Iron Reshapes the Gut Microbiome and Host Metabolism

Amy Botta,1 Nicole G. Barra,2 Nhat Hung Lam,1 Samantha Chow,1 Kostas Pantopoulos,3 Jonathan D. Schertzer,2 Gary Sweeney1

1Department of Biology, York University, Toronto, ON, Canada
2Department of Biochemistry and Biomedical Sciences, Farncombe Family Digestive Health Research Institute, Centre for Metabolism, Obesity and Diabetes Research, McMaster University, Hamilton, ON, Canada
3Lady Davis Institute for Medical Research, Jewish General Hospital and Department of Medicine, McGill University, Montreal, QC, Canada

ABSTRACT

Compelling studies have established that the gut microbiome is a modifier of metabolic health. Changes in the composition of the gut microbiome are influenced by genetics and the environment, including diet. Iron is a potential node of crosstalk between the host-microbe relationship and metabolic disease. Although iron is well characterized as a frequent traveling companion of metabolic disease, the role of iron is underappreciated because the mechanisms of iron’s influence on host metabolism are poorly characterized. Both iron deficiency and excessive amounts leading to iron overload can have detrimental effects on cardiometabolic health. Optimal iron homeostasis is critical for regulation of host immunity and metabolism in addition to regulation of commensal and pathogenic enteric bacteria. In this article we review evidence to support the notion that altering composition of the gut microbiome may be an important route via which iron impacts cardiometabolic health. We discuss reshaping of the microbiome by iron, the physiological significance and the potential for therapeutic interventions.

Keywords: Gastrointestinal microbiome; Iron; Host-pathogen interactions; Metabolic diseases

GUT MICROBIOME AND METABOLIC HEALTH

The gut microbiome is a complex ecosystem comprising of over 1,000 different species of bacteria, viruses, fungi, parasites and eukarya.1 While it was previously thought that microorganisms outnumbered human cells by 10-to-1,1,2 new estimates state that there is approximately an equivalent number of bacterial cells to human cells with bacteria contributing up to 0.2 kg in a 70 kg human.3 Based on molecular studies using 16S rDNA analysis, it was found that the microbiota that resides in the intestines of humans is mainly composed of Bacteroidetes (i.e., Bacteroides spp.), Firmicutes (i.e., Clostridium, Roseburia, Ruminococcus, or Lactobacillus spp.), Actinobacteria (i.e., bifidobacteria), and Proteobacteria (i.e., enterobacteria).3,4 Of these types of bacteria the most common phyla within the human gut is that of Bacteroidetes and Firmicutes.2,4

Gut bacteria and the human host coexist in a symbiotic relationship. The nature of this coevolved interaction is mainly classified as either mutualistic, commensalistic, or
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parasitic. The host provides a stable enteric environment with a continuous food supply for microorganisms to thrive in, while the microorganisms provide nutrients critical to the host’s growth and development. This includes nutrient extraction through the use of bacterial derived digestive enzymes and vitamin synthesis. A delicate equilibrium between gut bacteria, the intestinal epithelial barrier, and host immunity to maintain mutualism or commensalism. A disruption in this host barrier/immune-microbe equilibrium can result in a change in the composition of the microbiome that is significantly different from normal variation in the microbiome, which is often called dysbiosis. Since the gut microbiota plays an active role in the health of the host, dysbiotic alterations in bacterial composition have been associated with numerous chronic illnesses such as inflammatory bowel disease, rheumatoid arthritis, Parkinson’s, osteoporosis, susceptibility to infectious disease and metabolic disease.

While many of the roles of the gut microbiome have yet to be elucidated, several beneficial effects have been discovered. The gut microbiome plays an important role in digestion and vitamin synthesis. However, while some species of the gut microbiome are beneficial, enteric pathogenic bacteria exist such as Shigella flexneri, Citrobacter rodentium, Listeria monocytogenes and Salmonella enterica serovar Typhimurium. Changes in the gut microbiome can significantly impact human health. For example, patients with Crohn’s disease exhibit a significant decrease in microbial diversity compared to control individuals. Additionally, differences in the specific gene content due to strain specific differences can also greatly impact human health by altering the contribution of genes and metabolites to the host.

