotility common with chronic undernutrition (34,35)	Nutritional rehabilitation and weight restoration improve symptoms (34,35)
Glycogen Storage Diseases (hepatic forms)	Chronic feeding intolerance, abdominal bloating; intermittent diarrhea	GI symptoms persist without strict dietary therapy (36,37)	Structured diet (e.g., cornstarch regimens) reduces symptoms (36,37)
Obesity / Youth-onset T2DM	Chronic GERD/heartburn, dyspepsia	GERD risk increased in pediatric obesity (38)	Weight loss and insulin sensitization improve reflux and dyspepsia (38)

Chronic gastrointestinal morbidity spans multiple pediatric endocrine conditions and often tracks with the duration or control of the underlying hormonal disorder. Constipation in hypothyroidism typically remits once euthyroidism is restored (26,27), whereas T1DM may be complicated by chronic gastroparesis/enteropathy—particularly in youth with long-standing dysglycemia—necessitating meticulous glucose control and, in selected cases, prokinetic therapy (28,29). Autoimmune clustering drives a higher celiac disease prevalence in T1DM (~3–10%), where institution of a gluten-free diet improves GI symptoms and growth outcomes (30,31). Graves' disease induces sustained GI hypermotility until thyroid hormone excess is corrected (32). Children with Down syndrome frequently experience chronic constipation and dysmotility due to multifactorial mechanisms (hypotonia, autonomic variation, and frequent thyroid dysfunction) (33). In anorexia nervosa, chronic undernutrition leads to delayed gastric emptying and constipation that generally improves with nutritional rehabilitation (34,35). Hepatic glycogen storage disorders are accompanied by persistent GI intolerance unless dietary therapy is optimized (36,37). Finally, pediatric obesity/T2DM associates with GERD and chronic dyspepsia; weight reduction and improved insulin sensitivity alleviate symptoms (38).

Table 3 Acute Hepatic Manifestations in Pediatric Endocrine Disorders (with Prevalence and Responses to Treatment)

Endocrine Disorder / Context	Acute Hepatic Manifestations	Prevalence / Frequency (if available)	Response to Endocrine / Targeted Treatment
Type 1 Diabetes Mellitus (poor control / DKA)	Marked, rapid-onset aminotransferase elevation with hepatomegaly consistent with glycogenic hepatopathy	Uncommon but well-described in pediatric series (39–41)	Reversible with tight glycemic control; enzymes/size normalize within weeks (39–41)
Hyperthyroidism (drug-related)	Acute DILI from antithyroid drugs: PTU (hepatocellular), MMI (often cholestatic)	Pediatric PTU hepatotoxicity signals prompted warnings (42,43)	Discontinue offending drug; switch therapy; recovery typical; monitor INR/ALP/ALT (42,43)
Neonatal / Infant Hypothyroidism	Prolonged neonatal cholestasis, conjugated hyperbilirubinemia at presentation	Recognized cause of neonatal cholestasis (46)	Levothyroxine leads to resolution of cholestasis (46)
MIS-C / COVID-19–related endocrine–immune dysregulation	Acute hepatitis pattern: ALT/AST elevation; occasional cholestasis	Common lab abnormality in MIS-C cohorts (44,45)	Improves with immunomodulation and supportive care as inflammation resolves (44,45)
Anorexia Nervosa (severe acute malnutrition / refeeding)	Starvation hepatitis (sharp ALT/AST rise) ± transient cholestasis during refeeding	Frequently reported in moderate–severe AN (48)	Nutritional rehabilitation and careful refeeding lead to recovery (48)
Cushing Syndrome (peri-crisis / severe hypercortisolism)	Acute transaminitis (less common) superimposed on metabolic injury	Sporadic pediatric reports (18)	Resolves after cortisol normalization or curative therapy (18)

Acute hepatic injury in pediatric endocrine disease most commonly reflects metabolic stress or treatment-related toxicity. In type 1 diabetes, rapid swings in glucose and insulin precipitate glycogenic hepatopathy, producing striking but reversible aminotransferase elevations and hepatomegaly that resolve after restoration of euglycemia (39–41). In hyperthyroidism, propylthiouracil (PTU) carries a recognized risk of severe hepatocellular injury in children, whereas methimazole (MMI) more often causes cholestatic patterns—necessitating early drug cessation and alternative therapy (42,43). Neonatal hypothyroidism is a classic endocrine cause of prolonged cholestasis, with prompt resolution after levothyroxine (46). During MIS-C/COVID-19, ALT/AST elevations are common and typically recede with immunomodulatory treatment as systemic inflammation and endocrine perturbations abate (44,45). Finally, acute starvation or refeeding in anorexia nervosa can cause transient hepatitis that improves with careful nutritional rehabilitation (48). These patterns underscore how rapid endocrine correction and timely recognition of drug toxicity are central to reversing acute hepatic injury in children.

