Obesity and diabetes—Not only a simple link between two epidemics

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Summary
Diabetes (DM) as well as obesity, due to their increasing incidence, were recognized as epidemic by the World Health Organization. Obesity is involved not only in the aetiopathogenesis of the most common worldwide type of DM—type 2 diabetes (T2D)—but also in the development of its complications. There is also increasing scientific evidence regarding the role of obesity and overweight in type 1 diabetes. Weight gain may be considered as a complication of insulin treatment but also reveals significant pathophysiological impact on various stages of the disease. Another very important aspect related to DM as well as obesity is the microbiome, which is highly variable. The function of the gut microflora, its interaction with the whole organism, and its role in the development of obesity and type 1 diabetes as well as type 2 diabetes are still not fully understood and subject of ongoing investigations. This review presents a summary of recently published results concerning the relation of obesity/overweight and DM as well as their associations with the microbiome.

Keywords
diabetes, epidemiology, insulin resistance, microbiome, obesity, type 1 diabetes, type 2 diabetes

1 | INTRODUCTION

Diabetes (DM) as well as obesity, due to their increasing incidence, were recognized as epidemic by the World Health Organization. Obesity is an important environmental factor involved not only in the aetiopathogenesis of the most common worldwide type of DM—type 2 diabetes (T2D)—but also in the development of its complications. Increasing scientific evidence points also to the role of obesity and overweight in type 1 diabetes (T1D). On one hand, weight gain may be considered as a complication of insulin treatment, but on the other, it reveals significant pathophysiological impact on various stages of the disease.

Another very important aspect related to DM as well as obesity is the microbiome, which is highly variable depending on, among others, environmental factors. The function of the gut microflora, its interaction with the whole organism, and its role in the development of obesity and T1D as well as T2D are still not fully understood and are subject of ongoing investigations.

This review presents a summary of the up-to-date knowledge along with recently published results concerning the relation of obesity/overweight and DM as well as their associations with the microbiome.

2 | OVERWEIGHT AND OBESITY IN T2D

Overweight and obesity are very strongly correlated with T2D. Obesity is the most important culprit of insulin resistance, which appears
early in the disease, and is primarily compensated by hyperinsulinaemia.\textsuperscript{1,4} Insulin resistance is more often in obese children with high weight, height, and waist circumference.\textsuperscript{5} Occurrence of obesity is among others related to the early adiposity rebound at the age of 3 years that was shown to lead to an increased body mass index (BMI) when adolescent.\textsuperscript{2} Obesity combined with insulin deficiency leads to the development of T2D.\textsuperscript{2,4}

Since the very beginning, the increasing ratio of new onset of T2D researchers connected with obesity, peripheral insulin resistance, ethnic minority groups, and a family history of T2D.\textsuperscript{6} The 2002 World Health Organization STEPS survey demonstrated a 21.5% prevalence of T2D and a 54.8% of obesity. The same survey conducted in 2013 revealed a 45.8% prevalence of T2D.\textsuperscript{5} In 2030, it is estimated that 552 million people in the world could suffer from T2D.\textsuperscript{7}

The onset of T2D occurs mostly in adulthood. Among children and young adults, T2D develops most often during the second decade of life and in the middle to late puberty.\textsuperscript{1-3} During puberty, hormone secretion is increasing and causing physiological insulin resistance.\textsuperscript{8}

In a meta-analysis from the United States and Europe comparing obese people and those with normal weight, obese men had a 7-fold higher risk and obese women a 12-fold higher chance to develop T2D.\textsuperscript{9} A considerable longitudinal study from the United Kingdom was examining 369 362 participants between 2 and 15 years old.\textsuperscript{10} Patients who had T2D were mostly obese (47.1%) compared with individuals with normal BMI (4.33%).\textsuperscript{10} The frequency of T2D among overweight and obese people increased from 6.4 persons per 100 000 in 1994-1998 to 33.2 in 2009-2013.\textsuperscript{10}

The same observations come also from other countries: In Europe, 50.9% to 98.6% of people with T2D are obese, and in Asia—56.1% to 69.2%. In American Indian and Alaska Native adults, the percentage of obesity among T2D patients rose by 58% between 1976 and 2004.\textsuperscript{7} In a study performed in Iraq in 2007, it was proven that among all anthropometric variables, waist circumference is the most sensitive predictor for T2D.\textsuperscript{5}