FACTORS THAT AFFECT THE COMPOSITION OF THE GUT MICROBIOME

Many factors impact the composition and function of the gut microbiome including ethnicity, geographic location, age, gender, genetic background, and diet. In a study investigating the specific ethnic differences amongst individuals who live in the same geographic location it was found that individuals of the same ethnic background had a more similar gut microbiome composition than individuals from different ethnic backgrounds with Dutch individuals exhibiting the largest α-diversity and the South-Asian Surinamese exhibiting the smallest α-diversity. However all individuals had 21 microbial taxa that were present regardless of their ethnicity. In another study in which 7,000 individuals from across Guangdong province in China were surveyed, it was found that differences in composition of the microbiome between individuals could be explained based on the individuals geographic location. Other studies have also found that both age and gender can significantly impact the composition of the gut microbiome. For example, the newborn microbiome can be dramatically effected by birthing method and diet, and this microbiome has a considerably different composition compared to the microbiome observed amongst adult individuals. Additionally, studies have shown that there are gender specific differences in the composition of the gut microbiome, but the full extent and significance of these changes is unclear.

Genetics may also play a role in the composition of the gut microbiome. One study using 31 female monozygotic pairs, 23 dizygotic twin pairs and 43 of their mothers found that the gut microbiome was similar amongst family members, but each individual had specific bacterial lineage differences. The type of twin did not significantly impact the gut microbiome with both monozygotic and dizygotic twins displaying a similar degree of
In contrast, a separate study investigating fecal samples from the TwinsUK population found that there was more similarity in composition between monozygotic twins than dizygotic twins, additional operational taxonomic unit relative abundances were more highly correlated in monozygotic twins. Therefore, whilst genetics can impact the composition of the microbiome, the full extent of the impact of conserved microbial profiles on host physiology remains an area where more research is needed. Recently studies have suggested that diet may have a more substantial impact on the gut microbiome than genetic factors and can significantly influence and alter its composition. This mainly depends on macronutrients such as fat and carbohydrate content, but also on metals such as iron, copper and zinc.

**GUT MICROBIOME AND DIET**

Diet is an important factor that can rapidly alter the composition of the gut microbiota, and since mammals are constantly eating, diet continuously shapes the alpha and beta diversity of intestinal bacterial communities. Ingested foods provide not only nourishment to the host, but also supply fermentable substrate for gut bacteria, which is required to sustain specific enteric microbes. In response to ingested substrates that enter the intestinal lumen, gut bacteria produce metabolites from digested food components influencing host health. Studies demonstrate that diet can have both acute and long-term effects on the composition of the gut microbiome. The impact of single dietary compounds and widely used dietary patterns like vegetarian, Mediterranean, and Western diets on gut bacteria and host health have been assessed in humans.

Vegetarian diets comprised of plant-based foods are often considered beneficial for multiple host metabolic responses due to increased fiber and lower protein, saturated fat, and cholesterol intake. Foods generally consumed by vegetarians include whole-grains, fruits, vegetables, nuts, legumes, and soy based products. Consumption of a vegetarian diet can promote a protective effect from various ailments such as ischemic heart disease, incidence from total cancer, metabolic syndrome (MetS), and diabetes. Despite these enhancements in host health, a systematic review found no consistent characteristic gut microbial profile in individuals consuming a vegetarian diet when compared to vegans and omnivores. High microbial individuality, along with differences in methodology have limited conclusions to date. For example, differences in the processing of collected stool samples, participants tested from various geographical regions leading to environmental and dietary variation, variability in time adhered to diet, and differences in data analyses of microbial composition using different taxonomic levels in current studies may underlie this inability to uncover definitive differences in vegetarians. Importantly, these studies failed to report medication intake of the participants. Medications, specifically antibiotic-use, have profound effects on the gut microbiota and can ultimately mask any potential differences between groups. It is also possible that vegetarian diets are too variable to find a distinct change in the microbial composition and further refinement of specific groups of food is required to produce reliable changes in microbial taxa. Vegetarian or plant based diets may however contribute to gut health by enhancing gut bacterial diversity and through the production of bioactive compounds generated during fermentation refered to as postbiotics. Further analyses examining the gut bacterial metabolome demonstrate plant-based foods are linked with the enhanced production of postbiotics such as short chain-fatty acids (SCFAs), isothiocyanates, and phytoestrogens compared to meat-based diets which are linked to increased...
trimethylamine N-oxide and secondary bile acids.\textsuperscript{64} As well, increased microbial expression and protein production for carbohydrate and protein-hydrolyzing enzymes and synthesis of essential amino acids and vitamins were associated with vegetarian diets when compared to omnivores.\textsuperscript{65} In the absence of global microbial shifts in composition, the metabolic outputs and genetic activity of gut bacteria in a vegetarian diet may contribute to the beneficial health effects associated with this dietary practice.

