Review Article

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Role of gut microbiota in metabolic syndrome: a review of recent evidence

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Abstract

The metabolic syndrome is a complex entity comprised of multiple cardiovascular risk factors grouped in a single individual, contributing to an increased rate of cardiovascular events which goes beyond what would be expected given the impact of each individual risk factor. It is a multifactorial condition whose complete pathogenesis is not yet fully understood. Several studies have shown that not only the intestinal microbiota and dysbiosis may play a role in its pathogenesis, but also that modulating said microbiota may play a role in treating or at least ameliorating the metabolic syndrome. The purpose of this article is to review some of the most recent evidence linking the gut microbiome and the metabolic syndrome to help further understand this relationship and try to identify further research directions.

Keywords: gut microbiota, insulin resistance, intestinal microbiota, metabolic syndrome

Introduction

The metabolic syndrome is a grouping of several cardiovascular risk factor in 1 individual, including insulin resistance, dyslipidaemia and hypertension all occurring in a context of central obesity. This of particular importance because this combination of risk factor appears to raise the risk of cardiovascular events and of developing diabetes more than would be expected by the simple sum of the effect of each risk factor.[1]

Furthermore, studies in recent years have correlated specific profiles of intestinal microbiota with specific metabolic abnormalities, such as obesity and insulin resistance.[2,3] It is particularly interesting that some research has shown that changing and modulating the gut microbiome can have a positive impact in the treatment of several conditions and, although the most robust evidence pertains to the treatment of gastrointestinal infections, such as *Clostridium difficile*,[4] some evidence exists pointing towards a potentially beneficial effect in metabolic disorders.[5]

Given it is increasingly recognised that multiple interventions may be used to change the intestinal microbiome,[6] it makes sense to review current research to determine what is known and what gaps in knowledge still exist in the effects of targeting the intestinal microbiota.

Methods

The MESH terms [("microbiota" OR "microbiome") AND ("metabolic syndrome" OR "insulin resistance")] were used to perform a PubMed search focusing only on clinical trial and randomized controlled trial published between 2010 and 2020. The search resulted in 114 publications of which only those pertaining to interventions in human subjects and focusing on subjects with metabolic syndrome were selected. Apart from interventional trials, 2 systematic reviews were found and were also included in the review.

Results

In the past 10 years, several interventions were undertaken in individuals with metabolic syndrome to try and treat or ameliorate their condition via the modification of the intestinal microbiota with often conflicting results.

Several of the reviewed articles focused on dietary interventions to modulate gut microbiota and alter the parameter of metabolic syndrome, with differing results between them.

Three of the articles found focused on the effect of whole-grain products consumption. One of the articles, published in 2013, compared the effects of consuming whole-grain rye bread with the consumption of white bread and found that after the intervention only those consuming white bread had experienced a significant change in the microbiota composition, with a decrease in the proportion of *Bacteroidetes* and an increase in the proportion of *Firmicutes*. This contrasted with biochemical markers, which showed a decrease in C-reactive protein but only in the individuals consuming whole-grain foods.[7]

A second article focusing on whole-grain food products used a different approach with individuals being given prepared food containing whole grains, medicinal foods and prebiotics and consisting of a whole food substitution diet, and this approach did not affect the relative amount of *Bacteroidetes* or *Firmicutes* but led to an increase in *Bifidobacterium* sp. Patients undergoing

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the diet also experienced a decrease in several inflammatory parameters, including C-reactive protein, TNF-α and IL-6, as well as an increase in adiponectin. It should be noted that the intervention was also a low-calorie diet (1100–1600 kcal) which produced significant weight loss in the subject, which could explain the observed benefits.[8]

The other article focusing on whole-grain food consumption observed that after the study period whole-grain rye consumption was associated with an increase in *Bifidobacterium* sp. (compared to baseline) and a decrease in *Clostridium* sp. bacteria (compared with whole-grain wheat consumption) but without any significant impact on glucose metabolism. The authors also determined that the profile of gut bacteria at the start of the study might be associated with changes in either blood lipids or blood pressure, although this analysis was exploratory and should be interpreted with care.[9]