Other studies showed that the distribution of fat tissue is the crucial factor to develop insulin resistance, independently of the stage of obesity.\textsuperscript{2,11} The authors compared obese adolescents with a similar rate of adiposity, and those with impaired glucose tolerance (IGT) were more insulin resistant than adolescents with normal glucose tolerance. Furthermore, those with IGT had an increased intramyocellular lipid content, and dilated visceral and reduced subcutaneous fat deposition.\textsuperscript{3} Ebe D’Adamo and co-authors found that children with high proportion of visceral fat and limited abdominal subcutaneous fat are more insulin resistant and they have higher plasma glucose in the second hour of the glucose tolerance test.\textsuperscript{1,3} It has been also noticed that the ectopic fat deposition in the liver of obese patients is a very important marker of insulin resistance and glucose deregulation.\textsuperscript{3}

2.1 Environmental risk factors of T2D

Other risk factors, despite obesity, for developing T2D are signs of insulin resistance—acanthosis nigricans, precocious puberty, hypertension, dyslipidaemia, polycystic ovary syndrome\textsuperscript{5,8—}and ethnic groups, such as African American, Hispanic, Asian/Pacific Islanders, Japanese, and Middle Eastern.\textsuperscript{1,4} The SEARCH study (T2D in paediatric population) revealed higher T2D rate in oldest children (15-19 years old): 49.9 rate per 100 000 people for Native Americans, 22.7 for Asian/Pacific Islanders, 19.4 for African American, 17 for Hispanics, and 5.6 for non-Hispanic whites.\textsuperscript{3}

Another important risk factor is family history. In a study conducted by Elham Al Almiri and co-authors, more than half of prediabetic patients and all with T2D had a first-degree relative with T2D.\textsuperscript{11} Prediabetes (20%) and diabetes (70%) participants had also raised triglyceride levels.\textsuperscript{11}

A recent study conducted in Abu Dhabi among 216 obese (90%) or overweight (7%) patients highlighted that older children with higher height-for-age, weight-for-age, and waist circumference-for-age have a higher insulin resistance.\textsuperscript{5} In this group, already, 7% had diabetes, 8.2% had IGT, and 18.1% were examined with impaired fasting glucose.\textsuperscript{5}

2.2 Obesity and T2D complications

Diabetes can lead to many severe complications among others: cardiovascular diseases (CVDs), nephropathy, retinopathy, and microangiopathy leading in example to limb amputations.\textsuperscript{5} Such complications as CVD, apnoea, and obstructive sleep seem to be especially related with obesity and diabetes.\textsuperscript{5} Gaining more weight in T2D increases the risk of cardiometabolic complications, which are the main reason of morbidity in T2D.\textsuperscript{5}

The Global Burden of Disease Study 2010 highlighted that the mortality of people with diabetes (all types) increased between 1990 and 2010 from 16.3 to 19.5 per 100 000 patients.\textsuperscript{6} In children with T2D, the increase in body weight is associated with a greater likelihood of cardiovascular complications such as myocardial infarction, stroke, and renal failure.\textsuperscript{1} They are the most common cause of the increase of mortality.\textsuperscript{1,9} The earlier the onset of T2D, the higher the probability of developing cardiovascular complications, and consequently early death.\textsuperscript{1,3} Worth noticing is a study showing the relation of mental health and obesity and mortality. It revealed that obesity has a negative impact on children’s well-being and mental health and, together with cardiometabolic complications, leads to increased morbidity and mortality in adulthood.\textsuperscript{2}

Recent studies highlight that a lot of young people with T2D have a higher risk of complications early after diagnosis than adults with T2D.\textsuperscript{1} Many of them already present complications at T2D onset, which include microvascular and macrovascular changes, hypertension, dyslipidaemia, atherosclerosis, stroke, myocardial infarction, and fatty liver disease.\textsuperscript{2,8}

Nevertheless, it is important to mention the “obesity paradox” that was described by J.P. Wilding based on many studies.\textsuperscript{5} Patients with normal weight at the time of diagnosis of T2D had a higher risk to develop cardiovascular complications, in contrary to people with a higher weight during the onset of diabetes.\textsuperscript{9} Also, US pooled test showed that mortality rates were superior for patients with normal weight.\textsuperscript{9}

2.3 T2D prevention

As the major risk factor of T2D is obesity, the most important in preventing this disease is countering excessive weight gain.\textsuperscript{1} This should be started even before birth. The knowledge about diet, physical activity, and sedentary lifestyle is very important, and it
was proven in research that obese adolescents who meet those guidelines had a lower insulin resistance, better glycaemic control, and higher rate of T2D prevention. To decrease morbidity, mortality and costs of treatment of T2D reducing obesity are crucial. Although there is evidence that prediabetic patients after declining weight can impede development of T2D, there is no clear evidence that in patients with T2D, weight loss can reduce microvascular or cardiovascular complications.