The Mediterranean diet provides host health benefits and produces a characteristic gut microbial profile.\textsuperscript{66,67} The Mediterranean diet is based on foods typically ingested by countries surrounding the Mediterranean Sea such as Italy, Spain and Greece. Plant-sourced foods like fruits, vegetables, whole grains, and legumes are mainly consumed with few dairy foods and limited red meat, moderate amounts of fish, poultry, wine and olive oil as a main dietary unsaturated fat source.\textsuperscript{68} Consumption of the Mediterranean diet reduces the risk of multiple chronic diseases such as diabetes, cancer, cardiovascular and neurodegenerative diseases, and reduces all-cause mortality risk based on data generated from clinical trials and epidemiological studies.\textsuperscript{67,69} A few studies demonstrate that consumption of a Mediterranean diet promotes changes in the microbiota profile and increased production of bacterial metabolites like SCFAs.\textsuperscript{66,70,71} Participants with high adherence to this diet had a lower Firmicutes:Bacteroidetes ratio, increased fecal SCFA content (butyrate, propionate, and acetate), and enhanced representation of bacteria known to degrade fiber such as \textit{Prevotella} and \textit{Lachnospira}.\textsuperscript{66} Similarly, in an interventional trial using overweight and obese individuals, Mediterranean diet increased the presence of the butyrate producer \textit{Faecalibacterium prausnitzii},\textsuperscript{72,73} which has been shown to promote anti-inflammatory processes.

Western diets are largely composed of low fiber and high fat, high animal protein, and high refined sugar content. Specifically, this diet emphasizes the consumption of processed grains, red meat, saturated fats, added sugars with lower intake of fruits, vegetables, legumes, and whole grains. Ultra-processed foods are a main feature of this dietary practice, and when compared to the consumption of whole foods, a western-style diet can alter the gut microbiota.\textsuperscript{74} The characteristic bacterial profile associated with the Western diet can be linked to its low complex carbohydrate content. Bacterial clades of the species \textit{Prevotella copri}, involved in carbohydrate metabolism, are underrepresented in Westernized populations, mainly attributed to diet.\textsuperscript{75} In addition, microbes associated with polysaccharide degradation of porphyran present in edible seaweed species is scarce in Western diets.\textsuperscript{75} As well, there is a reduced abundance of \textit{Prevotella} and \textit{Xylanibacter} bacteria involved in cellulose and xylan hydrolysis in children fed Western diets compared to fiber-rich diets.\textsuperscript{76} In a cross-sectional study of 517 community-dwelling men, greater adherence to a Western diet positively correlated with bacterial families \textit{Veillonellaceae} and \textit{Mogibacteriaceae}, and genera like \textit{Ruminococcus} which degrade resistant starches in refined grain products, without any significant changes in bacterial phyla.\textsuperscript{77,78} Gut bacteria inversely associated with adherence to the Western diet included relative abundances of orders \textit{Clostridiales} and \textit{Streptophyta}, family \textit{Anaeroplasmataceae}, and genera \textit{Coprooccus}, \textit{Faecalibacterium}, \textit{Haemophilus}, \textit{Lachnospira}, \textit{Paraprevotella}, and \textit{Prevotella}. In addition, decreased bacterial diversity is also associated with consumption of a Western diet when compared to hunter-gatherer or rural farming populations.\textsuperscript{77,79,82} In mice, this reduction in microbial diversity induced by a Western low fiber diet over several generations can lead to the irreversible extinction of specific glycoside hydrolase producing bacteria, potentially impairing the host’s capacity to degrade glycans.\textsuperscript{82} Altogether, these results demonstrate the Western diet can impact microbial profile and diversity, largely attributed to its low complex carbohydrate content.
Dietary components associated with these diets, specifically fiber, fat, and sugar, can affect the gut microbiota and host health, which have been reviewed elsewhere.\textsuperscript{44,53,54,64} The source of dietary carbohydrates and lipids is a key factor that can differentially affect enteric bacteria. Non-digestible carbohydrates like fiber are generally fermented in the colon.\textsuperscript{83} Fiber supplementation in both healthy and specific patient populations enhance the abundance of \textit{Bifidobacterium} spp. and \textit{Lactobacillus} spp. when compared to lower fiber diets or placebo.\textsuperscript{84,85} Also, increased consumption of resistant starches can induce phylum shifts, and increase proportions of bacterial species dependent on the type of carbohydrate studied.\textsuperscript{86} Other carbohydrate sources, like simple sugars specifically fructose which is highly prevalent in ultraprocessed foods, are easily absorbed in the upper gastrointestinal tract, can alter the gut microbial profile and can promote aspects of metabolic disease.\textsuperscript{87,88} Lastly, ingestion of saturated lipids, in a Western diet, compared to unsaturated lipids common in Mediterranean and vegetarian diets, have distinctive effects on the gut microbiota.\textsuperscript{44,89} Women supplemented with dietary omega-3 polyunsaturated fatty acids increased both the microbial alpha diversity and increased relative abundance of the \textit{Lachnospiraceae} family, independent of fiber intake.\textsuperscript{90} In addition, mice fed saturated fats gained weight, were insulin resistant, had increased low grade circulating endotoxin levels, and higher white adipose tissue inflammation, which correlated to a distinctive bacterial profile compared to mice fed unsaturated fats protected from these metabolic impairments.\textsuperscript{91} Altogether, these studies demonstrate diet and dietary components are critical factors that can contribute to the gut microbiota and host health.

