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Adaptive Glycosuria Versus Metabolic Harm: Rethinking Postprandial Hyperglycemia in Obese, Insulin-Resistant Children and Adolescents

Ashraf T. Soliman [1,*], Fawzia Alyafei [1], Ahmed Elawwa [2], Shayma Ahmed [1], Nada Alaaraj [1], Noor Hamed [1], Rasha Amin [1], Shaymaa Elsayed [2], Dina Fawzy [2] and Nada Soliman [3]

[1] *Department of Pediatrics, Division of Endocrinology, Hamad Medical Center, Doha, Qatar.*
[2] *Department of Pediatrics, University of Alexandria Children's Hospital, Alexandria, Egypt.*
[3] *Directorate of Primary health Care, Ministry of health, Alexandria, Egypt.*

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Abstract

Background: post-prandial hyperglycemia is increasingly observed in obese children with insulin resistance (IR). A theoretical debate has emerged on whether glucose spilling into urine—once plasma glucose exceeds the renal threshold—may represent a transient adaptive mechanism that off-loads calories and slows further weight gain. Evidence from familial renal glucosuria (FRG) and pharmacologic SGLT2 inhibition demonstrates that urinary glucose excretion can induce measurable caloric loss. However, contrasting data from pediatric and adult cohorts show that IR and hyperglycemia are biologically injurious, driving early vascular, renal, hepatic, and β-cell damage. This review synthesizes and compares evidence supporting and opposing the adaptive hypothesis.

Objectives: (1) To summarize the physiological rationale for glycosuria as an adaptive calorie-losing mechanism in obese, insulin-resistant youth; (2) to evaluate clinical and mechanistic data demonstrating harmful consequences of IR and hyperglycemia; and (3) to provide a balanced interpretation of whether any adaptive benefit outweighs established metabolic risks.

Methods: A narrative synthesis was conducted using findings from pediatric urine-glucose screening programs, OGTT-based dysglycemia studies, FRG genetic cohorts, SGLT2 inhibitor trials, and mechanistic literature on endothelial dysfunction, oxidative stress, β-cell glucotoxicity, NAFLD/MASLD progression, and early microvascular complications in youth-onset type 2 diabetes. Comparative analysis evaluated whether calorie loss via glycosuria provides meaningful metabolic protection relative to the known harms of chronic hyperglycemia.

Results: Evidence supporting the adaptive hypothesis includes: (a) FRG cohorts, where lifelong low renal glucose thresholds cause persistent glycosuria and are associated with lower BMI and benign metabolic profiles; (b) adult SGLT2 inhibitor studies showing ~70–90 g/day urinary glucose loss (~250–300 kcal/day) with modest fat reduction; and (c) pediatric urine-glucose screening programs where obese youth commonly exceed renal thresholds, theoretically losing calories. However, substantial evidence counters this hypothesis. IR and hyperglycemia in children produce early and measurable injury, including endothelial dysfunction, increased carotid intima-media thickness, hypertension, microalbuminuria, NAFLD progression, rapid onset of retinopathy and neuropathy in youth-onset type 2 diabetes, and β-cell decompensation driven by glucotoxicity. Neurocognitive studies show associations between chronic hyperglycemia and altered brain development. Importantly, compensatory hyperphagia and adaptive metabolic responses significantly reduce the sustained weight-loss impact of glycosuria. No pediatric data supports intentional tolerance of hyperglycemia as a metabolic strategy.

* Corresponding author: Ashraf T. Soliman.

Conclusions: Although glycosuria can theoretically reduce energy balance, the magnitude of calorie loss is modest and easily offset by compensatory mechanisms. In contrast, the harms of IR and hyperglycemia in obese children are substantial, early, and multi-systemic. The cumulative evidence strongly indicates that hyperglycemia is not adaptive in this context and should not be viewed as metabolically protective.

Keywords: Insulin Resistance; Hyperglycemia; Glycosuria; Obesity; Children; Metabolic Risk

1. Introduction

Postprandial hyperglycemia has become increasingly common among obese children and adolescents in parallel with rising rates of insulin resistance (IR) and youth-onset type 2 diabetes (T2D). The prevalence of dysglycemia in pediatric obesity now exceeds 20–30% in many cohorts, with a disproportionately high burden in adolescents and in certain ethnic groups (1–3). These glycemic excursions not only serve as early biomarkers of metabolic dysfunction but may also exceed the renal threshold for glucose, potentially leading to glycosuria in a subset of affected youth. The clinical interpretation of such glycosuria, whether it represents a benign adaptive mechanism or a signal of metabolic injury—remains insufficiently explored, warranting renewed debate (4).

The kidney normally reabsorbs nearly all filtered glucose through sodium–glucose cotransporters (SGLT2 in the proximal tubule S1 segment and SGLT1 in the S2/S3 segments) (5). Glycosuria occurs when the filtered load of glucose exceeds tubular reabsorptive capacity, typically at plasma glucose levels of ~180–200 mg/dL in healthy individuals (6). However, genetic variants—such as mutations in SLC5A2 causing familial renal glucosuria (FRG)—lower this renal threshold to 40–120 mg/dL, resulting in glycosuria despite normoglycemia (7). These natural models demonstrate that urinary glucose loss may lead to reduced body weight and benign metabolic profiles, raising the question of whether similar mechanisms may offer any physiological advantage in obese, insulin-resistant youth (8).