One study evaluated the effect of diets rich in either unsaturated fat, saturated fat or carbohydrates on intestinal microbiota. This study showed a decrease in bacteria in the faecal microbiota of subjects taking high-fat diets compared with high carbohydrate diets, with the high carbohydrate diets even showing a significant increase in *Bifidobacterium* sp. compared to baseline. Although no differences were noticed in biochemical or anthropometric parameters after the intervention between groups, a decrease in blood lipids in the high carbohydrate groups compared with baseline was detected.[10]

An article published in 2016 explored the effects of specific dietary fibres in the faecal microbiota of individuals with metabolic syndrome reported that a diet rich in arabinoxylan and resistant starch led to an increase in *Bifidobacterium* sp. and a decrease in *Clostridium* sp. and some *Firmicutes* phyla. These changes were accompanied by an increase in the concentrations of acetate and butyrate in faecal matter. However, no changes were observed in anthropometric data and blood biochemistry was not analysed.[11]

One study evaluated the effect of consumption of kimchi, a dish typical of Korean cuisine, on intestinal microbiota.[12] In this research, the consumption of kimchi correlated with an increase in bacteria of the *Bacteroides* and *Prevotella* genus and a decrease in the *Blautia* genus. Furthermore, when kimchi was fermented, an increase in *Bifidobacterium longum* was also observed which correlated with a decrease in waist circumference, possibly indicating that fermented kimchi might function as a probiotic.[12]

Several beneficial effects have been attributed to red wine and a study reported the effects of red wine polyphenols on the gut microbiome.[13] The study evidenced an increase in *Bacteroidetes* and a decrease in *Firmicutes* with an increase also observable in regards to *Bifidobacterium* sp., all of these compared to baseline measurements. It is particularly interesting to note that this study used healthy subjects as controls and that while the mentioned bacteria had significant differences between groups at baseline, their numbers did not differ between groups after the intervention. Furthermore, the changes in microbial species were accompanied by reductions in serum triglycerides, cholesterol and C-reactive protein.[13]

Like the previously mentioned trial with kimchi, other studies have also focused on fermented foods. A paper comparing the effect of kefir consumption with the ingestion of regular milk showed that kefir consumption was associated with a decrease in insulin, insulin resistance, TNF-α, IFN-γ and both systolic and diastolic blood pressure from baseline, although no difference was found between groups after the intervention. In regards to the impact on bacterial microbiota, several changes were observed but the only one to reach statistical significance was an increase in the *Actinobacteria* genus from baseline in the kefir group. Despite not reaching statistical significance, several of the changes were correlated with improvements in anthropometric measurements.[14]

Yoghurt consumption also appears to have an effect on gut microbiota, biochemical parameter and body composition. In a randomized controlled trial comparing the consumption of yoghurt and milk, yoghurt was associated with a decrease in insulin and insulin resistance as well as plasma triglycerides, cholesterol and TNF-α, along with fat mass and waist circumference. This was accompanied by a decrease in the percentage of *Firmicutes* and an increase in the percentage of *Negativicutes*.[15]

For this review, several studies looking at the effect of probiotic supplementation were also selected.

One study evaluated the effect of administering a probiotic with *Lactobacillus salivarius* to adolescents with metabolic syndrome and, although the bacteria was detected in faecal samples, no benefit was observed.[16]

Three other studies observed the effect of *Lactobacillus casei* Shirota and found similar results. One study reported no effect on gut permeability and even observed a small increase in high sensitivity C-reactive protein in the intervention group[17] while another observed no change in the atherogenic trimethylamine-N-oxide[18] and a third one was unable to demonstrate an impact on the relation between the number *Bacteroidetes* and *Firmicutes*.[19]

Two articles published in 2019 described the effects of multi-species probiotics in individuals with metabolic syndrome and seemed to find positive results, contrasting the previously mentioned studies using only one single species of bacteria.