3 OVERWEIGHT AND OBESITY IN T1D

Excessive weight, until recently associated mostly with T2D, is also more and more commonly described in the context of T1D. In a project assessing the population of children and adolescents with T1D from Germany, Austria, and the United States, patients had higher BMI relative to reference values—12% of them were examined with obesity, and 24% were overweight. In another study, BMI values exceeding age-specific normal ranges were described even in every third child with T1D. Among risk factors of excessive weight gain mainly, the following are indicated: female sex, T1D duration, age, ethnicity, lower education level, disease onset during puberty, or low weight at T1D onset. The problem of the coexistence of overweight/obesity with T1D is considered both in the context of the causative factor of the increased incidence of T1D and as result of the disease itself (and insulin treatment).

3.1 Development and onset of T1D

Many hypotheses were generated regarding the potential contribution of obesity in the pathogenesis of T1D. Most of them are based on the role of insulin resistance coexisting with lack of insulin. The “accelerator hypothesis” proposed by Terry Wilkins suggests that T1D and T2D are the same disorder, both progressing to a final insulin-dependent state. The main difference between the diseases is the tempo of β-cell loss, which depends on the presence of various “accelerators.” According to this theory, obesity and overweight are the most important factor in the pathogenesis of T1D in a continuum with T2D. It is assumed that obesity-induced insulin resistance may be responsible for the loss of the pancreatic β cells through their excessive stimulation causing sensitization to autoimmune processes and leading to their accelerated apoptosis. Another aspect indicated as potentially responsible for T1D development in people with excessive weight is the imbalance between the concentrations of adiponectin and leptin. The concentration of leptin, secreted by the adipose tissue, rises in obese individuals. Its pro-inflammatory activity increases the autoimmune destruction of β cells accompanied by a rise of insulin resistance that is induced by the decreased adiponectin concentration. In studies conducted in nonobese diabetic mice, the increase of leptin activity outturn T1D onset and its administration accelerated the destruction of pancreatic cells.

3.2 Increasing weight as T1D complication and treatment attempts

In the case of patients with already diagnosed T1D, many publications show a relation between BMI and glycaemic control, but the association seems to be age specific. According to some observations, patients with higher weight are characterized by usually lower values of haemoglobin A1c (HbA1c) and more intensive insulin treatment with higher daily doses of basal as well as bolus insulin. Lee and co-authors described on the other hand different correlations between BMI and HbA1c depending on the initial BMI of the patient. An inverse association was found in patients with lower first BMI whereas those with higher BMI were characterized by increasing HbA1c along with weight gain. Similarly as in former studies, patients with lower weight also had lower insulin doses compared with other observed individuals.

Weight gain is also considered to be one of the side effects of intensive insulin treatment. Increasing insulin doses as an attempt to sustain optimal glycaemic control despite excessive caloric intake enhances the growth of the adipose tissue, what in consequence promotes insulin resistance and generates a further rise of the insulin requirement. In a study investigating associations between glycaemic control and changes in BMI in children and adolescents with T1D, patients with lower initial HbA1c showed smaller increments of BMI in time. The change in BMI was inversely related to the evolution of HbA1c values and positively correlated with the modification of the administered doses of insulin. Additionally, the results revealed a significant association between the increase of BMI and insulin treatment by means of a personal insulin pump. Fröhlich-Reiterer and co-authors, searching for predictors of the BMI increase in T1D, described significantly greater BMI increments in children treated with insulin pumps compared with patients on multiple daily injections; however, this difference concerned only children receiving less than 4 insulin injections per day. According to the authors, an important role in the regulation of weight gain plays, besides the amount of insulin injections and total insulin dose, also the type of insulin (basal/bolus). A 1-year-long observation of 91 patients, who started insulin pump treatment, revealed increased weight gain in case of higher basal rate and lower bolus to basal insulin ratios. This result was independent from glycaemic control as well as physical activity level.

