Cell Reports Medicine

CellPress
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Review

Gut microbiota and metabolic disease risk in youth

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https://doi.org/10.1016/j.xcrm.2025.102571

SUMMARY

The rapidly increasing global incidence of youth-onset diabetes is a critical public health concern. Earlier type 2 diabetes (T2D) onset in children and young people is characterized by faster progression and higher risk for complications. An area of expanding research is understanding how obesogenic environments modify the composition and function of the gut microbiota and, in turn, modulate host immune response as well as metabolism. The association between obesity and altered gut microbiota is complicated by hormonal changes during puberty and chronic inflammation that potentiates insulin resistance in multiple responsive tissues. This review examines the risk factors and mechanisms underlying T2D pathogenesis in children and young people and current evidence connecting gut microbiota to stages of disease progression and treatment opportunities. The potential for early intervention through modifications of the gut microbiota opens avenues to alleviate metabolic complications in critical developmental period and blunt the risk for early T2D onset.

INTRODUCTION

In 2021, diabetes affected over half a billion people worldwide, accounting for 37.8 million years of life lost and 41.4 million years lived with disability.[1,2] Research advances since the mid-20th century have established the distinct autoimmune and metabolic bases of type 1 diabetes (T1D) and type 2 diabetes (T2D), respectively, with the latter previously characterized as adult onset due to long-term insulin resistance.[3] Population-based T2D studies in high-income countries demonstrate a rising trend in youth-onset T2D since the 2000s.[4,5] In the United States, youth-onset T2D incidence has risen more rapidly than T1D since 2002, and by 2017 to 2018 the two rates were similar.[4]

A major driver of the increase in youth-onset T2D incidence is childhood obesity, which is robustly associated with adult obesity, accelerated T2D progression, greater risk of metabolic complications, and premature mortality.[6–8] Up to 90% of pediatric T2D patients are affected by obesity, with contribution of body mass index (BMI) to T2D risk decreasing with age.[9] Between 1990 and 2021, obesity in children and adolescents increased by 244%, and one-third of the world's children and adolescents are predicted to be living with overweight or obesity by 2050.[10] This increase is disproportionately borne by population subgroups in low- and middle-income countries (LMICs), including territories in Oceania (e.g., the Cook Islands, Tonga, Northern Mariana Islands, and Nauru) and densely populated countries (e.g., Nigeria, India, and China).[10] Given these regional trends, LMICs are estimated to account for 87.5% of undiagnosed diabetes.[1] Concurrently, significantly higher risk of youth-onset T2D has been reported among people of the First Nations in Manitoba,[11] the Navajo Nation,[12] and the Australian Aboriginal and Torres Strait Islander communities,[13] emphasizing the impact of social determinants of health (SODH) on diabetes in these populations.

Indeed, risk of T2D development, progression, and mortality is heavily influenced by SODH such as education, income, and occupation.[14] In the SEARCH study, over 80% of youth with T2D had experienced barriers to quality health care due to SODH, including cost of care, access to information, communication, and contextual care.[15] Moreover, youths of black ancestry, Hispanic ethnicity, and low-income families had a higher risk of diabetic ketoacidosis at diagnosis and a higher risk for worsening glycemic status.[16] While these health inequities reflect societal and structural disadvantages outside of individual control,[17] other intermediary to SODH are potentially modifiable, such as diet and physical activity. The metabolic effects of these obesogenic factors are partially mediated through gut microbiota,[18–21] which, in turn, affect immune system development and function[22–26] as well as metabolite production or utilization.[27–33] The few studies examining the gut microbiome in indigenous populations found that community-level differences in microbial composition are associated with diet, degree of westernization, and other SODH-related factors.[34–37]

While T2D is a complex chronic disease for which remission is difficult to achieve, overweight and obesity can be considered a reversible risk exposure to which targeted interventions can be effectively directed. Obesity intervention is particularly important in adolescents due to hormone fluctuation, body composition, and insulin resistance during this key developmental period.[38,39] Return to a non-obese state before puberty reverses heightened risk of T2D and metabolic dysregulation later in life.[6] Identification of modifiable risk factors to enable early, effective intervention is

urgently needed to curb youth-onset T2D and alleviate these burdens in vulnerable populations.[12] Given that gut microbiota may serve as a critical determinant of response to risk exposures through its influence on host immune- and metabolic-regulation,[40,41] attempts have been made to manipulate gut microbiota with prebiotics,[42,43] probiotics,[44,45] and fecal microbiota transplant (FMT).[46–48]

In this review, we examine the risk factors, the pathogenesis, the opportunities for interventions and prevention, and the evidence connecting gut microbiota to stages of disease progression, with a focus on youth-onset T2D. The rates at which cases of childhood obesity and T2D increase worldwide and the accelerated course of T2D progression in youth emphasize that the window for intervention is short in many populations. Harnessing the potential of gut microbiota for early identification and targeted treatment may prove crucial for disease prevention and intervention in high-risk individuals and reducing the burden on global healthcare systems.

Genetic risk of T2D

The estimated heritability of T2D ranges from 18% to 70% in genetic studies.[9,49] Hundreds of loci have been associated with T2D, with common variants explaining a large portion of disease heritability and some rare variants having larger effect sizes.[49,50] Genetic association signals have been mapped to regulatory and coding sequences in genes expressed in the pancreatic islets, as well as regulatory regions active in insulin-sensitive tissues, muscle, liver, brain, and intestine.[49] For example, *TCF7L2*, the susceptibility gene with the largest effect, encodes a transcription factor in the Wnt signaling pathway responsible for keeping insulin-secreting granules in proximity to the voltage-gated Ca^{2+} channels.[51] In addition to glucose-stimulated insulin secretion (GSIS) in β cells, *TCF7L2* also regulates adipocyte size and secretory function. In mice challenged with a high-fat diet, early loss of *TCF7L2* had a sustained effect on response to insulin.[52] Another T2D risk gene, *NEUROG3*, encodes the neurogenin-3 transcription factor required for lineage specification and development of pancreatic endocrine and enteroendocrine cells, which displays lower expression level in adult islet cells.[53] Different alleles that cause *NEUROG3* deficiency confer T2D with variable age of presentation, from neonatal onset due to deficiency in pancreatic endocrine cells to early childhood onset due to the loss of enteroendocrine cells.[54] These associations suggest that genetic factors influence T2D through crosstalk between multiple tissues that increase adiposity, disrupt insulin secretion, or decrease glucose absorption and regulation in the gut. Genetic risk variants associated with cardiometabolic traits and T2D revealed distinct clusters implicating β cell dysfunction, obesity, lipodystrophy, and liver and lipid metabolism.[50] In the European IMI (Innovative Medicines Initiative) DIRECT (Diabetes Research on Patient Stratification) study, individuals newly diagnosed with T2D could be clustered into four archetypes suggestive of different etiological processes.[55] Compared to the three archetypes characterized by obesity and variable insulin sensitivity and glucose regulation, the archetype with lower BMI, older age, high insulin sensitivity, and high cholesterol was associated with greater genetic predisposition for T2D.[55] Similarly, in lean populations with higher T2D prevalence, the genetic burden for compromised β-cell function is increased compared to the European population.[56] Consistent with the understanding of obesity-related processes underlying metabolic dysregulation, there are overlaps between risk variants for coronary artery disease, peripheral artery disease, and end-stage diabetic nephropathy.[50]