One of the studies showed a decrease in the prevalence of increased fasting plasma glucose, hypertriglyceridemia and hypertension, with several patients no longer meeting the criteria for the diagnosis of metabolic syndrome after the intervention.[20]

Another trial concluded that the supplementation with a multi-species symbiotic was associated with a decrease in fasting plasma glucose, insulin, insulin resistance, GLP-1 and body mass index coupled with an increase in PYY. This study is particularly interesting because both the intervention and the control group undertook a diet program with 500 fewer Kcal than their calculated daily need, which would imply that any difference between the control and the symbiotic group is due to the intervention and not to the diet or the weight loss.[21]

Unfortunately, both of these last 2 studies suffer from an important shortcoming which is the fact that they assume that the probiotics or synbiotics are changing the gut microbiota, but this change is never analysed.

Some trials have also been undertaken in recent years using faecal matter transplantation to try and alter the intestinal microbiota.

One trial showed promising results when transplanting faecal matter from lean donors to individuals with metabolic syndrome. In these patients, the transplant was associated with increased gut microbial diversity, with a particularly large increase in butyrate-producing bacteria. Furthermore, this was also associated with a significant improvement in insulin resistance, suggesting that faecal matter transplant from healthy individuals may help improve metabolic syndrome.[5]

One trial looked at the effects of transplanting faecal microbiota from a single vegan donor to individuals with metabolic syndrome, using as controls individuals with autologous faecal matter transplant. Although the individuals

undergoing transplant from the vegan donor experienced a change in intestinal microbiota, this did not seem to produce changes in either the production of trimethylamine-N-oxide or inflammation. What is interesting to see is that in the individuals who underwent autologous faecal matter transplant had an increase in the abundance of bacteria from the *Akkermansia* genus, a group of bacteria usually associated with healthy metabolic effects[22] (Table 1).