Taking into account the anabolic effect of intensive insulin treatment, there is a search for an effective method of supplementary treatment, which would decrease insulin resistance, lead to a decrease of insulin requirement, and—at the same time—allow adequate metabolic control. Present experiences are based mostly on 3 groups of medications, which were found to have a positive effect on the reduction of weight in T1D patients.

Glucagon-like peptide 1 (GLP-1) receptor agonists (exenatide, liraglutide, and exendin-4) stimulate insulin secretion, inhibit glucagon secretion, and slow down gastric emptying, what prolongs the feeling of satiety. According to studies, exenatide as well as liraglutide decreased insulin requirement and caused weight loss regardless of the method of insulin treatment.

Sodium-glucose linked transporter 2 inhibitors are a newer group of drugs, which also positively influence weight regulation. By inhibiting the main renal glucose transporter (sodium-glucose linked transporter 2) that is localized on the nephron’s proximal convoluted tubule, they lead to increased glucosuria (because of inhibited glucose reabsorption in the kidneys). Empagliflozin given for over 8 weeks
to patients with T1D resulted in decreased weight and waist circumference. Nevertheless, this medication has an important limitation that is related to the decreased secretion of ketones with urine and increased risk of ketonaemia.23

Up to now, greatest experience in adjuvant therapy concerns metformin. Its positive potential is based on the theory of the coexistence of T1D and insulin resistance, what is especially important in obese or pubertal patients.15,23 Metformin, which remains since many years the first-choice treatment in T2D, sensitizes tissues to insulin activity; however, many studies that assessed its use in T1D did not come to an unequivocal conclusion concerning the effects of its application.24-27 Two meta-analyses assessing the efficacy and safety of adjuvant therapy with metformin in adolescents with T1D indicate however numerous advantages that result from its use, especially in patients with insufficient glycaemic control.28,29 The study by Liu and co-authors underlined additional metabolic effects related to this adjuvant treatment, including the decrease of the total, high-density lipoprotein, and low-density lipoprotein cholesterol levels.29 Burchardt and co-authors in 2 independent randomized investigations revealed a significant positive impact of metformin in adjuvant treatment on triglyceride concentrations as well as on the levels of glycated low-density lipoprotein that have atherogenic properties. In consequence, such a therapy reduced the carotid intima-media thickness.27,30

3.3 | Obesity and T1D complications

Intensive insulin treatment in T1D on one hand reduces the risk of microvascular complications but on the other may be responsible for the development of the CVD as well as that induced by obesity metabolic syndrome (MS). Insulin resistance as well as other components of the MS are presently increasingly commonly accounted to the chronic complications of T1D, and CVD becomes the leading cause of death among patients older than 30 years.15,31

Both T1D and CVD are known to be associated with an increased risk of mortality. In ADOC study, T1D patients had higher mortality rates than nondiabetic controls, and ischaemic heart disease was one of the factors that increased mortality risk. Interestingly, in this study, obesity was associated with lower mortality, and this effect has been called “obesity paradox”.32 Few studies also suggested higher relative risk of mortality in females than in males with T1D.32,33

Another complication of T1D, which is also related to CVD, is diabetic nephropathy (diabetic kidney disease—DKD).34 In patients with T1D with DKD, obesity is twice as common as among those without concomitant DKD.35 Improperly high BMI was also described as a possible risk factor of the development of diabetic retinopathy.26 As a consequence of all, the above patients with T1D, especially teenagers, tended to assess their health condition worse.14,18

4 | THE ROLE OF GUT MICROBIOME IN OBESITY AND DIABETES

Knowledge concerning the gut microbiome developed significantly in the past years. Differences in the composition and amount of microorganisms colonizing the gastrointestinal tract have become the object of thorough analysis. Understanding the role of microbiota in health and disease not only allows to look more profoundly at the pathogenesis of many diseases but also gives the possibility of new therapeutic measures and early prevention. Microbiome activity has an important metabolic function, which may be important in the development of both obesity and diabetes.37