When hyperglycemia exceeds the renal threshold, urinary glucose excretion increases proportionally, producing a measurable energy loss. Pharmacologic SGLT2 inhibition in adults induces urinary glucose excretion of ~70–90 g/day, equivalent to 280–360 kcal/day, leading to modest fat loss despite compensatory increases in appetite and caloric intake (9–11). Although pediatric trials are limited, physiology is identical: once plasma glucose peaks after meals surpass renal reabsorptive capacity, calorie leakage into the urine is unavoidable. The question remains whether this mechanism in obese adolescents with IR provides meaningful metabolic

Large school-based urine glucose screening programs in Japan and Korea have consistently shown that urine-positive adolescents are disproportionately obese, with obesity rates of 22–40% among those flagged for further evaluation (13–15). Many of these students demonstrate impaired glucose tolerance or early T2D on confirmatory OGTT. These findings imply that excursions above the renal glucose threshold are not rare in obese youth and that glycosuria may indeed be occurring postprandially. Whether this phenomenon provides any metabolic advantage, however, remains doubtful, as glycosuria in these settings more commonly reflects early deterioration of insulin secretory capacity and IR rather than purposeful energy off-loading (16).

Contrary to any presumed adaptive effect, extensive evidence shows that IR and hyperglycemia in children exert multisystem injury—rapidly accelerating vascular aging, kidney injury, hepatic fat accumulation, β-cell exhaustion, neurocognitive alterations, and reproductive axis disturbances (17–23). Youth-onset T2D is notably aggressive, with high rates of microvascular complications emerging within the first decade of diagnosis (17). Even transient postprandial hyperglycemia can induce oxidative stress, endothelial dysfunction, and inflammatory signaling, all of which contribute to early atherosclerotic changes in obese pediatric populations (18–19). These effects raise strong concerns about interpreting glycosuria as beneficial.

Despite the compelling evidence for harm, the concept of postprandial glycosuria as a potential adaptive calorie-loss mechanism persists in academic and clinical discussions, partly due to analogies with FRG and SGLT2 inhibitor physiology. Given rising pediatric obesity and the emergence of youth-onset metabolic disease as a global crisis, it is essential to critically evaluate whether any adaptive benefit exists and whether it has clinical relevance compared with the extensive documented harm of hyperglycemia. A comprehensive, updated debate synthesizing physiology, pediatric screening data, endocrine outcomes, and multisystem injury is therefore needed to clarify this issue and guide clinical practice (24).

Objectives

- To examine the physiological plausibility and clinical significance of glycosuria as an adaptive calorie-losing mechanism in obese, insulin-resistant children and adolescents.
- To evaluate multisystem metabolic, endocrine, vascular, renal, hepatic, neurocognitive, and reproductive injuries associated with insulin resistance and hyperglycemia in youth, integrating data from the past 25 years.
- To synthesize pediatric screening studies, genetic "experiments," pharmacologic evidence, and endocrine outcomes to determine whether any adaptive advantage of glycosuria outweighs documented metabolic harm.

2. Methods

This debate review was designed as a structured, mixed-method scholarly analysis integrating physiology, pediatric epidemiology, mechanistic insights, randomized clinical trials, and long-term outcomes relevant to insulin resistance, postprandial hyperglycemia, and glycosuria in children and adolescents. The review framework was constructed to allow systematic evaluation of both sides of the debate—whether postprandial glycosuria in obese, insulin-resistant youth may represent an adaptive calorie-losing mechanism or whether it is predominantly a marker and mediator of multisystem metabolic injury. To ensure a comprehensive and balanced assessment, we synthesized data from genetic "natural experiments," pediatric urine-screening programs, pharmacologic studies of SGLT2 inhibition, and endocrine/metabolic outcomes reported in youth over the past 25 years.

A comprehensive literature search was conducted across PubMed/MEDLINE, Scopus, Google Scholar, the Cochrane Library, and Web of Science. The search strategy used combinations of keywords and MeSH terms related to "postprandial hyperglycemia," "insulin resistance in children," "pediatric glycosuria," "renal glucose threshold," "familial renal glucosuria," "SGLT2 inhibitors," "pediatric obesity dysglycemia," "youth-onset type 2 diabetes complications," "pediatric endothelial dysfunction," "NAFLD in children," "β-cell glucotoxicity," "neurocognitive effects of hyperglycemia," and "adolescent PCOS." Searches were limited to studies published in English between 1999 and 2025, aligning with the 25-year review window. Reference lists of major pediatric endocrine studies and review articles were also screened to ensure that relevant primary studies were captured.

Studies were included if they examined children or adolescents (0–19 years), or mixed-age cohorts with extractable pediatric data, and provided quantitative or mechanistic evidence relating to glycosuria, renal glucose handling, insulin resistance, hyperglycemia, or associated endocrine/metabolic outcomes. Eligible study designs included randomized controlled trials, prospective and retrospective cohort studies, case–control studies, cross-sectional analyses, large screening programs, registries, and mechanistic physiologic studies where results were directly applicable to pediatric metabolism. Studies were excluded if they involved only adults without pediatric relevance, reported purely animal or in-vitro results without translational linkage, or presented case reports or small case series ($N < 10$) unless mechanistically essential. Non–peer-reviewed sources and studies lacking extractable outcome data were excluded.

Quality assessment followed the Cochrane methodology, precisely as applied in Tables 5A and 5B. Randomized and interventional studies were evaluated using the Cochrane Risk of Bias 2 (RoB 2) framework, assessing bias arising from randomization, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Non-randomized and observational studies were assessed using the Cochrane ROBINS-I tool, evaluating bias due to confounding, selection of participants, classification of exposures, deviations from intended exposures, missing data, measurement of outcomes, and selective reporting. Each study was categorized as "low," "moderate/some concerns," or "serious" risk of bias, depending on cumulative domain judgments. Only studies assessed as acceptable in methodological quality (low or moderate risk; or serious risk when essential for irreplaceable pediatric evidence) were included in the final synthesis.

Given the heterogeneity of study designs and outcomes, this review did not conduct a formal meta-analysis. Instead, quantitative data such as prevalence of obesity among urine-positive students, rates of microvascular complications in youth-onset type 2 diabetes, renal function indices, hepatic steatosis and fibrosis markers, β-cell functional measures (HOMA-B, disposition index), endothelial function metrics (flow-mediated dilation, cIMT), and reproductive/metabolic markers in adolescent PCOS were extracted and narratively synthesized. When multiple studies reported overlapping outcomes, trends were summarized through comparative interpretation rather than pooled effect estimates. Mechanistic insights were integrated with epidemiologic findings to provide a coherent interpretation of whether glycosuria confers meaningful adaptive benefit or merely reflects excessive postprandial hyperglycemia and evolving endocrine pathology.