Genetic associations for youth-onset T2D largely overlap with those for adult-onset T2D; however, genetic liability is greater in children and young people compared to adult-onset individuals especially for rare variants.[57] At the extreme of the spectrum for genetic risk, variants in *HNF1A, MC4R, ATXN2L* are associated with monogenetic forms of diabetes.[57] *HNF1A* encodes the transcription factor HNF-1α, which regulates β-cell glucose sensing and insulin secretion through expression of GLUT2, calcium-channel, and granule-maturation gene programs, with pathogenic variant in patient-derived human-induced pluripotent stem cells causing reduced glucose uptake and GSIS.[58,59] Importantly, many of these T2D susceptibility genes modulate cell development and function in the gut, suggesting plausible pathways by which host genetics could interact with microbial communities and metabolites to shape gut epithelial barrier function, hormone production, and mucosal immune responses. *Hnf1a* along with *Hnf1b* regulates gut epithelial cell fate commitment and differentiation into enteroendocrine, goblet, or Paneth cells[60]; MC4R activation on enteroendocrine L cells in the intestinal mucosa enhances secretion of glucagon-like peptide 1 (GLP-1) and peptide tyrosine tyrosine (PYY), which are anorexigenic gut hormones promoting termination of feeding.[61] Moreover, *HNF1A* variant identified in Oji-Cree First Nation population in Canada is associated with decreased insulin production and youth-onset T2D at lower degrees of insulin resistance[62] and replicated in African American, European, and Hispanic subgroups.[57] These findings of increased genetic risk burden and heightened risk of metabolic complications in youth-onset T2D suggest differences in pathogenesis compared to adult-onset disease. There is a critical gap in understanding of the mechanisms of progression to metabolic dysfunction in children and young people, necessary to discover and implement effective intervention strategies for youth-onset T2D.

Environmental risk of obesity and T2D

The epidemiological trends in youth-onset T2D presents compelling evidence of environmental influences on disease risk. The primary modifiable risk factor, obesity—particularly the accumulation of visceral fat—plays a critical role in insulin resistance and β-cell dysfunction.[63] The gut microbiota has been increasingly studied in the context of obesity and metabolic dysfunction. These microbial communities are directly impacted by an obesogenic environment: increased caloric intake and decreased physical exercise.[18–21,41,64] Indeed, a causal role of the gut microbiota in obesity has been well-established in mouse models.[41,65] Colonizing germ-free (GF) mice with a specific-pathogen-free (SPF) microbiota led to increased body weight and adipose tissue (AT) mass, despite reduced calorie intake, suggesting increased energy supply from the gut microbiota.[66] The phenotypes of obese and lean discordant human twins can be transferred to recipient mice via FMT. Interestingly, cohousing obese recipient mice with lean counterparts is enough to induce a lean

phenotype, likely through the transmission of lean-associated microbiota, such as *Bacteroides* spp.[67]

In humans, environmental influences on obesity and metabolic functions are shown to be mediated through gut microbiota. Both a fiber-rich Mediterranean diet and increased physical activity are associated with increased microbial capacity to degrade plant carbohydrates and produce short-chain fatty acids (SCFAs) and reduction in secondary bile acids (BAs)[68] and branched-chain amino acids (BCAAs).[18,20] Such lifestyle interventions can increase the abundance of butyrate producers, like *Faecalibacterium prausnitzii* and *Alistipes putredinis*, and change the abundance of *Bacteroides* spp. implicated in obesity, such as *Bacteroides uniformis* and *Bacteroides vulgatus*.[18,20] Interestingly, specific gut microbial members seem to be crucial for the benefits of these lifestyle changes. For instance, the cardiovascular benefits of a Mediterranean diet are more pronounced in individuals lacking *Prevotella copri*, strains of which have been associated with insulin resistance[69] and a Western diet.[37]

Early-life microbiota and obesity risk

In infancy, the microbiota is characterized by *Bifidobacterium* predominance and undergoes rapid changes in the first 2–3 years of life before stabilizing toward an adult-like microbiota with higher bacterial diversity.[70,71] Maternal factors,[72,73] delivery mode,[70,74] breastfeeding,[70,73] and antibiotic exposure[74,75] are the major factors influencing microbial composition and their metabolic capacity and have been associated with obesity risk later in life. For instance, a shorter duration of exclusive breastfeeding was associated with a distinct fecal microbiota composition in 1-month-old infants indicative of accelerated maturation such as depletion of *Bifidobacterium* and enrichment of *Blautia*, as well as broad-ranging metabolic reprogramming such as reduced concentrations of neuro-endocrine signals. The precocious fecal microbiota composition was associated with higher risk for obesity/overweight at 2 years.[76] In contrast to the increased bacterial diversity, decreased fungal richness is associated with gut microbiome maturation in infant growth trajectory. An increase in fungal richness during the first year of life is linked to parental and infant BMI.[75] Maternal pre-pregnancy obesity and excessive gestational weight gain have also been associated with childhood BMI, and with changes in infant microbes reflecting transfer from maternal microbiota (e.g., *Bifidobacterium bifidum*) and shared environmental exposures (e.g., *Blautia* sp.).[72] These findings highlight the important role of differences in maturational patterns on growth outcomes in early life, suggesting that interventions for healthy colonization, such as longer breastfeeding[76,77] and timed introduction of probiotics (e.g., *Bifidobacterium, F. prausnitzii*),[72] may help steer microbiota toward a resilient configuration and reduce later obesity risk.