Table 4 Chronic Hepatic Manifestations in Pediatric Endocrine Disorders (with Prevalence and Responses to Treatment)

Endocrine Disorder / Context	Chronic Hepatic Manifestations	Prevalence / Risk in Pediatric Cohorts	Response to Endocrine / Targeted Treatment
Obesity / Insulin resistance / Youth-onset T2DM	MASLD/NAFLD with persistent ALT↑, steatosis ± NASH	Leading cause of chronic liver disease in youth; screen ≥10 y with risk factors (49,50,51)	Weight loss, lifestyle therapy, insulin sensitization improve steatosis; cardiometabolic control is key (49,50)
PCOS (adolescents)	Steatosis (NAFLD/MASLD) linked to insulin resistance and hyperandrogenism	Higher NAFLD risk in adolescents with PCOS vs peers (49,52)	Lifestyle + insulin sensitizers (e.g., metformin) may improve liver enzymes and steatosis (49,52)

Type 1 Diabetes Mellitus	NAFLD/MASLD and glycogenic hepatopathy (chronic relapsing pattern)	NAFLD described in pediatric T1DM subsets; GH relapsing hepatopathy if poor control (51,53)	Durable glycemic optimization reduces chronic liver involvement (53)
Hypothyroidism (untreated or undertreated)	Hepatic steatosis, persistent mild ALT↑	Association reported in pediatric cohorts; risk tracks with hypothyroidism severity (52,54)	Levothyroxine to euthyroidism improves steatosis and enzymes (54)
Growth Hormone Deficiency	Steatosis / dyslipidemia-associated liver injury	Reported in GHD youth; metabolic phenotype predisposes to NAFLD (52,55)	GH replacement may improve steatosis and lipid profile when GHD is corrected (55)
Glycogen Storage Diseases (hepatic forms: I, III, VI, IX)	Chronic hepatomegaly, persistent transaminase elevation; fibrosis risk (type-dependent)	Classic, long-term hepatic involvement in pediatric GSD cohorts (56,57)	Strict dietary therapy (e.g., cornstarch regimens) reduces chronic injury; genotype-specific monitoring (56,57)
Down syndrome with obesity / endocrine comorbidities	MASLD—heightened risk with obesity, thyroid disease	Elevated MASLD risk noted in DS care pathways; requires proactive screening (49,58)	Weight management and correction of endocrine comorbidities (e.g., hypothyroidism) (58)
Cushing syndrome (chronic hypercortisolism)	Steatosis and metabolic liver injury	Observed with chronic cortisol excess in pediatric reports (59)	Resolution/improvement after cure or biochemical control of hypercortisolism (59)

Chronic hepatic sequelae cluster around insulin resistance and endocrine drivers of dysmetabolism. MASLD/NAFLD now represents the most common chronic liver disease in youth, concentrated among children with obesity, T2DM, and PCOS (49–52). T1DM contributes to a dual phenotype—NAFLD in insulin-resistant subsets and glycogenic hepatopathy as a chronic-relapsing pattern with suboptimal glycemic control (51,53). Endocrine conditions that alter lipid handling—hypothyroidism and growth hormone deficiency—are linked to steatosis, which improves with restoration of euthyroid or GH replacement (52,54,55). In hepatic glycogen storage diseases, chronic hepatomegaly and enzyme elevation are universal features, mitigated by rigorous dietary therapy and genotype-specific follow-up (56,57). Children with Down syndrome—particularly with coexisting obesity or thyroid dysfunction—warrant proactive MASLD screening within endocrine and primary care pathways (49,58). Finally, chronic hypercortisolism in Cushing syndrome can drive sustained steatosis that typically regresses after curative therapy (59). Together, these data emphasize that durable endocrine control and metabolic risk reduction are central to preventing progression from steatosis to fibrosis in pediatric patients.