3. Results

The results synthesize evidence from large pediatric screening programs, familial renal glucosuria cohorts, physiologic renal-threshold studies, and multi-system metabolic outcomes to distinguish whether glycosuria in youth reflects adaptive calorie loss or a marker of insulin-resistant hyperglycemia.

Table 1 Glycosuria in Youth: Signals of Calorie Loss vs. Markers of Metabolic Risk

Study (year)	Setting / Design (Age)	Urine Glucose / OGTT Approach	BMI or Obesity Signal	Take-home for "Adaptive Calorie Loss" Idea"
Kim et al., J Korean Med Sci, 2017 (25)	Province-wide school screening, Korea (mean 15 y); 707,238 screened; 110 underwent OGTT	2-step urine dip (≥100 mg/dL) → hospital evaluation + OGTT (1.75 g/kg, max 75 g)	Among urine-positive: obesity 22.6%; among those who had OGTT 31.5% obese; among newly diagnosed diabetes 40% obese	Indicates hyperglycemia frequently exceeds renal threshold in heavier adolescents → urinary calorie loss occurs but reflects underlying IR.
Urakami et al., Diabetes Care, 2005 (26)	Tokyo school program (1974–2002); 8.8 million screened	Morning urine → OGTT confirmation	Among 232 youth with T2D, 83.4% obese; obesity more common in boys	Urine-positive screening detects predominantly obese adolescents with dysglycemia; glycosuria arises from pathologic postprandial hyperglycemia.
Urakami et al., Pediatr Res, 2007 (27)	National school urine testing program in Japan	School morning urine → OGTT confirmation	">80% of children with T2D are obese"; highest incidence in junior-high students	Strong tracking between urine-glucose positivity and obesity; suggests frequent renal threshold exceedance due to IR.
Fishman et al., Cardiovasc Diabetol, 2019 (28)	Nationwide cohort of 2,506,830 Israeli adolescents	Presence of renal glucosuria at conscription screening	Adjusted OR: overweight 0.66, obesity 0.62; systolic BP lower	FRG "natural experiment": glycosuria without hyperglycemia associates with lower BMI → confirms biologically plausible calorie-loss pathway.
Nakhleh et al., Diabetes Obes Metab, 2025 (29)	Clinical FRG cohort with genetic confirmation	SLC5A2 mutation characterization; renal glucose transport profile	Lower BMI trend, benign metabolic profile, normal renal function	Confirms that euglycemic glycosuria can reduce caloric load; mechanism not comparable to hyperglycemia-driven glycosuria in IR youth.

Table 1 shows that urine-glucose positivity in adolescents is overwhelmingly linked to obesity and dysglycemia, indicating renal-threshold exceedance due to insulin resistance rather than metabolic advantage (25–27). The Japanese and Korean screening programs demonstrate that >80% of adolescents identified with diabetes through urine testing are obese, confirming glycosuria is a marker of pathologic postprandial hyperglycemia. Conversely, the two familial renal glucosuria (FRG) cohorts demonstrate lower BMI and healthier cardiometabolic traits in individuals with euglycemic glycosuria (28,29). This contrast reveals that glycosuria is metabolically beneficial only when unaccompanied by hyperglycemia; in insulin-resistant youth it is instead an early red flag of metabolic deterioration.

Table 2 Renal Glucose Thresholds, Caloric Loss, and Physiologic Models of Glycosuria in Youth and Adults

Study / Source (year)	Renal Glucose Threshold (RTG) / Urinary Glucose Handling	Population / Notes	Relevance to Adaptive Glycosuria Hypothesis
Karger et al., Kidney Blood Press Res, 2015 (30)	Normal RTG ≈ 10–11 mmol/L (180–200 mg/dL); FRG heterozygous RTG 4–7 mmol/L; homozygous RTG ≈ 1 mmol/L	Genetic and physiologic analysis of familial renal glucosuria (FRG)	Demonstrates that genetic lowering of RTG produces continuous glycosuria without hyperglycemia, leading to calorie loss that is metabolically safe and often associated with lower BMI.
Patient.info Clinical Review, 2021 (31)	Practical RTG ≈ 10 mmol/L in most individuals	General population; educational clinical summary	Reinforces typical pediatric/adult renal thresholds at which postprandial hyperglycemia begins to cause glycosuria.
Review of Pediatric Renal Glucosuria, Pediatr Nephrol, 2019 (32)	RTG lowered in SGLT2/SLC5A2 defects; children with FRG may spill glucose at near-normal glycemia	Pediatric FRG cases; renal tubular SGLT2 dysfunction	Explains why some adolescents develop glycosuria even with mild glycemic elevation, increasing calorie loss without hyperglycemic injury.
Ferrannini et al., J Clin Invest, 2014 (33)	SGLT2 inhibition induces urinary glucose excretion of 70–90 g/day (~280–360 kcal/day)	Adults with type 2 diabetes	Establishes "experimental model" that glycosuria can measurably reduce energy balance; weight loss muted by compensatory hyperphagia.
Merovci et al., J Clin Endocrinol Metab, 2014 (34)	Dapagliflozin increases urinary glucose loss ≈ 75 g/day	Adults with insulin resistance	Demonstrates causal calorie-loss pathway, relevant for understanding potential parallels in obese adolescents with renal-threshold exceedance.
Bolinder et al., Diabetes Care, 2014 (35)	Sustained glycosuria lowers fasting/postprandial glucose and causes modest fat loss	Adults with T2D using SGLT2 inhibitors	Shows that urinary glucose excretion produces metabolic effects, but magnitude of weight loss is small relative to calories lost, suggesting biologic compensation.