Gut microbiota changes in children and young people with obesity

While studies of gut microbiota in children and young people are limited compared to those in adults, these studies observed similar compositional and functional alterations, especially in SCFAs[78] and BCAAs,[79,80] reported in adults with obesity. There is an overall reduction in gut microbiome richness[81,82] attributed to the loss of butyrate-producing bacteria, such as *Faecalibacterium*,[78,81] *Subdoligranulum*, and *Alistipes* species,[71,79,82] associated with increased obesity and metabolic dysfunction. In children and young people, obesity associated changes in the ratio of Bacillota (formerly Firmicutes), which include many SCFA producers, and Bacteroidota (formerly Bacteroidetes), however, remains inconclusive.[71,78] Interestingly, increased fecal SCFAs in children and young people with obesity[78,80,83] have been consistently observed despite the metabolic benefits of SCFA in simulating colonic production of PYY and GLP-1.[41,64,84] One potential explanation is that changes in microbial metabolism with increased substrate utilization and energy harvest result from colonic fermentation in persons with obesity. In addition, gut microbiota alterations may influence host metabolism through crosstalk with the immune system. In children and young people with obesity or metabolic dysfunction, higher levels of inflammation are associated with the gut microbiota through greater pathogenicity of the gut bacteria[81] neutrophil activation[82] and decreased gut-derived anti-inflammatory indole derivatives.[85]

While gut microbiome studies in obesity and T2D provided insights into how altered gut microbiota may impact metabolic dysfunction, high-throughput sequencing of gut microbes at a single time point or sparse snapshots are not sufficient to capture the complex dynamics of gut bacterial interactions within community as well as with the host. Recent gut microbiome research using larger sample sizes, frequencies, or harmonized publicly available sequences has identified previously overlooked factors contributing to microbiome variance, including circadian rhythms, geographical locations, and fecal microbial load.[86–88] In a European cohort, decreased microbial oscillations in individuals with obesity and T2D suggests that modulation of microbial rhythm may provide a strategy to improve host metabolism.[86] In addition, fecal microbial load is an indicator of gut ecological environment dependent on host factors such as age, sex, diet, lifestyle, and medication. Bacterial biomass modifies effect size and strength of association between gut microbes and a number of disease phenotypes such as Crohn's disease and colorectal cancer.[87] Decreased fecal microbial load is associated with lower gut microbiome diversity, enriched pro-inflammatory taxa, dyslipidemia, and higher level of systemic inflammation in cohorts of adolescents[82] and adults[89] with obesity. These results emphasize the importance of accounting for host influences in gut microbiome studies and experiments in animal models to improve mechanistic understanding of the role of gut microbiota in metabolic dysfunction.

Gut microbiota regulation of energy uptake

One of the ways through which gut microbiota may be mechanistically involved in host metabolism is that obesity-associated gut microbiome may be more efficient at harvesting energy, directly supplying additional energy to the hosts (Figure 1A).[90] Energy uptake can be regulated by the gut microbiota, demonstrated by a study on T cell-specific *Myd88* deletion mice prone to obesity with aging. These mice display altered gut microbiome composition with increased *Desulfovibrio* and decreased *Clostridia*. The latter repressed lipid absorption by down-regulated expression of the scavenger receptor CD36 on intestinal epithelium and liver in an IgA-dependent manner (Figure 1B).[91] Reduced IgA-bound bacteria, inappropriate IgA targeting of *Clostridia*, and expansion