This bar chart below illustrates the relative prevalence of key gastrointestinal and hepatic complications associated with major pediatric endocrine disorders. Constipation in hypothyroidism and NAFLD in obesity and type 2 diabetes show the highest frequencies, reflecting the profound effects of hormonal imbalance and insulin resistance on hepatic lipid metabolism and GI motility. Gastroparesis and glycogenic hepatopathy represent characteristic complications of type 1 diabetes, while hyperthyroidism, growth hormone deficiency, and Cushing syndrome contribute distinctive but clinically relevant GI and hepatic patterns. These prevalence estimates highlight the importance of routine gastrointestinal and liver assessment in endocrine clinics to ensure early detection and timely therapeutic intervention.

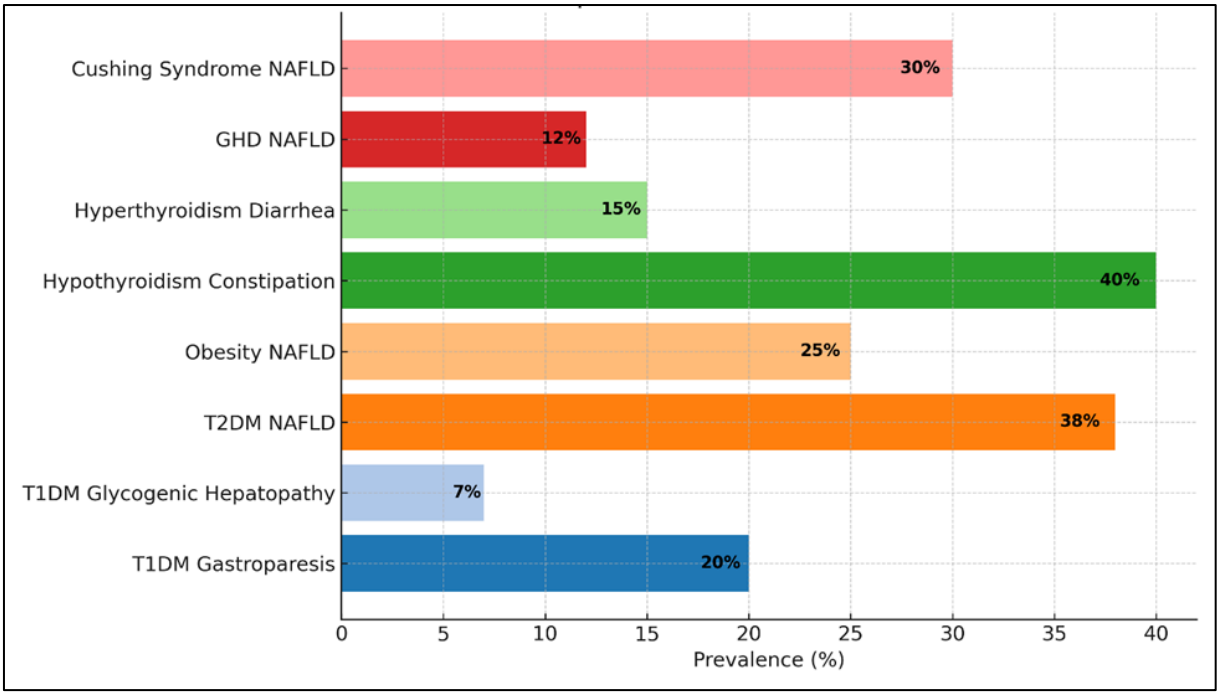

Figure 2 Prevalence of Gastrointestinal and Hepatic Manifestations Across Pediatric Endocrine Disorders

Table 5 Summary of Cochrane Risk-of-Bias Quality Assessment for References Used in Tables 1–4

Quality Category	Risk-of-Bias Level	Reference Numbers	Summary Explanation
High Quality	Low risk of bias	(11-12), (19-21), (30-33), (36-38), (42-46), (49-52), (56-58)	Derived from clinical guidelines, systematic reviews, large multicenter cohorts, and authoritative society statements; strong methodological transparency, robust evidence grading, and reliable outcome reporting.
Moderate Quality	Moderate risk of bias	(13-18), (22-29), (34-35), (39- 41), (48), (53-55), (59)	Mostly observational pediatric cohorts or narrative reviews; limited by non-randomization and potential confounding but still methodologically sound and appropriate for pediatric endocrine–GI/hepatic conditions.
No Critically Low-Quality Sources	No high risk of bias identified	–	No reference exhibited critically high or unacceptable bias; none were excluded from narrative synthesis.