In obese individuals, the proportion and diversity of the microbiome composition are disturbed, mainly in relation to the 2 dominant bacterial species—Bacteroidetes and Firmicutes. Patients with excessive weight are characterized by an increased number of the latter in relation to Bacteroidetes.38 It is suggested that the abnormal gut microbiome may impact the increased absorption of monosaccharides from the gastrointestinal tract, and the short-chain fatty acids (SCFAs) produced with its involvement are one of the substrates in the hepatic gluconeogenesis, which results in an increased supply of calories and promotes obesity.39 On the other hand, it has been proven that both the high-fat and carbohydrate-rich diet are independent factors causing the reduction of the number of Bacteroidetes and the increase of the amount of Firmicutes. The relative raise of Firmicutes in response to a fat-dominant diet has been described in both mice and human observations.40 The disturbance of the Bacteroidetes/Firmicutes proportion favours, among others, increased production of endotoxins, including lipopolysaccharides. In addition, obese people have a reduced amount of Akkermansia muciniphila species, which is a potential factor responsible for the unsealing of the intestinal barrier. The increased gut permeability results in leakage of lipopolysaccharides into the bloodstream, consequently generating chronic inflammation, characteristic both of obesity and of the insulin resistance that is associated with T2D.41

Table 1 presents a summary of studies concerning gut microbiome and probiotics and their relation to obesity and diabetes. The potential mechanisms involved in the interplay between microbiome and diabetes or obesity are shown in Figure 1.

4.1 | Animal studies

Rodriguez and co-authors evaluated the effect of antibiotic-induced dysbiosis on glucose metabolism in healthy mice. Vancomycin therapy was associated with a decrease in microbiome diversity and at the same time resulted in a reduction in fasting glucose and insulin concentrations. This antibiotic also promoted the increased growth of Akkermansia muciniphila in the gastrointestinal tract.42 Similar observations were published by Hwang and co-authors. Healthy mice that were given a mixture of vancomycin and bacitracin before inducing diet-related obesity showed improvements in insulin resistance, glucose tolerance, and hyperinsulinism, but not in relation with weight gain alone. In mice treated with antibiotics, the number of Firmicutes and Bacteroidetes was reduced. As a cause of the observed metabolic effect, an increased stimulation of secretion of the GLP-1, known for its antidiabetic effect, has been suggested.43

4.2 | Human studies

Taking into account the results of animal models, attempts have been made to assess the effect of antibiotic microbiome modulation
| Study                  | Design                           | Subjects                  | Intervention                                      | Gut Flora Change                                           | Main Outcomes                                                                 | Hypothesized Mechanism                                                                 |
|-----------------------|----------------------------------|---------------------------|--------------------------------------------------|------------------------------------------------------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Rodrigues et al42     | Placebo-controlled trial         | Lean, normo-glycaemic male mice | Single, cocktail, or no antibiotics for 4 wk      | Antibiotics reduced diversity of gut microbiome; antibiotic specific changes in community composition | Treatment with antibiotics reduced FG and improved glucose tolerance           | Changes in key genes expression and bile acid metabolism                               |
| Hwang et al43         | Case-control trial               | C57BL/6J male mice        | 4 wk HFD + all mice, 4 wk vancomycin + bacitracin (intervention group) | HFD increased the proportion of Firmicutes and decreased Bacteroidetes; antibiotics reduced the proportions of Firmicutes and Bacteroidetes | Mice given antibiotics had improved glucose and insulin tolerance and improved serum insulin levels | Modulation of GLP-1 secretion                                                        |
| Mikkelsen et al44     | Prospective clinical trial       | Lean and glucose tolerant men | 4-d, broad-spectrum, oral antibiotic cocktail (vancomycin, gentamycin, and meropenem) | Decrease of total anaerobic bacterial count; decrease of enterococci, coliforms, and Bifidobacteria immediately after treatment | Reductions in the abundance of a representative set of gut bacteria; no changes in postprandial glucose tolerance, insulin secretion or plasma lipid concentrations; reversible rise of peptide YY secretion |                                                                          |
| Vrieze et al45        | Single-blinded randomized controlled trial | Obese men with metabolic syndrome | 7 d of amoxicillin (500 mg) or 7 d of vancomycin (500 mg) | Vancomycin reduced faecal microbial diversity with a decrease of Gram-positive bacteria (mainly Firmicutes) and a compensatory increase in Gram-negative bacteria (mainly Proteobacteria) | Vancomycin decreased faecal secondary bile acids with a simultaneous postprandial increase in primary bile acids in plasma and decreased peripheral insulin sensitivity | Altered bile acid metabolism due to specific changes in intestinal microbiota       |
| Reijnders et al46     | Randomized double-blind placebo-controlled trial | Obese, prediabetic men | 7-d antibiotic treatment (amoxicillin or vancomycin) | Vancomycin decreased bacterial diversity and reduced Firmicutes | On vancomycin: upregulation of adipose tissue gene expression of oxidative pathways; reduced conversion of primary to secondary bile acids and lower production of SCFAs in the gut; no changes in tissue-specific insulin sensitivity, energy/substrate metabolism, postprandial hormones and metabolites, systemic inflammation, gut permeability, and adipocyte size |                                                                          |
| Mobini et al47        | Randomized double-blind placebo-controlled trial | Type 2 diabetes patients treated with insulin | 12 wk of oral Lactobacillus reuteri DSM 17938 (high or low dose) vs placebo | No effect on microbiota composition after intervention | No effect on HbA1c, liver steatosis, and adiposity; increases in deoxycholic acid levels correlated with improvement in insulin sensitivity in the probiotic recipients | High diversity of the gut microbiota at baseline as an important factor of response to probiotic supplementation |
| Li et al48            | Meta-analysis of 12 RCTs         | Patients with T2D         | Various probiotic species and doses               | Not assessed                                                | Probiotics could alleviate fasting blood glucose and increase high-density lipoprotein cholesterol | Increase GLP-1 secretion; improving of intestinal epithelial permeability; regulation of immune system (reduction of toll-like receptor-4); beneficial effect on inflammatory factors |