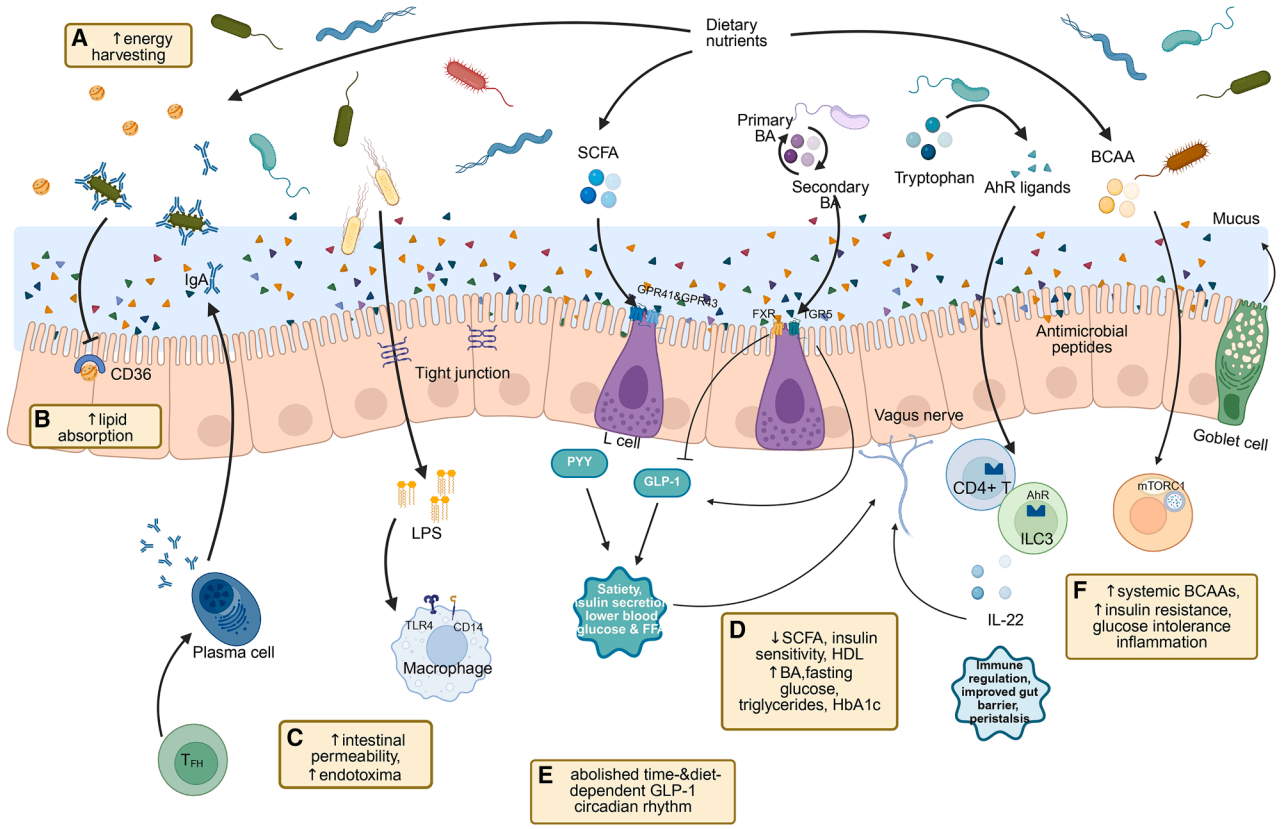

Figure 1. Microbial metabolites and signals affect host metabolism

(A) Gut microbiota serves as direct energy supply to the host by metabolizing dietary nutrients that have not been absorbed into the small intestine into energy-rich molecules that can be taken up by the host. Obesity-associated gut microbiome may be more efficient at harvesting energy.

(B) Certain gut bacteria can modulate expression of receptors or transporters for metabolites to affect host energy uptake. For example, *Clostridia* can repress lipid absorption by down-regulating the expression of the scavenger receptor CD36 on intestinal epithelium and liver. In obese mice, there is reduced IgA-bound bacteria, inappropriate IgA targeting of *Clostridia*, and expansion of *Desulfovibrio*, which do not confer the host equal metabolic benefit.

(C) Alterations in gut microbiota composition can destabilize tight junction, induce gut permeability and inflammation, and lead to glucose intolerance. Moreover, a systemic low-grade inflammation has been observed in individuals with obesity and metabolic dysfunction due to impaired gut barrier and increased translocation of microbial-associated molecular patterns. These observations, collectively termed *endotoxemia*, has been shown to lead to elevated fasting glycemia and insulinemia in mice. Blocking TLR signaling can reduce macrophage recruitment and protect from weight gain as well as some metabolic complications in mice.

(D) SCFAs play an important role in modulating host metabolism to promote homeostasis in the gut. Through G protein-coupled receptor (GPR) 41 and GPR43, SCFAs stimulate the secretion of anorexigenic peptides GLP-1 and PYY from enteroendocrine L cells to reduce appetite as well as glucose and lipid production. Decreased capacity for butyrate production by the gut microbiota is observed in prediabetes and T2D and is associated with metabolic dysfunction metrics such as impaired glucose tolerance and increased fasting glucose triglycerides.

(E) Gut microbiota modifies BA structure to produce secondary BAs, which can be re-absorbed by the host and affect glucose homeostasis. When signaled through FXR, BAs counteract SCFA action on secreting GLP-1, while signaling through TGR5 increases circulating GLP-1. Moreover, SCFAs and BAs may collectively regulate GLP-1 release. Under physiological conditions, GLP-1 levels exhibit time- and diet-dependent fluctuations to modulate insulin secretion and glycemia, with greater release in response to identical glucose loads at the onset of the dark/feeding period compared with the light/fasting period in rodents. The peak of GLP-1 release coincides with decreased SCFA, increased BAs, and higher abundance of *A. muciniphila.* The circadian release of GLP-1 requires gut microbiome and is disrupted in HFD-fed mice, accompanied by increased fasting glucose and insulin secretion.

(F) Gut microbiota can metabolize BCAAs and tryptophan, modify their availabilities to the host, and modulate host glucose tolerance. Tryptophan catabolism by gut bacteria can generate ligands for AhR that produces non-inflammatory IL-22 important for barrier function, immune homeostasis, peristalsis, and improving glucose and insulin responses. BCAA can activate rapamycin complex 1 (mTORC1) that affects insulin signaling and induce pro-inflammatory cells. Increased biosynthesis of BCAAs by the gut microbiota is associated with low-fiber diet, insulin resistance, glucose intolerance, obesity, and T2D.

of *Desulfovibrio* may drive obesity, which is transmissible through mouse co-housing.[91]

Pro-inflammatory gut environment in obesity

In addition to direct supply of energy, gut microbiota may modify host metabolism through metabolites that interact with the immune system, the endocrine system, and other tissues. Increased intestinal permeability is seen in individuals with obesity and metabolic dysfunction and is associated with endotoxemia, a systemic inflammation in response to elevated gut-derived lipopolysaccharide (LPS).[22,23,92] In mouse models, a high-fat diet has been shown to increase plasma LPS levels, leading to

elevated fasting glycemia and insulinemia. CD14 knockout mice with impaired Toll-like receptor (TLR)-mediated sensing of bacteria are relatively protected from weight gain, hyperinsulinemia, or visceral fat accumulation compared to wild-type littermates (Figure 1C).[92] Supporting the interplay between gut inflammation, intestinal permeability, and metabolic dysregulation, IgA deficiency alters gut microbiome composition leading to glucose intolerance and insulin insensitivity.[22] Microbial signals may destabilize epithelial cell tight junctions, inducing gut permeability, inflammation, and abnormalities in glucose metabolism.[23] Changes in the abundance of pro-inflammatory taxa, particularly species of Pseudomonadota (previously Proteobacteria), which dominate the pathway for LPS precursor synthesis, have been observed in human obesity studies.[37,93,94]

Microbial products and host metabolism

SCFAs are well-studied gut metabolites that modulate host metabolism to promote homeostasis in the gut. These metabolites enhance gut motility, maintain tight junction integrity, and promote anti-inflammatory responses mediated by Treg, IgA, and tolerogenic innate immune cells.[30,95,96] By binding to the G protein-coupled receptors GPR41 and GPR43, SCFAs directly stimulate the secretion of GLP-1 and PYY from enteroendocrine cells, which work through the vagus nerve to reduce appetite, and decrease hepatic glucose and lipid production (Figure 1D).[41,64,84] In humans, changes in capacity for butyrate production by the gut microbiota is observed in prediabetes and T2D and associated with impaired glucose tolerance, increased fasting glucose triglycerides, increased HbA1c, and decreased HDL cholesterol (Figure 1D).[94,97–99] The mechanistic links between SCFAs and host metabolic regulation are ambiguous in humans. While gut microbiota of individuals with prediabetes or T2D exhibit decreased abundance of genes for butyrate biosynthesis, the putative effects of differentially abundant butyrate producers do not display a uniform direction of effect.[98] Moreover, in a Mendelian randomization study of healthy Dutch adults, host-genetic-driven upregulation of a butyrate-producing pathway was associated with improved insulin response, whereas increased fecal propionate levels were associated with T2D risk.[100] Increased SCFAs have also been observed in children with obesity, suspected to be a result of increased energy supply from the gut microbiota.[78,80,83] SCFAs play a critical role in maintaining gut homeostasis and regulating host metabolism, but their mechanistic links to metabolic diseases remain complex, with varying effects observed across different populations and sites of production.