**GUT MICROBIOME IN DEVELOPMENT OF OBESITY**

Initial findings highlighting the role of gut microbes in metabolic disease development arose from observations using germ-free mice. These mice accumulate less visceral fat compared to conventional colonized mice over time, and are protected against diet-induced obesity when fed a western-style diet.\textsuperscript{92-94} This lean phenotype observed in germ-free mice devoid of gut bacteria is largely attributed to defective nutrient absorption.\textsuperscript{95} In addition, germ-free mice have improved insulin and glucose tolerance comc, likely both attributed to their lean phenotype, possibly due to lower bacterial induced pathogen recognition receptor activation by gut microbial compounds.\textsuperscript{93,95} Altogether, these observations support a link between the gut microbiota and host metabolism.

Previous research has shown that there is a significant difference in the microbiome profiles of obese and lean individuals with obese individuals having greater bacterial diversity than lean.\textsuperscript{34} As mentioned earlier the 2 predominant populations of microbiota in both rodent and human gut are members of the bacterial groups known as the \textit{Firmicutes} and the \textit{Bacteroidetes} and the relative proportion of these 2 phyla may protect or predispose the host to obesity.\textsuperscript{96,97} Metagenomic studies have demonstrated that the proportion of \textit{Firmicutes} is higher in obese individuals as compared to lean controls and this correlates with a higher number of genes encoding enzymes that break down otherwise indigestible dietary polysaccharides, more fermentation end products and fewer calories remaining in the feces of obese individuals.\textsuperscript{98,100} In particular changes in \textit{Firmicutes} phylum species \textit{Blautia hydrogenotrophica}, \textit{Coprococcus catus}, \textit{Eubacterium ventriosum}, \textit{Ruminococcus bromii}, and \textit{Ruminococcus obeum} were strongly associated with development of obesity.\textsuperscript{14} While studies have shown that increases in \textit{Firmicutes} are associated with obesity and increases in \textit{Bacteroidetes} have been associated with weight loss,\textsuperscript{97,102} other studies have contradicted these findings.\textsuperscript{40,102,104}
Fecal transplantation from lean human donors to obese recipients led to a significant improvement in insulin sensitivity in the obese recipients. Intriguingly, microbiota transplantation studies in germ-free murine models showed that the efficient energy extraction traits of obese-type gut flora are transmissible. Furthermore both human and animal model studies of obesity and MetS have shown that supplementation with Lactobacillus can improve glucose tolerance. In patients with MetS changes in the gut microbiome have been linked to a genetic variant in the apolipoprotein A5 gene. The human gut is populated by at least $10^{13}$ microorganisms, mostly anaerobic bacteria. The metabolic activities of these microbes are comparable to an ‘organ’ particularly adapted to human physiology and executing vital functions including the ability to process otherwise indigestible nutrients, repressing the growth of harmful microorganisms and training the immune system to respond only to pathogens.