Table 1

Brief description of reviewed articles

Article (author, year)	N	Intervention	Results
Gøbel, 2012	55	Administration of *Lactobacillus salivarius* Ls-33 probiotics to obese adolescents. Double-blind placebo-controlled trial.	No difference between groups.
Leber, 2012	30	Administration of *Lactobacillus casei* Shirota probiotic. Randomized trial.	No difference between groups.
Vrieze, 2012	18	Autologous or allogeneic transfer of gut microbiota from lean donors to individuals with metabolic syndrome. Double-blind randomized controlled trial.	Decrease in insulin resistance and increase in butyrate-producing bacteria in the gut in allogenic infusion group.
Fava, 2013	88	Comparison of the effect of high saturated fat, high monounsaturated fat/high glycemic index, high monounsaturated fat/low glycemic index, high carbohydrate/high glycemic index and high carbohydrate/low glycemic index diets gut microbiota and biochemical markers. Single-blind randomized controlled parallel trial.	High-fat diets reduced total gut bacteria. High carbohydrate diets increased *Bifidobacterium* in faecal samples and reduced plasma cholesterol and fasting plasma glucose. High carbohydrate/high glycemic index diet increased faecal *Bacteroides*. High carbohydrate/low glycemic index diet increased faecal *Faecalibacterium prausnitzii*. A correlation was observed between faecal *Bacteroides* and lower body weight
Lappi, 2013	51	Consumption of either whole grain rye bread or refined wheat bread. Randomized parallel trial	No difference between groups. Decrease in *Bacteroidetes* and increase in *Collinsella* and *Clostridium* bacteria compared with baseline in the refined wheat bread group.
Xiao, 2014	123	Dietary regimen using prepared formulas of whole-grain foods, traditional Chinese medicine foods and prebiotics. All patients underwent intervention.	The intervention was associated with weight loss, decreased insulin resistance, plasma triglycerides, and blood pressure. The intervention was also associated with an increase in *Bifidocateriaceae*.
Han, 2015	24	Consumption of fresh or fermented kimchi by obese women. Randomized controlled trial.	Consumption of both fresh and fermented kimchi changed intestinal microbiota, showing a decrease in *Firmicutes* and an increase in *Bacteroidetes*.
Stadlbauer, 2015	30	Administration of *Lactobacillus casei* Shirota supplement in individuals with metabolic syndrome. Comparison of data with healthy controls. Randomized controlled pilot study.	Supplement administration had no effect on measured parameters. Metabolic syndrome was associated with higher Bacteroidetes/Firmicutes ratio compared with healthy controls.
Tripolt, 2015	30	Administration of *Lactobacillus casei* Shirota supplement in individuals with metabolic syndrome. Randomized controlled trial.	Supplement administration had no effect on trimethylamine-N-oxide levels.
Hald, 2016	22	Diet enriched with arabinoxylan and resistant starch compared with low-fibre western diet. Randomized crossover trial.	Diet enriched with arabinoxylan and resistant starch was associated with an increase in the proportion of Bifidobacterium, short-chain fatty acids, acetate and butyrate in faecal samples as well as a decrease in isobutyrate and isovalerate in the same samples when compared with western diet.
Moreno-Indias, 2016	20	Consumption of red wine polyphenols by individuals with metabolic syndrome and healthy subjects. Randomized crossover controlled trial.	Consumption of red wine and de-alcoholized red wine was associated with a decrease in *Firmicutes* and an increase in *Fusobacteria* and *Bacteroidetes* in patients with metabolic syndrome and an increase *Bacteroidetes* in healthy individuals when compared with baseline microbiota measurements. No significant differences were observed between groups.
Smits, 2018	20	Faecal microbiota transplantation from single lean vegan donor to patients with metabolic syndrome. Randomized double-blind controlled pilot study.	Vegan donor faecal matter transplant produced an increase in abundance of *Lachnospiraceae*. Autologous faecal matter transplant was associated with an increase in *Akkermansia* and *Alcaligenes faecalis* bacteria.
Bellikci-Koyu, 2019	40	Kefir consumption by patients with metabolic syndrome. Randomized controlled parallel trial.	Kefir consumption was associated with a decrease in insulin resistance and inflammatory cytokines compared with baseline but not with control. Kefir consumption was associated with an increase in the abundance of the *Actinobacteria* genus compared with baseline but not compared with control.
Chen, 2019	100	Yoghurt consumption by obese women. Randomized controlled trial.	Yoghurt consumption resulted in a decrease in insulin resistance, serum lipids, several biochemical parameters. *Firmicutes* were found to be lower and *Negativicutes* were found to be higher in the yoghurt consumption group compared with controls after the intervention.
Kassaian, 2019	120	Administration of a probiotic, a synbiotic or placebo in individuals with prediabetes. Double-blind placebo-controlled randomized parallel trial.	Probiotic and symbiotic supplementation was associated with a decreased prevalence of metabolic syndrome compared with placebo. No microbiota analysis was performed.
Rabiei, 2019	46	Administration of symbiotic in individuals with metabolic syndrome. Triple-blind randomized controlled trial.	Synbiotic supplementation was associated with changes in fasting plasma glucose, fasting insulin, PYY, C reactive protein, body weight and body mass index compared with placebo.
Eriksen, 2020	49	Consumption of whole-grain rye diet with and without supplementation with lignan and whole-grain wheat diet. Randomized crossover trial	Rye diets were associated with an increase in gut *Bifidobacterium* bacteria compared with baseline and a decrease in *Clostridium* bacteria compared with wheat diets

Conclusions

In recent years several studies have been undertaken to try and determine the potential role of the intestinal microbiome in metabolic disorder, although no conclusive results can yet be achieved.

Several different strategies can be used to try and modulate the intestinal microbiome with differing results on either the microbiota itself or metabolic markers of health and disease.

Several studies appear to show a beneficial effect of diet on both gut microbiota and both markers of inflammation and insulin resistance. However, given that these studies use dieting as an intervention it is extremely difficult to determine what effects are due to the diet itself and any weight loss and what effect is derived from the intestinal bacteria.

In this regard, studies using probiotics or faecal matter transplant offer better evidence of the effects of altering the gut microbiota. It is interesting to see that when using probiotics, effects of using multiple strains of bacteria appears to be far more marked than those obtained from a single species which might indicate that for a healthy microbiota, diversity might be as important as the bacterial species themselves.

Unfortunately, all of the studies reviewed here show 1 important flaw, which is the limited number of subjects enrolled in the studies. All trials included a very low number of subjects, with only 2 studies having more than 100 subjects, with most having less than 50 and the largest having only 123 enrolled individuals

It is paramount, that further large-scale studies be undertaken if we intend to understand the full scope of the role of the intestinal microbiota in human health and how altering its composition may help improve or even treat different medical conditions.

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