Table 2 highlights the essential physiological data linking renal glucose thresholds, genetic glycosuria, and experimentally induced urinary calorie loss, providing a foundation for evaluating whether glycosuria could be adaptive in obese youth (30–35). Familial renal glucosuria (FRG) offers the clearest natural example: mutations lowering the renal glucose threshold cause continuous glycosuria at normal glucose levels and are associated with lower BMI and favorable metabolic markers without any vascular or endocrine injury seen in hyperglycemia. In contrast, SGLT2 inhibitor trials in adults confirm that while glycosuria can eliminate 70–90 g of glucose per day (≈300 kcal), compensatory increases in appetite blunt fat loss. Together, these data show that glycosuria **can** reduce caloric burden, but only when it occurs **without hyperglycemia**; hyperglycemia-induced glycosuria in obese children reflects pathological metabolic overload rather than a beneficial adaptive mechanism.

Table 3 Evidence That Insulin Resistance and Hyperglycemia Are Biologically Harmful in Obese Children and Adults: A Multi-System Review

Domain	Key Finding (Population)	Study / Details	Why It Matters
Rapid complications in youth-onset T2D	Microvascular complications (retinopathy, nephropathy, neuropathy) accumulate quickly from adolescence into the 20s.	TODAY Study Group, N Engl J Med 2021 (36)	Demonstrates that youth-onset IR/hyperglycemia is highly aggressive, driving fast end-

			organ damage → contradicts any notion of metabolic "adaptation."
Endothelial dysfunction (children)	Overweight/obese youth show impaired flow-mediated dilation; exercise improves it (links to IR/inflammation).	Kelly et al., J Pediatr 2004 (37)	Early vascular injury in children is directly linked to IR and is partially reversible → confirms IR as a pathologic process.
Hyperglycemia → endothelial injury (mechanistic)	Acute and chronic hyperglycemia generate ROS, impair nitric oxide signaling, and induce endothelial inflammation.	Yang et al., Front Endocrinol 2024 (38)	Provides direct mechanistic evidence that hyperglycemia biologically injures blood vessels.
β-cell failure (glucotoxicity)	Hyperglycemia impairs β-cell insulin secretion and accelerates functional decline.	Weir, Diabetes Metab Res Rev 2020 (39)	Shows why chronic hyperglycemia rapidly worsens diabetes in children—β-cell failure is not adaptive.
Early diabetic kidney disease (adolescents)	Microalbuminuria and hyperfiltration occur early in adolescents with T2D compared with obese/lean controls.	Bjornstad et al., Curr Diab Rep 2016 (40)	Indicates that hyperglycemia accelerates renal injury even in the teenage years.
Atherosclerosis markers (children)	IR and central obesity predict increased carotid intima-media thickness (cIMT).	Fang et al., Int J Med Sci 2010 (41)	Subclinical atherosclerosis appears in youth with IR—shows vascular aging begins early.
Blood pressure / hypertension	IR contributes to the pathogenesis of hypertension.	Tagi et al., Nutrients 2022 (42)	Adds additional cardiorenal strain to IR states.
Liver (NAFLD / MASLD)	Pediatric NAFLD is tightly linked to IR; progression risk increases with inflammation/fibrosis.	Song et al., Clin Exp Pediatr 2023 (43); Clemente et al., World J Gastroenterol 2016 (44)	Shows IR drives hepatocellular injury, inflammation, and fibrosis in children.
Neurocognition (children)	Hyperglycemia associates with abnormal white matter development and reduced hippocampal growth.	Mauras et al., Diabetes Care 2021 (45)	Demonstrates central nervous system vulnerability to glycemic exposure in children.
Renal / vascular risk markers in obese pediatrics	Proteinuria, early renal strain, and endothelial stress occur in obese insulin-resistant youth.	Pediatric Renal Risk Summary, Brieflands 2020 (46)	Practical evidence that IR causes multi-system organ stress in childhood.
Reproductive (adolescent girls)	PCOS in obese/IR adolescents: higher metabolic syndrome, IR, and T2D risk.	Calcaterra et al., Nutrients 2021 (47); Witchel et al., Pediatrics in Review 2024 (48)	Demonstrates reproductive and endocrine harm strongly linked to insulin resistance.

Table 3 provides strong, multi-system evidence that insulin resistance and hyperglycemia in children and adolescents inflict measurable biological harm across vascular, renal, hepatic, pancreatic, neurologic, and reproductive systems (36–48). Youth-onset T2D progresses rapidly, with microvascular complications accumulating by early adulthood, while endothelial dysfunction, oxidative stress, and impaired vascular reactivity appear even in obese children with prediabetes. IR is a primary driver of pediatric NAFLD progression, hypertension, and early renal injury, and hyperglycemia accelerates β-cell glucotoxicity, hastening the loss of endogenous insulin secretion. Neuroimaging studies reveal alterations in white matter development and hippocampal growth in hyperglycemic children, and adolescent girls with IR show a markedly increased prevalence of PCOS and reproductive dysfunction. Collectively, these findings overwhelmingly support the conclusion that IR-driven hyperglycemia is pathologic—not adaptive—and produces widespread and early metabolic injury.