Additional gut microbial metabolites have also been implicated in obesity or T2D. Gut bacteria can conjugate primary BAs derived from endogenous cholesterol to produce secondary BAs, which modulate hepatic fat and glucose homeostasis.[65] BAs can bind different receptors to regulate GLP-1 level in a context-dependent manner along with SCFAs. For example, BAs binding to farnesoid X receptor (FXR) counteract SCFA-induced GLP-1 secretion, but Takeda G protein-coupled receptor 5 (TGR5) increases GLP-1 (Figure 1D).[33] SCFAs and BAs might also be involved in the diurnal regulation of GLP-1 release and glycemic control by the gut microbiota.[101] In mice, there is greater GLP-1 release in response to glucose at the onset of the dark/feeding period compared with the light/fasting period, coupled with decreased SCFAs and increased BAs in the cecum and an increased abundance of *Akkermansia muciniphila* at the peak of GLP-1 release.[101] Conversely, the time- and diet-dependent GLP-1 circadian rhythm is abolished in high-fat diet (HFD)-fed mice and requires the gut microbiota (Figure 1E).[101] Moreover, some Clostridia can deplete intestinal and circulatory BCAAs and tryptophan in host and modulate host glucose tolerance.[28] Gut bacteria catabolize tryptophan to produce ligands for the aryl hydrocarbon receptor (AhR), which in turn stimulates the production of non-inflammatory interleukin (IL)-22. This cytokine is key in immune homeostasis, maintaining the intestinal barrier, supporting peristalsis, and enhancing glucose and insulin responses.[102–104] BCAA can activate rapamycin complex 1 (mTORC1) that affects insulin signaling and induces pro-inflammatory cells such as polymorphonuclear (PMN) myeloid-derived suppressor cells (MDSCs).[103,105] In humans, increased BCAA biosynthesis by the gut microbiota is associated with a measure of insulin resistance (homeostatic model assessment of insulin resistance [HOMA-IR]) and glucose intolerance, involving strains of *P. copri*.[37,69] These functions are associated with T2D risk in the US and European populations.[37] Overall, no conclusive evidence for a direct effect of these gut metabolites on T2D have been established in humans. A deeper understanding of the mechanisms regulating host metabolism requires considering differences in interactions between diet, host metabolism, and gut microbiota.

Pathogenesis of T2D

Obesity, the excess accumulation and storage of triglycerides, is not equivalent to metabolic dysfunction. The hyperglycemia in T2D involves multi-organ insulin resistance and glycemic control failure, indicating that a systemic breakdown in energy regulation further progressed from obesity influenced by multiple factors,[106] including immune system dysregulation. Obesity is associated with chronic low-grade inflammation of insulin-sensitive organs including AT, liver, skeletal muscle, pancreatic islets, and the brain. Inflammatory responses in AT coordinated by multiple immune cell types has been implicated in systemic complications of insulin resistance, hyperglycemia, and dyslipidemia.[107]

Myeloid cells in adipose tissue and systemic inflammation

Lipid droplets account for over 80% of AT mass, with the remaining cell types consisting of stromal cells and diverse immune cell populations.[108] Lipid release and storage in AT in response to fluctuations in nutrients are tightly regulated by hormones and immune mediators. Under homeostatic conditions, immune cells maintain low inflammation phenotypes for immune surveillance, cell debris clearance, and adipocyte support for metabolic activities.[109] Macrophages in AT are indispensable for tissue integrity and lipid buffering. Depletion of AT macrophages in mouse disrupts AT vascularization and results in altered lipid storage, adipocyte hypertrophy, and AT dysfunction.[109] Additionally, AT macrophages participate in a lipid cycle, where adipocytes release triglycerides in extracellular vesicles for macrophage uptake, hydrolysis, and eventual free fatty acid return to adipocytes for triglyceride synthesis.[110] This process is the primary source

of lipid for AT macrophages and may prevent the accumulation of oxidized or perioxidized lipids in adipocytes.[109,110]

The homeostasis is disrupted in individuals with obesity, where chronic excess of calories causes excessive triglyceride accumulation, adipocyte hypertrophy, and AT hyperplasia.[63] Excessive adiposity results in AT hypoxia, lipotoxicity, and adipocyte death, escalating pro-inflammatory cytokine production, immune cell recruitment, and insulin resistance.[63,109] Indeed, elevated macrophage numbers in visceral AT of individuals with obesity are associated with insulin resistance and predictive of HbA1c concentrations.[111] The accumulation of AT macrophages is contributed by increased local cell proliferation, tissue retention, as well as recruited circulating monocytes and forms crown-like structures (CLSs).[109] CLS-associated macrophages upregulate lipid metabolism-related genes, including fatty acid transporter CD36 and TREM2, and an activated metabolic profile to clear dead adipocytes through reactive oxygen species (ROS) production.[109] Heterogeneity in accumulated macrophages exists among AT macrophages. One study identified distinct AT macrophage subpopulations: lipid-laden CD206+ cells with higher proinflammatory cytokine expression such as tumor necrosis factor-α, IL-6, and IL-8 and lower intracellular lipid and CD11c+ or double-positive macrophages up-regulating scavenger receptors and antigen-presentation genes.[111] While AT macrophages seem to perpetuate chronic inflammation, TREM2 deletion in mice inhibiting macrophage recruitment worsened HFD-induced metabolic dysfunction, characterized by dyslipidemia, hyperinsulinemia, and glucose intolerance.[112] The context-dependent functions of AT macrophages suggest their adaptation to metabolic challenges to compensate for loss of tissue homeostasis.