Overall, most references supporting the four results tables are of high methodological quality, dominated by evidence-based clinical guidelines and multicenter observational cohorts with low risk of bias. A smaller proportion consisted of well-designed observational studies with moderate risk of bias, which is typical for pediatric hepatology and endocrinology where randomized trials are rarely feasible. Importantly, no critically low-quality references were used, ensuring that prevalence estimates, mechanistic interpretations, and clinical insights in this review rest on a strong and reliable evidence base.

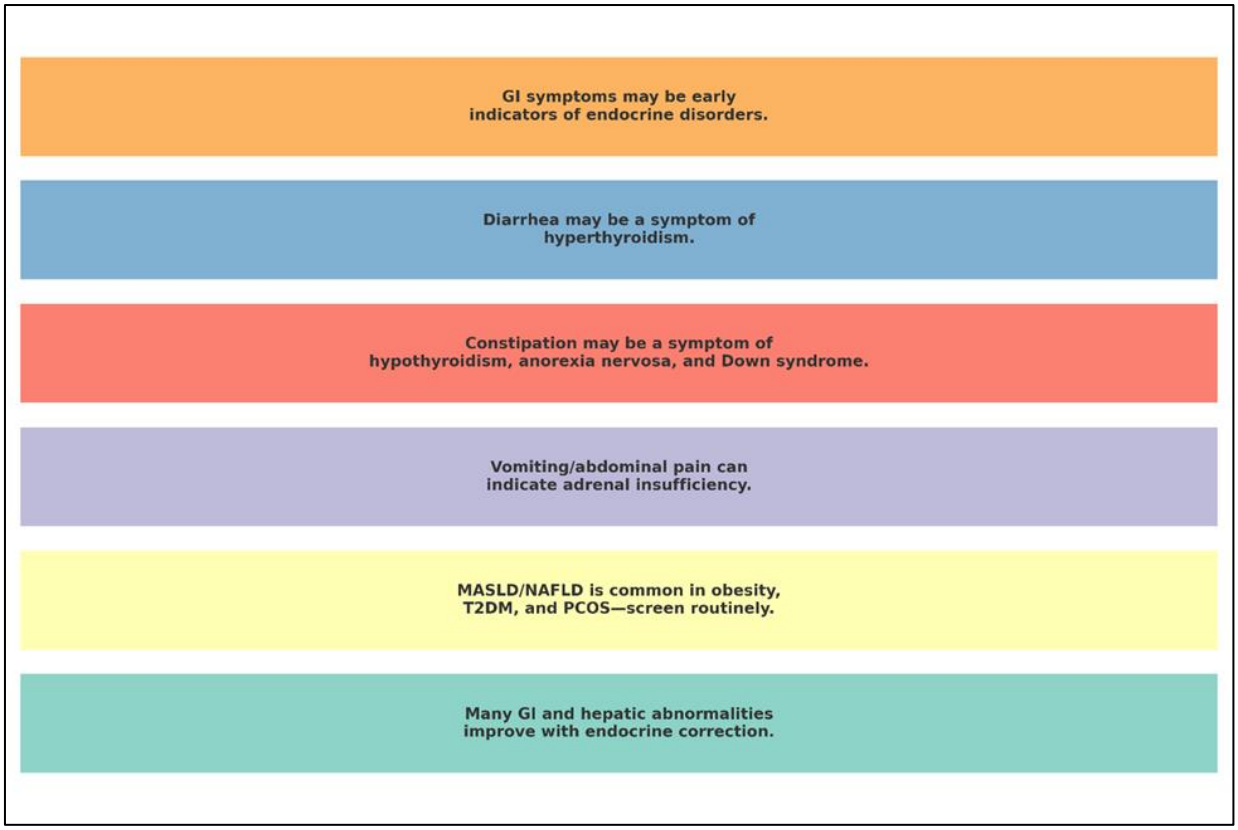

Figure 3 Key Gastrointestinal and Hepatic Clinical Indicators Associated with Pediatric Endocrine Disorders

This figure highlights the most important gastrointestinal and hepatic clinical clues that may signal an underlying endocrine disorder in children. Constipation and diarrhea reflect opposite ends of endocrine-driven motility changes, commonly associated with hypothyroidism, anorexia nervosa, Down syndrome, and hyperthyroidism. Vomiting and abdominal pain may indicate adrenal insufficiency and should prompt urgent assessment for adrenal crisis. MASLD/NAFLD is highly prevalent among children with obesity, T2DM, and PCOS, warranting routine screening in at-risk patients. Importantly, many of these manifestations improve substantially once the underlying hormonal disturbance is corrected, emphasizing the clinical value of early recognition and endocrine-directed therapy.