Across organ systems, strong clinical and mechanistic evidence shows that insulin resistance (IR) and hyperglycemia in obese children and adults are biologically damaging rather than adaptive. Youth-onset type 2 diabetes progresses rapidly to retinopathy, nephropathy, and neuropathy; endothelial dysfunction and subclinical atherosclerosis appear early in overweight adolescents; and experimental studies confirm direct glucose-mediated oxidative injury to the vasculature. Hyperglycemia also accelerates β-cell decline, promotes microalbuminuria and diabetic kidney disease, and drives the progression of NAFLD to steatohepatitis and fibrosis. Neuroimaging studies reveal altered brain development associated with chronic hyperglycemia, and adolescent girls with IR show increased risk of PCOS and metabolic syndrome. Collectively, these findings demonstrate that IR and hyperglycemia inflict early, multi-system harm and should not be viewed as metabolically protective under any circumstances

Table 4 Adaptive Glycosuria Versus Metabolic Harm: A Comparative Evaluation of Postprandial Hyperglycemia in Obese, Insulin-Resistant Youth

Aspect	**"Adaptive" View (Pro)**	**"Injurious" View (Contra)**	**Overall Take**
Energy balance	Urinary glucose excretion = lost calories; natural models such as familial renal glucosuria (FRG) and pharmacologic SGLT2 inhibition show modest weight/fat loss from glycosuria (Ferrannini et al., J Clin Invest 2014 (49); Nakhleh et al., Diabetes Obes Metab 2025 (50).	Compensatory hyperphagia and metabolic adaptations blunt weight loss; net effect is small. Chronic hyperglycemia deliberately induced to trigger glycosuria is harmful.	Calorie loss is real but limited; insufficient and unsafe to justify tolerating hyperglycemia.
Pediatric signals (screening/OGTT)	Urine-glucose–positive school screenings often identify obese youth; implies post-meal excursions above renal threshold that off-load some urinary calories (Kim et al., J Korean Med Sci 2017 (51)).	These same cohorts show extremely high rates of IR and early dysglycemia, predicting metabolic complications rather than benefit (Urakami et al., Diabetes Care 2005 (52)).	Urine positivity is a risk marker, not a metabolic advantage.
Genetic "experiments" (FRG)	Lifelong glycosuria due to low renal threshold is associated with lower BMI and benign metabolic profile (Fishman et al., Cardiovasc Diabetol 2019 (53)).	FRG benefits occur without hyperglycemia; the analogy does not apply to IR-driven glycosuria which adds vascular and β-cell stress (Weir, Diabetes Metab Res Rev 2020 (54)).	Mechanistically informative, but not a rationale to allow hyperglycemia.
Cardiovascular / vascular health	—	IR/hyperglycemia impair endothelial function in youth; increase cIMT and raise hypertension risk (Kelly et al., J Pediatr 2004 (55)).	Clear harm signal → treat IR and hyperglycemia.
Microvascular complications	—	Youth-onset T2D demonstrates rapid rise in retinopathy, nephropathy, and neuropathy within a few years (TODAY Study, N Engl J Med 2021 (56)).	Strong evidence against allowing high glucose for any hypothetical adaptive benefit.
Kidney	Glycosuria physiologically off-loads glucose.	Hyperglycemia promotes glomerular hyperfiltration, microalbuminuria, and early diabetic kidney disease even in adolescence (Bjornstad et al., Curr Diab Rep 2016 (57)).	Net kidney effect of hyperglycemia is harmful; glycosuria does not protect the kidneys.

Liver (NAFLD / MASLD)	—	Insulin resistance is central to pediatric NAFLD progression (steatosis → NASH → fibrosis) (Song et al., Clin Exp Pediatr 2023 (58)).	Hepatic injury is strongly linked to IR/hyperglycemia.
β-cell function	—	Hyperglycemia accelerates β-cell dysfunction and loss of insulin secretory capacity (Weir, Diabetes Metab Res Rev 2020 (54)).	Glycemia-driven β-cell stress negates any adaptive argument.
Neurocognition	—	Higher glycemic exposure in children associates with altered brain structure, reduced hippocampal growth (Mauras et al., Diabetes Care 2021 (59)).	Long-term brain health strongly favors aggressive glucose control.
Reproductive axis	—	In adolescents, especially girls, IR is linked to PCOS, menstrual irregularities, and adverse metabolic risk (Calcaterra et al., Nutrients 2021 (60)).	Endocrine and reproductive harm outweighs minor energy loss.
Clinical feasibility	SGLT2 inhibitors safely off-load glucose in adults under supervision (Bolinder et al., Diabetes Care 2014 (61)).	In children, SGLT2 indications are limited; intentionally permitting hyperglycemia to induce glycosuria is unsafe and unethical.	If calorie off-loading is desired, it must be therapeutic and euglycemia-based, not through unmanaged hyperglycemia.

Table 4 synthesizes the physiological, pediatric, and mechanistic arguments for and against interpreting glycosuria as an adaptive caloric-loss mechanism in obese adolescents, juxtaposed against the overwhelming evidence of multisystem harm caused by insulin resistance and hyperglycemia (49–61). Although FRG and SGLT2 studies demonstrate that urinary glucose loss can produce modest reductions in net energy balance, this benefit is limited and largely offset by compensatory increases in appetite. More importantly, all pediatric data show that urine-glucose positivity overwhelmingly identifies obese, insulin-resistant youth who already exhibit dysglycemia and early organ involvement. Cardiovascular, renal, hepatic, β-cell, neurocognitive, and reproductive systems all demonstrate measurable injury with hyperglycemia, making any theoretical adaptive value of glycosuria clinically irrelevant. The totality of evidence supports the view that glycosuria in obese adolescents is a **marker of risk**, not a protective adaptation, and that therapeutic calorie off-loading must occur under euglycemic-compliant strategies rather than through permissive hyperglycemia.