Another myeloid cell population, neutrophils, is recruited early to AT following HFD and contribute to systemic inflammation.[113] In humans, neutrophil proteins such as myeloperoxidase, calprotectin, and elastase are increased in people with obesity or T2D,[114–116] while serum levels of neutrophil elastase inhibitor α1-antitrypsin (A1AT) are negatively correlated with BMI and leptin.[117] Mice deficient in elastase or overexpressing human A1AT were protected from HFD-induced body weight gain, macrophage infiltration of AT, and insulin resistance.[117] Granulocytic myeloid-derived suppressor cells (G-MDSCs), a heterogeneous cell population encompassing granulitic precursors to mature PMN neutrophils, are also increased in obesity. These cells display immunosuppressive capacity through the production of stress-inducing molecules such as calprotectin and ROS.[118,119] Research on G-MDSC development points to two possible origins: emergency myelopoiesis under inflammatory conditions and pathologically activated neutrophils through prolonged exposure to cytokines during chronic inflammatory conditions such as autoimmunity, metabolic dysfunction, or cancer.[118,119] G-MDSCs adapt their cell metabolism for accelerated lipid transfer, uptake, and storage through upregulated expression of lipid receptors such as lectin-type oxidized LDL receptor 1 (LOX1) and fatty acid transporter protein 2 (FATP2).[118,120] An HFD can promote G-MDSC differentiation through microbiota-derived BCAA.[105] These findings suggest that neutrophil and G-MDSC pathways may be involved in mediating systemic inflammation observed in obesity and metabolic dysfunction.

Metabolic healthy obesity, sex differences, and puberty

In nondiabetic children and young people with obesity, there have been observations of compensatory increase in insulin concentrations and insulin secretion rate at the baseline and GSIS to maintain glucose tolerance.[38,39] Moreover, despite the excessive adiposity, certain individuals with obesity seem to maintain metabolic health, measured by multi-organ insulin sensitivity, blood lipids, and glycemic control, termed metabolically healthy obesity (MHO).[99,121] Compared to individuals with metabolically unhealthy obesity (MUO), MHO is associated with less visceral fat accumulation, decreased ceramides, and increased expression of genes involved in BCAA catabolism and mitochondrial structure and function. Additionally, MHO individuals exhibit decreased liver lipid synthesis, less AT inflammation, and improved insulin sensitivity.[121] In children and young people, the definition of MHO is difficult given the changes in body composition and cardiometabolic fitness in this period, with different estimates of MHO prevalence based on the criteria used for diagnosis.[122] In a cohort of adolescents enrolled in a Canadian weight management program, MHO was found to decrease with age and is negatively associated with BMI *Z* score and positively associated with physical activity and healthier eating habits.[123]

MHO prevalence is higher in women compared to men, who are more prone to transitioning to MUO.[121,124] The sex differences in obesity and T2D outcomes may result from hormone regulations.[125] Although visceral fat increases with age in both sexes, women have lower visceral adiposity across all ages.[126,127] Pre-menopausal women display heightened insulin sensitivity and lower cardiometabolic risk, with elevated adiponectin and leptin levels.[125] However, younger women with T2D have a higher risk burden than men at the time of diagnosis, manifested as excess weight gain and hypertension.[125] Testosterone also displays sex-dimorphic modulation on glucose homeostasis. In men, testosterone enhances GSIS and GLP-1 action, while in women, it leads to insulin hypersecretion, oxidative stress, and β cell death.[125]

Hormone-induced sex differences in metabolism are of special consideration in adolescents with obesity or T2D, as surges in growth hormone and sex steroids are known to influence adipose distribution,[126,127] energy balance,[128] insulin resistance,[129,130] and immune function.[131,132] In adolescents, peripheral insulin sensitivity is transiently decreased, while the insulin response to glucose increased throughout puberty regardless of obesity status.[39,133] Adolescents with obesity were shown to have lower insulin sensitivity and higher prevalence of hyperinsulinemia than normal-weight counterparts.[133] The interplay between hormones and glucose metabolism is further complicated by ancestries, since higher prevalence of insulin resistance and a lack of compensatory increase in insulin secretion have been observed in adolescents self-identified as black.[39,133] Collectively, these observations support that clinical thresholds of insulin resistance and glucose intolerance adapted to specific populations based on demographics such as age, sex, and ancestries.[129,130]

Finally, physiological changes in puberty complicate the interpretation of concomitant gut microbiota changes in children and young people with obesity and metabolic dysfunction. For example, associations between inflammation and metrics such as decreased gut bacteria-derived metabolites[85] and reduced

biomass[82] are specific to sex-stratified analyses, potentially due to sex differences in immune function. While female sex hormones have been associated with improved control of viral infection and risk of autoimmunity,[132] estradiol-treated mice displayed reduced myeloperoxidase activity and inflammatory cytokine production by neutrophils,[131] providing an explanation for the greater neutrophil protein levels and metabolic inflammation observed in males.[82,134] Additionally, gut bacteria-derived metabolites are implicated in healthy maturation and energy homeostasis. Loss of SCFA producers such as *Roseburia* and *Faecalibacterium* due to diets high in fat/sugar may potentiate hypothalamic-pituitary-gonadal axis signaling, resulting in earlier pubertal timing.[135] Decreased secondary BA biosynthesis and indole metabolites were associated with obesity and hyperphagic behavior.[68] Taken together, physiological changes in puberty, hormonal fluctuations, immune modulation, and changes in the gut microbiota collectively influence insulin sensitivity and adiposity. Understanding the interactions between these different tissues and biological systems is key to identifying the mechanisms of metabolic dysfunction and to identification of preventive and therapeutic strategies for early-onset T2D.

T2D prevention and treatment in youth

Timely management of youth-onset T2D can mitigate microvascular and macrovascular risk in mid-life from prolonged exposure to hyperglycemia and other atherogenic risk factors. Prior to T2D diagnosis, a transient rise in C-peptide levels has been observed, indicative of GSIS to maintain glucose tolerance and found to be a distinguishing factor between MHO and MUO.[121,136] Due to insulin compensation, glycemic thresholds for prediabetes recommended by American Diabetes Association (ADA) guidelines (39–47 mmol/mol [5.7%–6.4%] of HbA1c and impaired fasting plasma glucose between 5.6 and 6.9mmol/L [100–125mg/dL])[137] may not be sufficiently sensitive to detect impaired β cell function in individuals at risk.[130] Alternative measures for insulin sensitivity, such as insulinogenic index and HOMA-IR derived from fasting glucose and fasting insulin[138]; measure of β cell dysfunction and stress using proinsulin-to-C peptide ratio[139]; as well as measure of secreted insulin relative to the degree of insulin resistance, the disposition index, may facilitate early screening and risk assessment of individuals with metabolic dysfunction.