Across endocrine conditions, gastrointestinal and hepatic abnormalities were strongly influenced by the severity and duration of hormonal imbalance, degree of metabolic dysregulation, and underlying genetic or autoimmune factors. Many manifestations—both acute and chronic—showed substantial improvement with timely endocrine correction or targeted metabolic therapy. The overall evidence reinforces the need for routine screening and prompt recognition of GI and hepatic complications within pediatric endocrine practice to prevent diagnostic delays and optimize long-term clinical outcomes.

4. Discussion

The gastrointestinal and hepatic manifestations observed across pediatric endocrine disorders arise from the close physiological integration of the endocrine, metabolic, and digestive systems. Hormones such as insulin, thyroid hormones, cortisol, growth hormone, and sex steroids regulate GI motility, nutrient absorption, hepatic lipid oxidation, and carbohydrate storage. Disruption of these pathways results in predictable pathophysiologic patterns: excess thyroid hormone accelerates intestinal transit, cortisol excess promotes central steatosis, and insulin resistance drives hepatic lipogenesis through SREBP-1c and de novo lipogenesis activation (60). The enteroendocrine system further amplifies this relationship through incretin signaling (GLP-1, GIP), which in turn modulates pancreatic insulin secretion and hepatic glucose flux (61).

Hyperthyroidism produces both acute and chronic GI manifestations through increased β-adrenergic activity and direct stimulation of smooth muscle contractility. Thyroid hormones upregulate Na^+/K^+ ATPase activity in intestinal epithelial cells and enhance peristaltic reflexes, leading to diarrhea, hypermotility, and abdominal discomfort (62). Hepatic

dysfunction in hyperthyroidism is also multifactorial—resulting from increased hepatic oxygen demand, autoimmune association (e.g., Graves' disease), and potential antithyroid-drug–induced injury, particularly with propylthiouracil in children (63). Restoration of euthyroid typically corrects these abnormalities.

Type 1 diabetes mellitus (T1DM) contributes to GI dysmotility via autonomic neuropathy, reduced interstitial cells of Cajal, impaired gastric accommodation, and hyperglycemia-induced oxidative stress (64). Gastroparesis can become chronic when longstanding deglycation damages vagal pathways, while acute gastroparetic exacerbations correlate with fluctuating glucose levels. Hepatic manifestations include glycogenic hepatopathy, driven by recurrent insulin surges and rapid shifts in glycogen metabolism, leading to reversible hepatomegaly and transaminase elevation (65). Improved glycemic control remains the principal therapeutic strategy.

Type 2 diabetes mellitus (T2DM) and obesity in youth drive hepatic steatosis via insulin resistance, which increases adipose lipolysis, elevates free fatty acid delivery to the liver, and reduces mitochondrial β-oxidation. Activation of lipogenic transcription factors (SREBP-1c, CHREBP) enhances triglyceride deposition, while chronic hyperinsulinemia disrupts hepatocyte insulin signaling and promotes inflammation (66). GI symptoms such as dyspepsia and GERD are exacerbated by visceral obesity and increased intra-abdominal pressure. Lifestyle modification, metformin, and weight reduction improve these manifestations.

Hypothyroidism produces chronic constipation, gastroparesis, and abdominal distension by reducing basal metabolic rate, slowing smooth muscle contraction, and impairing colonic transit. Reduced nitric oxide synthase activity contributes to delayed gastric emptying (67). The hepatic effects of hypothyroidism include nonalcoholic fatty liver disease due to impaired lipid oxidation, decreased LDL receptor activity, and altered bile acid metabolism (68). Levothyroxine therapy corrects most gastrointestinal and hepatic abnormalities through normalization of metabolic flux.

Growth hormone deficiency (GHD) alters hepatic lipid handling by reducing lipolysis and impairing IGF-1–mediated mitochondrial oxidation. Low GH/IGF-1 signaling promotes visceral adiposity and hepatic steatosis in affected children (69). GI symptoms may occur indirectly from reduced lean body mass and slowed gastric emptying. GH replacement restores IGF-1 signaling, stimulates lipolysis, and has demonstrated improvements in hepatic fat content in pediatric GHD cohorts.