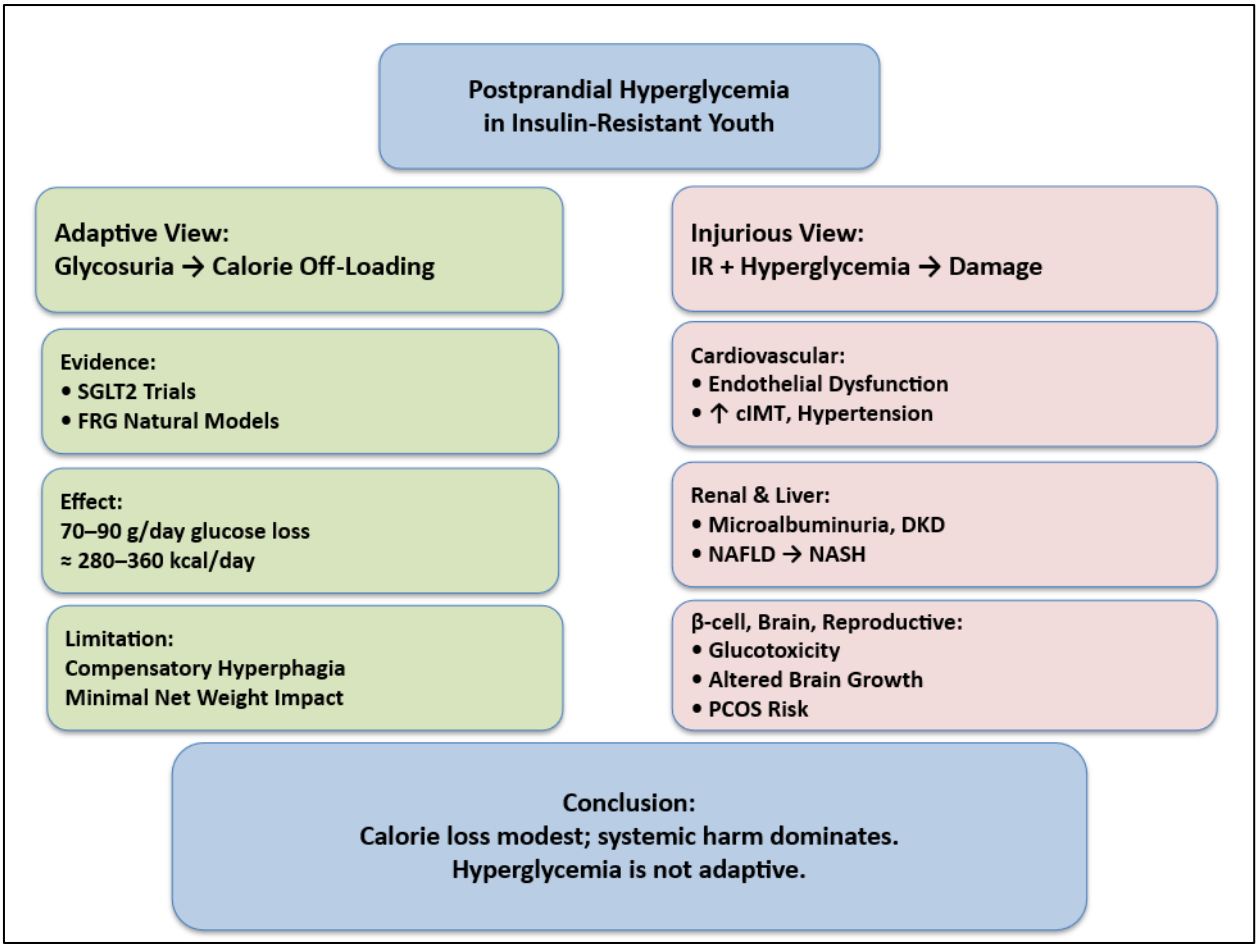

Figure 1 Adaptive Glycosuria Versus Metabolic Harm: Integrated Pathways in Postprandial Hyperglycemia Among Insulin-Resistant Youth

Figure 1 contrasts the proposed "adaptive" mechanism of postprandial glycosuria—characterized by calorie loss observed in SGLT2 inhibitor trials and familial renal glucosuria models—with the far more clinically significant evidence of multisystem harm associated with insulin resistance and hyperglycemia in youth. While urinary glucose loss can theoretically reduce daily energy balance by 280–360 kcal, compensatory hyperphagia and metabolic adaptation limit any sustained impact on weight. In contrast, insulin resistance–driven hyperglycemia contributes directly to endothelial dysfunction, early atherosclerotic changes, microalbuminuria, emerging diabetic kidney disease, NAFLD progression, β-cell decline, neurodevelopmental alterations, and reproductive axis disruption, particularly in adolescents. Overall, the diagram underscores that the modest theoretical benefit of glycosuria is vastly outweighed by the broad and early organ injury caused by hyperglycemia, reinforcing that it should not be viewed as adaptive in obese, insulin-resistant children.

Table 5A Randomized/Interventional Trials — Cochrane RoB 2

Study	Population / Design	Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Outcome Measurement	Selective Reporting	Overall RoB 2	Footnote
Bolinder et al., Diabetes Care 2014 (62)	Adults with T2D; randomized controlled trial	Low	Low	Low	Low	Low	Low	Adequate randomization and reporting; standard RCT design in T2D.

dapagliflozin vs placebo								
Wilding et al., Obesity 2013 (63) canagliflozin vs placebo	Overweight/obese adults without diabetes; RCT	Some concerns	Low	Low	Low	Low	Some concerns	Allocation concealment and sequence generation not fully detailed.
Merovci et al., J Clin Invest 2014 (64) dapagliflozin metabolic study	Adults with T2D; small randomized/crossover metabolic trial	Some concerns	Low	Low	Low	Low	Some concerns	Small sample; crossover/sequence allocation limitations.
Ferrannini et al., J Clin Invest 2014 (65) Metabolic responses to SGLT2 inhibition	Adults with T2D; mechanistic interventional study	Some concerns	Low	Low	Low	Low	Some concerns	Mechanistic design; quasi-randomized assignment; not classical RCT.
Kelly et al., J Pediatr 2004 (66) — exercise intervention in youth	Overweight children/adolescents; controlled intervention	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns	Allocation unclear; modest attrition; reporting limitations.