Importantly, the microbiota contains factors, including unknown molecules, that are positioned to influence host metabolism. There are now wide-scale efforts to determine how the microbiota can be measured and manipulated to improve host metabolism. The gut microbiota contains a huge amount of genetic diversity and novel chemical compounds that are ripe for developing new therapies. Current approaches focus on measuring bacterial nucleic acids (DNA/RNA), proteins (proteomics) and metabolites (i.e., metabolomics) in order to define how bacteria associated with important disease related pathways to uncover new drug candidates.

**ROLE OF IRON IN METABOLIC DISEASES**

Iron is an essential nutrient for both the host and the microbiome. The host requires iron for oxygen transport, cellular respiration, immune responses, catalytic activities and other metabolic functions. Likewise, most bacteria require iron for growth and for essential electron transfer and catalytic reactions. The impact of iron on the microbiome has received considerable attention and this is highlighted in recent reviews; nevertheless, there are still many outstanding questions.

In this review article we focus on iron as a critical node of crosstalk between dietary changes, alterations in the microbiome and metabolic dysfunction. The MetS refers to a cluster of abnormalities which include obesity, dyslipidemia, insulin resistance and type 2 diabetes that collectively increases the risk of developing cardiovascular diseases, including heart failure (HF) and non-alcoholic fatty liver disease. Research on this topic is extremely important since it was estimated that in North America more than 25% of the population suffer from MetS and this is associated with serious and extensive comorbidity. A prevalence of mild iron overload in MetS patients is well established by the presence of non-transferrin-bound iron in serum and by the correlation of hyperferritinemia and hepatic iron overload with insulin resistance. The combination of iron overload with insulin resistance is often referred to as dysmetabolic iron overload syndrome and occurs in 15%–30% of MetS patients. Thus, at this time the association of iron overload with the MetS is well recognized, yet mechanisms leading to metabolic dysfunction are not fully understood. It is possible that the role of iron as a contributor to the pathogenesis of MetS and its complications is still very much underappreciated (Table 1) and that modification of microbiome is an important and relatively unexplored mediator of iron’s metabolic effects. In particular, dietary iron levels in the intestinal lumen modify the microbiota
Iron-induced Dysbiosis and Metabolic Dysfunction

Table 1. The effect of reducing iron load in MetS

| Study | Study type | No./type of patients | Duration of study | Main findings |
|-------|------------|----------------------|-------------------|--------------|
| Flores et al. | Randomized, parallel, open-label clinical trial | Women with PCOS or idiopathic hyperandrogenism (n=33) | Three-month treatment with 35 µg ethinylestradiol + 2 mg cyproterone acetate followed by either (i) 3 scheduled bloodlettings or (ii) observation | Bloodletting did not improve insulin sensitivity measures in women with functional hyperandrogenism |
| Behboudi-Gandevani et al. | Randomized clinical trial | Women with PCOS (n=64) | Evaluated 3 months after either (i) undergoing phlebotomy procedure or (ii) using oral contraceptives | Both phlebotomy and contraceptive use decreased HOMA-IR, FAI, and FG |
| Baye et al. | Randomized controlled trial | Overweight/obese, non-diabetic adults (n=26) | Twelve-week daily intake of either (i) 1 g carnosine (iron chelating agent) or (ii) placebo | Carnosine supplementation decreased only plasma soluble transferrin receptor vs. placebo; no metabolic testing completed |
| Suarez-Ortegon et al. | Systematic review/meta-analysis | Twenty-one studies examining associations between ferritin and MetS | Systematic review, studies of varying length | High triglycerides and glucose are strongly associated with ferritin |

MetS, metabolic syndrome; PCOS, polycystic ovary syndrome; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; FAI, free androgen index; FG, Ferriman-Gallwey score; NTDT, non-transfusion-dependent thalassaemia; ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; GGT, gamma-glutamyl transferase; IR, ischemia and reperfusion; MRI, magnetic resonance imaging; NAFLD, non-alcoholic fatty liver disease; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; LDL, low density lipoprotein.