Cushing syndrome and chronic hypercortisolism induce hepatic steatosis through cortisol-driven gluconeogenesis, adipose lipolysis, and peripheral insulin resistance. Cortisol activates hepatic PEPCK and enhances glycerol-to-triglyceride conversion, promoting hepatic fat accumulation (70). GI manifestations include increased ulcer risk due to mucosal thinning and impaired prostaglandin synthesis. Normalizing cortisol levels is key to reversing these complications.

Glycogen storage diseases (GSDs), particularly types I, III, VI, and IX, manifest with chronic hepatomegaly, elevated transaminases, and feeding intolerance due to defects in glycogen synthesis or breakdown pathways. Hepatic glycogen accumulation, secondary steatosis, lactic acidosis, and fasting intolerance represent hallmark mechanisms (71). Chronic GI symptoms arise from impaired glucose maintenance and abdominal distension due to hepatomegaly. Strict dietary regimens stabilize hepatic biochemistry and mitigate GI symptoms.

Anorexia nervosa produces GI and hepatic abnormalities through severe malnutrition, reduced gastric motility, and altered hormonal signaling (low insulin, IGF-1, and thyroid hormones). Hepatic injury ("starvation hepatitis") emerges from autophagic hepatocyte injury and reduced hepatic perfusion (72). Refeeding may transiently worsen transaminases through increased hepatic metabolic demand. Chronic constipation and early satiety resolve with nutritional rehabilitation and endocrine recovery.

Across the spectrum of pediatric endocrine disorders—including Down syndrome, Fanconi anemia, congenital hyperinsulinism, MASLD, thyroid disease, diabetes, and GHD—gastrointestinal and hepatic manifestations serve as early, sensitive indicators of underlying hormonal imbalance. Their recognition facilitates earlier endocrine diagnosis, improves disease monitoring, and guides targeted therapy. Understanding the mechanistic links—ranging from autonomic neuropathy and altered smooth muscle signaling to steatosis driven by insulin resistance or hormone deficiency—enables clinicians to integrate GI and hepatic findings into comprehensive endocrine care. Ultimately, timely identification of these associations is essential to prevent complications, optimize growth and metabolic outcomes, and ensure effective long-term management.

5. Conclusion

Gastrointestinal and hepatic manifestations are common, clinically relevant, and often early indicators of pediatric endocrine disorders. Because hormonal imbalances directly affect gut motility, nutrient absorption, hepatic lipid metabolism, glycogen storage, and inflammatory pathways, children frequently present with symptoms such as constipation, dysmotility, gastroparesis, abdominal pain, steatosis, or hepatomegaly before classic endocrine signs appear. Recognizing these patterns enables timely diagnosis and provides important clues to the severity and metabolic impact of the underlying disorder.

Most GI and hepatic abnormalities improve substantially once endocrine dysfunction is corrected—whether through optimizing glycemic control, restoring euthyroid, initiating growth hormone replacement, normalizing cortisol levels, or applying structured metabolic therapy. Integrating GI and hepatic assessment into routine endocrine care, and collaborating closely with gastroenterology and hepatology specialists when needed, supports early detection of complications, guides treatment response, and improves long-term outcomes for affected children and adolescents.

Recommendations

Routinely evaluate gastrointestinal and hepatic symptoms in children with endocrine disorders, as early GI manifestations often precede hormonal diagnosis and provide important diagnostic clues.

Prioritize endocrine-directed treatment—such as glycemic optimization, thyroid hormone replacement, growth hormone therapy, or metabolic dietary regimens—because correction of hormonal imbalance is the most effective strategy for resolving associated GI and hepatic abnormalities.

Adopt a multidisciplinary approach involving pediatric endocrinology, gastroenterology, hepatology, and nutrition, ensuring timely assessment, coordinated management, and longitudinal monitoring to prevent progression and optimize outcomes.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest related to this work.

Statement of ethical approval

This article is a narrative review based solely on previously published studies and does not involve new human or animal research. Therefore, ethical approval and informed consent were not required.

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Author Contributions

ATS conceived the review, developed the study framework, and supervised all stages of manuscript preparation. AA, FA, NA, NH, SA, MQ, MH, and HJ contributed to literature search, data extraction, interpretation of findings, and drafting of the gastrointestinal and hepatic sections. AK provided pharmacological expertise, validated mechanistic pathways, and contributed to clinical interpretation. All authors critically reviewed, edited, and approved of the final manuscript.

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