Screening for youth-onset T2D is particularly challenging due to a lack of definitive clinical manifestations in prediabetes, as well as a reliance on clinical judgments given the variable sensitivities of screening tests and evaluation metrics usually directly adopted from adult care.[16,140,141] Reproducibility for measures of glycemia, such as HbA1c and oral glucose tolerance test (OGTT), is limited in individuals at risk for dysglycemia and more variable across visit and indices in children and young people compared to adults.[140] In addition, there is no efficient system for measuring degree of obesity and metabolic risk in children, although obesity is recommended by ADA as a primary criterion for diabetes risk screening in asymptomatic children and adolescents.[130] World Health Organization (WHO) defines childhood overweight and obesity based on BMI percentile, with >85th percentile as overweight and >95th percentile as obese, which does not accurately define metabolic risk.[142,143] A study involving large European adult cohorts identified a metabolite fingerprint with BCAAs as predictors of increased risk of T2D and mortality and outperforms BMI.[142] Similarly, in adolescents with severe obesity (defined as > 2 SDs above the WHO growth standard median), disease burden linked to mechanical and social issues increased with BMI, yet metabolic and mental health risks showed no significant variation across BMI categories.[143] Another study demonstrated that waist-to-height ratio outperformed other anthropometric indices such as BMI and body fat percentage in predicting insulin resistance and cardiometabolic status.[122] Ongoing progress in validating measures of metabolic dysfunction in children and young people with obesity[122,144] and expanding focus outside of weight reduction in pediatric patient care[123,145] will facilitate early identification and intervention in children and young people with obesity at risk for cardiometabolic comorbidities.

Lifestyle interventions for T2D

Promoting healthy lifestyle behaviors, such as regular moderate to vigorous physical activity and a nutritious diet, are first-line management of youth-onset T2D.[130] These lifestyle interventions to prevent or treat T2D in individuals with obesity often accompany shifts in gut microbiota composition and increased SCFA production.[18,20] An open-label, parallel group study compared the effect of a normal diet to a high-fiber diet, both coupled with prebiotic acarbose, which increases availability of fermentable carbohydrate in the colon.[42] While both interventions achieved reduced HbA1C and upregulated pathways for producing acetic acid, the metabolic benefit is more profound in the high-fiber diet group evidenced by lower HbA1C and fasting glucose.[42] These benefits are attributed to upregulation in butyrate acid-producing pathways, corresponding with increased fecal SCFA content and an acidified gut lumen. The upregulation of SCFA improves host glucose homeostasis through increased postprandial GLP-1, which, in turn, stimulates insulin secretion (Figure 1D).[42] Interestingly, an intervention with a 7-day homogeneous average American diet found little impact on microbiome-dependent metabolite variance, which is mainly influenced by host identity and age.[146] It is possible that a 7-day dietary regime is insufficient to induce long-term changes in gut microbiota for sustainable metabolic benefit. In a separate 6-month follow-up of males without coronary heart disease, Mediterranean diet is associated with specific functional and taxonomic components of the gut microbiome, with stronger benefit of reduced cardiometabolic disease risk associated with decreased abundance of *P. copri*.[18] These findings suggest that a personalized dietary plan taking into account host metabolic characteristics is needed to achieve remission from T2D.

Pharmacological approaches to T2D management

Lifestyle interventions can be combined with pharmacological interventions to maintain the desired level of glycemic control and BMI improvement, especially given the challenges of long-term adherence and varied accessibility to care due to socioeconomic status.[130] While the US Food and Drug Administration has approved over 10 general classes of pharmacological options for T2D treatment in adults, options remain limited for young people, with ongoing research yet to establish efficacy and long-term safety. Currently, common pharmacotherapy options for T2D

treatment in adolescents include metformin, insulin, and more recently, GLP-1 receptor agonists (GLP-1RA).[147,148]

Both metformin and GLP-1 are associated with gut microbiota, implicating its role in pharmacological actions for improving glycemic control.[102] Metformin has been shown to partially reverse dysbiosis associated with T2D, including increased relative abundance of *E. coli*, *A. muciniphila,* and multiple butyrate-producing bacteria, whereas the relative abundance of *Intestinibacter bartlettii* is reduced.[149–151] However, some side effects such as gas and diarrhea might also be explained by metformin-induced shift in microbiota composition, since *E. coli* is known to encode virulence factors such as LPS.[151] The role of gut microbiota in the antidiabetic effect of metformin is further elucidated in a study, where treatment-naive T2D patients were first randomized to placebo or metformin for 4 months and then a subset of the placebo group was switched to receiving metformin after 6-month interval.[149] Metformin-induced changes in gut microbiota composition after 2 and 4 months of metformin treatment correlated with the changes observed in the switched subgroup after 6 months on metformin. Fecal samples cultured in the presence of metformin *in vitro* are affected in LPS synthesis and SCFA metabolism pathways, along with an increased abundance of *A. muciniphila*. Finally, GF mice receiving metformin-altered microbiota exhibited increased glucose tolerance. These findings correspond to observations in HFD-fed mice that metformin treatment increased IgA-producing cells and intestinal barrier function,[22] suggesting that one of the metformin mechanisms is to protect intestinal barrier integrity, reduce bacterial LPS translocation, and attenuate colonic inflammation.