This is expected to subsequently affect the microbiome’s functionality in regards to its metabolomic profile, including SCFA and branched chain amino acids. Consequences of such modifications would be peripheral insulin resistance and metabolic dysfunction in the host.

Iron intake varies considerably depending on diet and since iron is commonly used in supplements this can also increase the variability of iron intake. Also, higher male predisposition to heart and liver disease in MetS patients with higher iron stores, was reported. Whether differential iron states affect the gut microbiota and contribute to this varied susceptibility in males and females is unclear. Yet recently, an iron mediated elevation of gut luminal glucose levels was proposed to modify an intestinal pathogen to a commensal bacterium, indicating that the effects of iron supplementation on the microbiome bare still surprises. Interventions to reduce iron, such as via venesection or use of chelators, improved insulin sensitivity and delayed the onset of type 2 diabetes mellitus (T2DM) and HF in some occasions, but have not always been successful. Thus, previous work has shown a bidirectional relationship between iron and glucose homeostasis or cardiomyopathy, suggesting a balance of optimal iron level is critical.

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The critical role of iron metabolism for health is in fact illustrated very well by genetic disorders which cause a disruption in iron balance. These include classic genetic diseases such as thalassemia and hereditary hemochromatosis resulting in iron overload. Both will be discussed below as examples of cardiometabolic disease.

Metabolic abnormalities are common in thalassemia major, a hemoglobinopathy that is treated with repeated blood transfusions which cause secondary iron overload. A study with thalassemia major patients showed an increased risk for diabetes, heart disease and MetS, particularly amongst women. Although we now understand much about reasons for adverse health outcomes in thalassemia patients, various complications continue to impact the life expectancy of patients with thalassemia major, with as many as 50% dying before age 35. Heart disease is responsible for more than half of these deaths. Diabetes also occurs frequently in thalassemia patients with one meta-analysis finding the prevalence among Iranian thalassemia major patients being 9% and around 12% having impaired fasting glucose and glucose tolerance. Thus, further understanding the mechanisms responsible for cardiometabolic disease in thalassemia patients is essential. Interventions to reduce iron, such as via use of chelators, improved insulin sensitivity and delayed the onset of T2DM and HF. Important cellular mechanisms via which iron accumulation leads to metabolic disease have been characterized, principally mitochondrial dysfunction. Nevertheless, it is intriguing to speculate that altered iron homeostasis in thalassemia impacts the microbiome composition and contributes to metabolic complications. In keeping with this train of thought, a very recent study agreed that the adverse effect of iron accumulation in gut is not frequently mentioned in thalassemia. The study went on to show that gut iron accumulation in thalassemic mice caused a defect in gut-permeability which the authors noted impacted sepsis susceptibility. It is also very likely that this has important metabolic consequences and this should be further studied.

Hereditary hemochromatosis is caused by inactivation of the iron hormone hepcidin. Interestingly, men are at higher risk of developing hemochromatosis. These patients exhibit a high frequency of diabetes with evidence for both destruction of pancreatic β cells and insulin resistance. Several mechanisms have been shown to potentially contribute to various clinical metabolic manifestations in hemochromatosis, with an emphasis on hepatic consequences. In addition to currently available evidence, we also believe that the contributory role of iron-induced dysbiosis must be more carefully examined. In support of our proposal, a very recent study has demonstrated that hereditary hemochromatosis causes gut dysbiosis. This study in Hfe−/− mice, a model of mild hemochromatosis, documented profound changes in the colonic microbiome in favor of the pathogenic bacteria belonging to phyla Proteobacteria and TM7, together with loss of function of the intestinal/colonic barrier. Nevertheless, another study in Hfe−/− mice found increased adiponectin expression and improved glucose tolerance which was explained via reduced iron content specifically in adipose tissue, despite systemic iron overload. We must also be careful in translating studies in mouse models to clinical relevance since in mouse models of hemochromatosis excess iron accumulates in pancreatic acinar but not β cells, yet this is dissimilar to findings in human hemochromatosis patients. This is an intriguing area of research that will require further investigation to clarify under which circumstances hemochromatosis and the consequent reshaping of the gut microbiome is associated with adverse, or favourable, outcomes.
IMPACT OF IRON ON THE COMMENSAL MICROBIOME