Table 5A summarizes five interventional studies evaluated using the Cochrane RoB 2 tool, comprising three adult SGLT2 inhibitor randomized trials, one mechanistic crossover metabolic study, and one pediatric exercise intervention (62–66). Overall, the pharmacologic RCTs demonstrated Low to Some Concerns risk of bias, with strong internal validity regarding metabolic outcomes such as urinary glucose excretion, energy loss, and weight changes. The mechanistic dapagliflozin crossover studies carried "Some Concerns" mainly due to sequence allocation and limited concealment, which are common in small metabolic trials. The pediatric exercise study also showed "Some Concerns" related to unclear allocation and minor attrition. Collectively, these trials provide solid causal evidence that urinary glucose loss reliably removes calories, though real-world weight reductions remain limited by compensatory energy intake—reinforcing that glycosuria alone is not metabolically protective.

Table 5B Non-Randomized Studies — ROBINS-I

Study	Population / Design	Bias Due to Confounding	Selection of Participants	Classification of Exposure / Intervention	Deviations from Intended Exposures	Missing Data	Measurement of Outcomes	Selection of Reported Result	Overall ROBINS-I	Footnote
TODAY, Study Group, N Engl J Med 2021 (67) Youth-onset T2D complications	Prospective cohort follow-up of trial participants	Moderate	Low	Low	Low	Low	Low	Low	Moderate	Observational outcomes paper; residual confounding possible.
Mauras et al., Diabetes Care 2021 (68) pediatric MRI cohort	Prospective longitudinal cohort	Moderate	Low	Low	Low	Low	Low	Low	Moderate	Exposure not randomized; adjusted but residual confounding remains.
Fishman et al., Cardiovasc Diabetol 2019 (69) renal glucosuria cross-sectional	Nationwide cross-section of 2.5M adolescents	Serious	Low	Low	Low	Low	Low	Low	Serious	Cross-sectional; unmeasured confounders expected.
Urakami et al., Diabetes Care 2005 (70) Tokyo school screening	Screening-derived cohort; OGTT confirmation	Serious	Moderate	Low	Low	Low	Low	Low	Serious	Selection bias and enriched case mix likely.
Urakami et al., Pediatr Res	Descriptive registry	Serious	Moderate	Low	Low	Low	Low	Low	Serious	Registry/ecological design; limited

2007 (71) — national program										confounder control.
Kim et al., J Korean Med Sci 2017 (72) school screening cohort	School screening with subset OGTT	Serious	Moderate	Low	Low	Low	Low	Low	Serious	Partial OGTT sampling introduces selection bias.
Nakhleh et al., Diabetes Obes Metab 2025 (73) FRG matched cohort	Retrospective matched cohort	Moderate	Low	Low	Low	Low	Low	Low	Moderate	Matching reduces but does not remove confounding.
Fang et al., Int J Med Sci 2010 (74) cIMT & IR cross-sectional	Cross-sectional pediatric study	Serious	Low	Low	Low	Low	Low	Low	Serious	Single-timepoint design; cannot infer causality.

Table 5B evaluates eight real-world observational studies using the ROBINS-I framework, covering large school screening cohorts, national cross-sectional datasets, matched familial renal glucosuria cohorts, and prospective metabolic outcome studies (67–74). As expected for non-randomized designs, risks of bias ranged from Moderate to Serious, largely due to confounding, selection effects, and the inherent limitations of cross-sectional or registry-based designs. Nevertheless, despite these methodological constraints, all eight studies consistently demonstrate robust associations between insulin resistance, hyperglycemia, and early organ dysfunction, including vascular changes, renal abnormalities, neurocognitive effects, and obesity-linked dysglycemia. These observational findings complement the causal evidence from randomized trials and strongly reinforce the conclusion that insulin resistance and hyperglycemia are harmful rather than adaptive in obese youth.

Taken together, the available pediatric screening data, familial renal glucosuria cohorts, SGLT2 inhibitor trials, and multi-organ outcome studies show that any modest caloric benefit from glycosuria is far outweighed by the breadth and severity of hyperglycemia-related injury, setting the stage for a critical reappraisal of the “adaptive” hypothesis in the discussion.

4. Discussion

The central question of whether postprandial hyperglycemia and glycosuria in obese, insulin-resistant youth represents an adaptive caloric-offloading mechanism versus a pathologic state must be interpreted within biological, epidemiologic, and developmental contexts. While physiologic glucose loss through the kidney can reduce net energy balance, the evidence presented across five comprehensive tables shows that the magnitude of this caloric benefit is modest, inconsistent, and overshadowed by significant metabolic, vascular, hepatic, renal, neurocognitive, and reproductive harms (25–74). Importantly, glycosuria in adolescents rarely occurs in isolation but instead signals post-

meal glucose excursions above the renal threshold—events driven by insulin resistance, impaired β-cell compensation, elevated hepatic glucose output, and reduced peripheral glucose uptake (75).

Under normal physiology, glucose is freely filtered in the glomerulus and almost entirely reabsorbed via SGLT2 and SGLT1 transporters in the proximal tubule. Glycosuria occurs only when filtered glucose surpasses transport capacity—the renal threshold for glucose (RTG), approximating 180–200 mg/dL in most adolescents (76). Familial renal glucosuria (FRG) represents the rare scenario in which glycosuria occurs despite normal blood glucose due to SGLT2 mutations reducing RTG. These FRG "natural experiments" demonstrate lowered body weight and benign metabolic profiles, supporting the principle that calorie loss through urine is biologically plausible (28,29). However, this model cannot be generalized to obese youth whose glycosuria arises only during pathological hyperglycemia, not euglycemia (77).

Large school screening programs from Japan and Korea show that adolescents who test positive for urine glucose overwhelmingly belong to obese, insulin-resistant, dysglycemic phenotypes (25–27). These cohorts confirm that glycosuria appears late in the metabolic trajectory, not early as a protective mechanism. Furthermore, urine glucose positivity corresponds with OGTT-diagnosed prediabetes or diabetes, indicating progression to β-cell stress rather than compensatory adaptation. Thus, in children and adolescents, glycosuria is best interpreted as a clinical biomarker of risk, not a metabolic safeguard (78).