Gut microbiota is known to regulate GLP-1 release,[101] although its role in GLP-1RA benefits on glucose metabolism or body weight is less clear. Modulation of microbiota composition by GLP-1RA through gut intraepithelial lymphocytes has been shown to reduce T cell-induced local and systemic inflammation.[26] Moreover, gut microbiota has been shown to influence response to an antidiabetic drug through a GLP-1-dependent pathway. A gut microbial dipeptidylpeptidase IV (DPPIV), homologous to host DPPIV, has been shown to degrade GLP-1 in HFD-fed mice with increased intestinal permeability.[152] Higher baseline DPPIV activity in stool samples of low responders to human DPP4 inhibitors correlates with minimal reductions in HbA1c and fasting blood glucose.[152] A combination therapy of inhibitors for host and microbial DPPIV has been shown to increase active GLP-1 levels and improve glucose metabolism in diabetic mice.[152] These observations highlight the importance of considering the gut microbiota in the development of treatment strategies to improve tolerability and efficacy of pharmacological agents.

Previous evidence of gut microbiota contribution to the effects of metformin and GLP-1RA is derived from studies in adult. Comparable data in children and young people remain scarce, with few intervention studies examining the gut microbiota following metformin treatment alone or with co-interventions.[153–155] Two studies reported shifts in bacterial taxa associated with these therapies, but the strength of evidence was limited by small sample sizes, heterogeneous study designs, and lack of controls for false-positive discoveries. With the recent approval of GLP-1RA for treatment of adolescents,[147,148] multiple clinical trials are underway for obesity in young people that will examine microbiome endpoints.[156–158] These outcomes will be crucial to advance our mechanistic understanding of these pharmacological interventions in children and young people, and whether treatment responses are impacted by immune-gut microbiota interplay as well as developmental factors, such as pubertal hormones and body composition changes.

Gut microbiota-based treatment

Despite ample evidence connecting gut microbiota to metabolic benefits of antidiabetic interventions, direct manipulation of the gut microbiota has yielded inconclusive results. A 3-month randomized clinical trial in 32 overweight/obese insulin-resistant volunteers with daily oral administration of live *A. muciniphila* found no significant metabolic benefit.[44] However, the same group showed that heat-deactivated *A. muciniphila* improved aspects of metabolic dysfunction in overweight or obese insulin-resistant individuals, including lower circulating insulin levels, reduced insulin resistance, and lower total blood cholesterol, by lowering circulating DPPIV—the same pathway implicated in resistance to anti-diabetic treatment.[44]

In addition, FMT has been explored as a method to induce weight loss and reverse metabolic dysfunction in individuals with obesity. In a randomized, double-masked, placebo-controlled trial (Gut Bugs Trial), 87 adolescents with BMI >30 were treated with a single course of oral encapsulated fecal microbiome of the same sex and followed up for 26 weeks for BMI, body composition, cardiometabolic parameters, and gut microbiome composition.[46] Recipients were found to maintain a shift in gut microbiome composition for 12 weeks, with decreased relative abundance of *E. coli* and increased *Alistipes* spp. abundance. While the intervention did not significantly modify BMI, android-to-gynoid-fat ratio was reduced, indicating reduced abdominal fat and improvement in metabolic health.[46] Similar findings were reported in two double-blind randomized FMT trials in adults. One study tested the effects of high- versus low-fermentable fiber supplements, provided with or without FMT, in 70 patients with severe obesity and metabolic syndrome. HOMA-IR was assessed from baseline to 6 weeks.[47] A second study tested the effects of allogenic FMT from lean donor versus autologous FMT in 44 males with metabolic syndrome on peripheral insulin sensitivity at 18 weeks.[48] FMT from lean donors transiently improved insulin sensitivity, along with increased fecal acetate, increased representation of butyrate-producing bacteria, and alterations in plasma amino acids such as increased γ-aminobutyric acid in responding recipients.[47,48] The lack of metrics for evaluating FMT efficiency is one of the major barriers to its clinical application for T2D management. Different approaches across studies to define, track, and model strain and community dynamics complicates measure of engraftment efficient.[159] A critical question is whether certain characteristics of the gut microbiota of the recipients or donors facilitate donor strain colonization.[159] In the Gut Bugs, higher engraftment efficiency, measured by the ratio between engrafted donor taxa and total donor taxa, is seen in donors with higher phageome α-diversity. Female recipients displayed increased variability and diversity in both phage and bacterial populations.[160] The increased abundance is observed in temperate phages, distinct

from virulent phages, posing question on the effect of FMT on ecological dynamics of resident and donor species and their physiological impact.[160] In another trial, responders with short-term improvement in insulin sensitivity in one of the FMT trials were found to have lower fecal microbiota diversity, with higher abundance of *Subdoligranulum variabile* and *Dorea longicatena* and lower *Eubacterium ventriosum* and *Ruminococcus torques* at baseline.[47] It is possible that engraftment would be more efficient in recipients with disturbed and depleted microbial communities, or where donor species can exploit unoccupied niches, such that differences or ratios between donor and recipient species abundance may optimize donor-recipient match.[160] More recently, a longitudinal follow-up on gut microbiota of FMT recipients with inflammatory bowel disease or *Clostridium difficile* infection demonstrated that strain richness is a specific property of microbial species influenced by host conditions, the size of the species' core and accessory genomes, and metabolic diversity.[161] Furthermore, three types of strain engraftment dynamics are observed among recipients' gut microbial species following FMT, with those having low strain richness likely to result in either replacement or unsuccessful engraftment, whereas those with higher strain richness more likely to persist and co-exist with donor species.[161] While open questions exist for methods to evaluate and optimize FMT efficacy, these trials represent early efforts to disentangle correlational and causal influence of gut microbiota on T2D pathogenesis and to explore the potential of gut microbiota for disease intervention.

Conclusion

Previously, the primary focus of T2D prevention and treatment strategies has been on adults. While the high prevalence of adult-onset T2D requires continued attention, global health priorities must expand to include young people and the primary disease driver—childhood obesity. The alarming rise in youth-onset T2D, disproportionately affecting populations of non-European ancestry and those experiencing socioeconomic disadvantages, demands urgent action. The gut microbiota offers new prevention and treatment targets as an interface between environmental factors and host metabolism, with emerging evidence supporting its role in obesity reversal and improved metabolic control. Given the forecasted rise in childhood obesity in multiple regions of the world, obesity intervention strategies should account for the effect of gut microbiota on treatment response and T2D risk, with particular attention to the critical developmental window around puberty for effective prevention of long-term metabolic complications.

AUTHOR CONTRIBUTIONS

Writing – original draft, Q.Y.X.; writing – review and editing, Q.Y.X., J.K.H., and J.S.D.; supervision, J.S.D.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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