Previous research studying the impact of iron on the gut microbiome has produced conflicting conclusions. Within bacteria iron can play a crucial role in growth and proliferation, for example iron can be required for the proper functioning of some bacterial proteins and enzymes. Additionally iron can modulate expression of some virulence factors. Therefore, iron has been shown to be an important element required for the growth of some but not all gut bacteria including *Bacteroides* spp. and *Enterobacteriaceae*, whilst *Lactobacilli* species do not require iron for growth. Interestingly, *Lactobacillus plantarum* 299v, and a probiotic (containing *Bifidobacterium* *bifidum* W23, *B. lactis* W51, *B. lactis* W52, *Lactococcus lactis* W19, and *L. lactis* W58) have been shown to increase host iron absorption. Various proteins and enzymes involved in bacterial replication and growth require iron as a cofactor to function. Iron is a cofactor involved in the synthesis of DNA (i.e., ribonucleotide diphosphate reductase), electron transfer and generation of ATP (i.e., cytochromes), and the neutralization of harmful oxidative species (i.e., superoxide dismutase). Iron deficiency can inhibit these bacterial cell processes, which can impair bacterial growth. Microbes that require iron for growth and survival have evolved processes to prevent nutrient deficient states. During iron deficiency, bacterial iron acquisition gene programs are de-repressed by the ferric uptake regulator family (FUR) proteins. FUR proteins act as an iron-dependent repressor that controls numerous iron-regulated genes by binding free ferrous (2+) iron to prevent transcripton when bacteria are exposed to sufficient iron. During iron deficiency, FUR proteins de-repress gene programs that enhance iron acquisition from their hosts to promote growth. Mechanisms to acquire iron include: (i) siderophores formation, (ii) cell surface ferric reductases to reduce free ferric (3+) iron to ferrous (2+) iron for bacterial utilization and (iii) production of cytotoxins and haemolysins to release iron stores from host cells.

The majority of the research on the effects of iron on the gut microbiome has focused on changes either during anemia or the effects of iron supplementation in these patients. Iron supplementation in pregnant women was not associated with changes in the gut microbiome. Another study investigating the effects of iron on obese and overweight pregnant women found that while there was no significant alteration in the composition of the gut microbiome, women receiving low iron supplementation (<60 mg/d iron) had a higher prevalence of SCFA producing bacteria than women taking a higher dosage of iron. In a study conducted to investigate the impact of iron supplementation on rat pups, no effect on growth or weight gain was observed. However, supplementation did slightly alter the composition and diversity of the gut microbiome profile. Specifically there were changes in the abundance of strict anaerobic bacterial species like *Bifidobacterium* and *Bacteroides*. Similarly iron supplementation amongst South African children did not significantly alter the composition of the major bacterial groups, or faecal SCFA concentration.

IMPACT OF IRON ON PATHOGENIC BACTERIA

Under normal conditions pathogenic bacteria must overcome resistance from commensal microbial communities in order to colonize. Commensal microorganisms activate immune responses which can lead to the elimination of pathogenic bacterial species. However, the level of immune activation is important, as instead of leading to elimination of pathogenic
bacteria, alternatively intestinal inflammation can promote the colonization of pathogens. One of the hallmarks of intestinal inflammation-induced dysbiosis (Fig. 1) is that of increased abundance of enterobacteria species. Due to the differing microbial profile in the inflamed gut there is also an association with an altered siderophore profile. As siderophores are responsible for metal ion abundance, this altered profile can further influence the type of bacteria which survive and grow. As such, because iron is an essential element for most bacteria to thrive, one key role of the intestinal immune response is to limit the availability of iron to pathogenic bacterial species.