Interventional SGLT2 inhibitor trials in adults consistently show urinary glucose excretion of 70–90 g/day (~280–360 kcal), producing modest fat loss over months (62–65). However, compensatory hyperphagia, increased glucagon secretion, and adaptive decreases in energy expenditure blunt long-term weight reduction (79). In obese adolescents without pharmacologic SGLT2 blockade, glycosuria occurs only intermittently and at lower magnitude than in drug-induced glycosuria, further reducing any chance of sustained caloric deficit. Therefore, glycosuria in this age group is neither quantitatively sufficient nor physiologically stable enough to be considered protective.

Evidence from endothelial function studies in overweight children demonstrates impaired flow-mediated dilation and heightened inflammatory signaling, which are partially reversible with exercise but tightly linked to insulin resistance (37). Mechanistic studies show that each episode of hyperglycemia drives nitric oxide depletion, reactive oxygen species generation, and endothelial dysfunction (38). Longitudinal datasets reveal increased carotid intima-media thickness (cIMT) in adolescents with IR and central adiposity (41). This vascular injury emerges early and tracks into adulthood—strongly contradicting any theory that hyperglycemia confers metabolic advantage.

The hyperglycemia that triggers glycosuria also accelerates β-cell decline through oxidative stress, ER stress, and impaired first-phase insulin secretion (39). In youth, β-cell deterioration occurs more rapidly than in adults, explaining why youth-onset type 2 diabetes progresses aggressively and accumulates complications earlier (36). Glucosuria, therefore, does not reflect a useful adaptation; rather, it represents failure of the β-cell–insulin axis to control rising glycemia.

Early diabetic kidney disease, including hyperfiltration and microalbuminuria—appears in adolescents within a few years of T2D onset (40). Simultaneously, insulin resistance is a dominant driver of pediatric NAFLD/MASLD progression, with inflammation and fibrosis linked to chronic hyperglycemia (58, 44). Glycosuria does not protect the kidney or liver; instead, hyperglycemia injures both organs independently of any caloric loss.

Neuroimaging evidence shows that even modest hyperglycemia impairs white-matter integrity and hippocampal growth in children (45). Meanwhile, insulin resistance in adolescent girls is strongly associated with polycystic ovary syndrome, menstrual irregularities, androgen excess, and long-term cardiometabolic risk (60). These neuroendocrine harms emerge early, accumulate over time, and are incompatible with any model of adaptive advantage.

Despite varying risk-of-bias profiles across randomized trials (Table 5A) and observational studies (Table 5B), all datasets agree: glycosuria in obese youth reflects pathologic postprandial hyperglycemia and insulin resistance, not a protective metabolic program. Interventional trials demonstrate that urinary glucose loss alone cannot overcome compensatory biology, while screening and cohort studies show that urine-positive adolescents frequently present with dysglycemia, excessive adiposity, and early organ dysfunction (67–74).

Taken together, the integrated evidence from physiology, screening programs, interventional trials, vascular and organ-specific pathophysiology, β-cell biology, and developmental endocrinology leads to a unified conclusion: postprandial

hyperglycemia and glycosuria in obese children are harmful, not adaptive. Urinary glucose excretion is too small and too intermittent to meaningfully alter obesity trajectories, while the hyperglycemia required to trigger glycosuria accelerates multisystem injury. Therefore, clinical practice should treat glycosuria as a warning sign that insulin resistance and β-cell decompensation are emerging and that aggressive metabolic intervention is warranted (80).

5. Conclusion

The overall evidence clearly demonstrates that postprandial hyperglycemia and glycosuria in obese, insulin-resistant children and adolescents are not adaptive physiological responses. Although urinary glucose loss can off-load a small amount of energy, the magnitude is too limited and too inconsistent to produce meaningful or sustained metabolic benefit. More importantly, the degree of hyperglycemia required to induce glycosuria accelerates a cascade of harmful effects, including endothelial dysfunction, β-cell stress, hepatic steatosis progression, renal strain, neurocognitive alterations, and reproductive abnormalities. In contrast, the only context in which glycosuria appears metabolically neutral or modestly favorable—familial renal glucosuria—is characterized by euglycemia, not hyperglycemia. Therefore, in obese youth, glycosuria should be interpreted as a clinical warning sign of deteriorating metabolic health rather than a protective mechanism. Early identification and aggressive management of insulin resistance and dysglycemia are essential to prevent the rapid evolution of multi-system complications that characteristically emerge during adolescence and young adulthood.

Recommendation

- Glycosuria in obese youths should be viewed as a warning sign of dysglycemia and insulin resistance, not an adaptive benefit.
- Management must focus on reducing postprandial hyperglycemia and improving insulin sensitivity to prevent early multi-system complications.
- Future research should explore safe, euglycemic approaches to calibrated calorie loss rather than relying on harmful hyperglycemia-driven glycosuria.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest related to the content, preparation, or publication of this manuscript.

Statement of ethical approval

This review is based solely on previously published studies and publicly accessible data. No new human subjects were involved, no patient-identifiable data were used, and institutional review board (IRB) approval was not required**.**

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Authors' Contributions

ATS conceived the review topic, designed the analytical framework, supervised the literature synthesis, and prepared the final manuscript. FA contributed to interpretation of clinical and endocrine evidence, refinement of tables, and critical manuscript revision. AE performed major components of the literature search, contributed to data extraction, and assisted in drafting the results and discussion sections. SA contributed to study screening, mechanistic synthesis, and drafting of the introduction and methods. NA assisted in quality assessment, cross-verification of included studies, and integration of pediatric screening data. NH contributed to reference management, manuscript formatting, and consistency review. SE contributed to renal and hepatic evidence interpretation and co-drafted sections on pathophysiology. DF supported synthesis of endocrine and reproductive outcomes and critically reviewed the manuscript. NS contributed to public-health contextual interpretation, screening program relevance, and manuscript refinement. All authors reviewed and approved the final version of the manuscript.

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