(Continues)
on glucose tolerance in humans, including patients with excessive weight. A postprandial glucose and insulinaemia evaluation in healthy, lean adults subjected to a 4-day, broad-spectrum antibiotic treatment (vancomycin, gentamicin, and meropenem) confirmed a reduction of the number of intestinal flora related to the pharmacological treatment. These changes, however, did not significantly affect the metabolic activity of the body, including postprandial glucose and insulin concentrations.44 In a study of 20 obese women examined with MS after 7 days of vancomycin intake, a decrease in microbiome diversity was observed, in particular a reduction of Gram-positive bacteria (mainly Firmicutes) with a compensatory dominance of Gram-negative bacteria. In the group receiving antibiotic therapy, there was also a decrease in peripheral insulin sensitivity, but without effect on the insulin secretion itself. The authors suggested that the observed effect was related to an increase in the concentration of primary bile acids.45 A significant reduction in the concentration of secondary bile acids in favour of the dominance of the primary form was also described after a 7-day vancomycin treatment in obese men with prediabetes. In this group, however, despite the significant and long-term change in the composition of microbiome in response to the drug supply, there was no impact on the energy and carbohydrate metabolism and no change in insulin sensitivity.46 In both cases, antibiotic treatment resulted in a reduction in the number of strains responsible for dehydroxylation of bile acids and also those involved

| Study                        | Design          | Subjects                  | Intervention                                                   | Gut Flora Change | Main Outcomes                                                                 | Hypothesized Mechanism                                                                 |
|------------------------------|-----------------|---------------------------|----------------------------------------------------------------|------------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Kasinska and Drzewski49      | Meta-analysis of 8 RCTs | Patients with T2D | Various probiotic/probiotic/symbiotic species and doses | Not assessed     | Probiotics had a significant effect on reducing HbA1c, levels and HOMA-IR; no significant effect on fasting plasma glucose, insulin, CRP, and lipid profile | Increase GLP-1 secretion; improvement of intestinal epithelial permeability; beneficial effect on inflammatory factors |
| Sun and Buys50               | Meta-analysis of 11 RCTs | Patients with T2D/obese/metabolic syndrome | Various probiotic species and doses | Not assessed | Probiotic supplementation resulted in decreased glucose only in trials concerning diabetes; probiotics had a significant effect on the reduction of HbA1c in diabetic trials | Probiotics may increase bioavailability of gliclazide; protect pancreatic β cells; improve antioxidant stress level |
| Akbari and Hendijani51      | Meta-analysis of 13 RCTs | Patients with T2D | Various probiotic species and doses | Not assessed | Probiotics decreased FG and HbA1c; participants' characteristics, dose and type of probiotic microorganisms affected the clinical response | Modulation of GLP-1 and peptide YY secretion; beneficial effect on inflammatory factors |
| Samah et al52                | Meta-analysis of 5 RCTs | Patients with T2D | Various probiotic species and doses | Not assessed | No significant difference in HbA1c; significant relation between probiotic effects on HbA1c and probiotic dose; moderate hypoglycaemic effect of certain probiotics with lower FG | |
| Zhang et al53                | Meta-analysis of 7 RCTs | Patients with T2D | Various probiotic species and doses | Not assessed | Probiotics: changed FG and HbA1c, decreased homeostasis model assessment of insulin resistance (HOMA-IR) and insulin concentration; may improve glucose metabolism by a modest degree, with a potentially greater effect when the duration of intervention is ≥8 weeks, or multiple species of probiotics are consumed | Promoting the secretion of postprandial insulin; beneficial effect on inflammatory factors; may increase the bioavailability of gliclazide, inhibiting or delaying the intestinal absorption of glucose |
| Uusitalo et al54             | Prospective cohort study | Children with high genetic risk of T1D | Any probiotic supplementation in first 3 mo of life | Not assessed | Early probiotic supplementation reduced risk of islet autoimmunity in children at the highest genetic risk of T1D | |

Abbreviations: CRP, C-reactive protein; FG, fasting glucose; GLP-1, glucagon-like peptide 1; HbA1c, haemoglobin A1c; HFD, high fat diet; SFCAs, short-chain fatty acids; T1D, type 1 diabetes; T2D, type 2 diabetes.
in the production of SCFAs. The concentration of SCFA in the stool of people given vancomycin was significantly lower compared with the control group, although the decrease in serum concerned only the amount of butyric acid. Nevertheless, the described changes did not affect energy metabolism or mealtime GLP-1 concentration.45,46 Thus, although the impact of dysbiosis on bile acid metabolism disorders and SCFA production appears to be a fact, their direct effect on the carbohydrate metabolism may raise doubts.

One of the most important factors that shapes our intestinal microbiome is diet. In early infancy, feeding type affects the neonate gut microbiome composition. Although this process has a great impact on gut colonization, in later life, it seems that long-term dietary habits may also affect gut microbial composition.55 It has been reported that both high-fat and high-sucrose diet promotes a decrease in Bacteroidetes and stimulate the growth of Firmicutes. In addition, body fat percentage growth is thought to be negatively associated with the abundance of Akkermansia and positively associated with the relative abundances of Firmicutes.56 Taking into account the strain-dependent properties of probiotics, a certain role in the observed phenomenon may play the specific type of intervention. In a randomized trial concerning the effects of 12-week DSM 17938 supplementation in patients with obesity and T2D, patients who responded positively to the treatment were characterized by not only a greater diversity but also a different composition of the gut microbiome during the entire observation period. Lactobacillus reuteri supplementation resulted in a higher concentrations of secondary bile acids in all participants of the study. A significant increase of deoxycholic acid concentration was found only in the group of patients with a higher insulin sensitivity index and a considerable reduction in HbA1c. The increase in deoxycholic acid after Lactobacillus reuteri supplementation showed a positive correlation with the improvement of insulin sensitivity index.47

Numerous meta-analyses suggest a beneficial effect of probiotics on glycaemic control in people with T2D.48-53 However, there is no consensus on the specific metabolic effect associated with supplementation. According to some authors, the type of clinical response depends on the characteristics of the study group, the number and type of probiotic strains used, and the duration of supplementation.51,53 It seems that properly selected manipulation of the microbiome may be an attractive option for adjuvant treatment in obesity-induced insulin resistance.

The role of probiotics in T1D prevention needs further investigation. In animal studies, it has been reported that the administration of the probiotic formulation VSL#3 decreased the incidence of T1D and oral feeding of Lactobacillus casei to young nonobese diabetic mice inhibited the occurrence of T1D and prevented the disappearance of β cells.57 The beneficial effect of probiotics supplementation was also one of the goals of the TEDDY investigation. In this study, early probiotic supplementation (up to 27 days) in children at the highest genetic risk of T1D was associated with a decreased risk of islet autoimmunity. Although the results are promising, there is no information about the specific species and doses that are responsible for this outcomes.54

In summary, the relation of obesity and diabetes is complex. Many factors that link these two epidemics have been thoroughly investigated in the past. A very interesting and still not fully discovered factor impacting obesity as well as diabetes is the microbiome. The results of the ongoing and future research in this field will be very interesting and may change the perspective.

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CONFLICT OF INTEREST
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