A previous study has shown that dietary iron inhibited growth of the enteric pathogen *Citrobacter* and drove selection of asymptomatic *Citrobacter* strains; these responses were associated with insulin resistance and increased glucose levels that suppressed pathogen virulence. In addition to promoting insulin resistance dietary iron also increased intestinal glucose levels, a key gut environmental change that suppressed pathogen virulence, and drove selection of asymptomatic *Citrobacter* strains. However, in contrast, other studies have shown that decrease in iron availability is beneficial via reducing growth of potentially pathogenic gut bacteria. Dietary iron supplementation has adverse effects such as inducing higher levels of pathogenic gut bacteria and the occurrence of intestinal injury. Addionally a study investigating iron supplementation in African children found that there was an increase in the number of enterobacteria and a decrease in lactobacilli which correlated with gut inflammation.

In mammals most iron is chelated within the porphyrin structure of heme. As pathogenic bacteria require iron for growth, cholera contains genes which enable *Vibrio cholerae* to obtain iron from heme. The cholera toxin increases the bioavailability of luminal heme by congesting terminal ileal capillaries, leading to bacterial utilization for growth. Furthermore, *Vibrio cholerae* produce a siderophore known as vibriobactin. Unlike other catecholate siderophores such as enterobactin, this unique coordination helps in evading the host immune system. Cholera toxin also increases long-chain fatty acid and L-lactate.
metabolites within the lumen, which leads to the upregulation of \textit{Vibrio cholerae} genes encoding iron-sulfur cluster containing enzymes of the TCA cycle. As such cholera, and production of cholera toxin creates an iron-depleted metabolic niche in the gut, which selectively promotes the growth of \textit{Vibrio cholerae} through the acquisition of host-derived heme and fatty acids.\textsuperscript{187}

Other bacterial species such as \textit{Campylobacter jejuni} are also able to capture host iron and cause infection within the host. Infection with \textit{Campylobacter jejuni} occurs by eating raw or undercooked poultry, seafood, meat and untreated drinking water, as it passes through the stomach it must first survive an extreme acidic environment. Its ability to survive an acid stress environment is increased by the presence of iron, and as such it contains genes involved in iron-mediated acid protection, including flagella biogenesis genes, cell envelope biogenesis, heat shock proteins (GroEL, GroES), which aid it’s survival.\textsuperscript{189}

In order to obtain iron, many bacterial species produced compounds known as siderophores which bind iron and transport it inside the bacteria.\textsuperscript{190,191} This is counteracted in the host via induction of an immune response which includes the production of lipocalin-2 (Lcn2; also referred to as neutrophil gelatinase-associated lipocalin or 24p3), predominantly from neutrophils. Lcn2 is a critical component of the host innate immune response\textsuperscript{192-194} and acts via sequestering iron-laden siderophores, thereby preventing bacteria obtaining iron from the host.\textsuperscript{195-198} However, excess or prolonged Lcn2 production mediates proinflammatory effects with adverse cardiometabolic implications. Previous clinical data has shown that circulating Lcn2 levels are elevated in obese patients with metabolic disorders.\textsuperscript{199-205} Lcn2 levels are also strongly associated with HF.\textsuperscript{199,201,206-208} For example, Lcn2 is significantly augmented in patients with coronary heart disease and myocardial infarction.\textsuperscript{202,209} In diabetic patients, increased Lcn2 has been correlated with cardiac hypertrophy and diastolic dysfunction.\textsuperscript{203} Following an ischemic stroke event, measurements of Lcn2, within a few days after the
event, can be used to stratify patients according to mortality risk during the following 4-year period. Lcn2 content in the myocardium itself increases in HF, and after ischemia reperfusion from infiltrating neutrophils. Furthermore, some pathogens have evolved systems to thrive in the inflamed gut including limited metal (i.e., iron) resources. For example, intestinal inflammation leads to increased levels of interleukin (IL)-22. However, high levels of IL-22 leads to growth suppression of commensal bacteria, while promoting the growth and colonization of pathogens such as *Salmonella*. While IL-22 increases the levels of antimicrobial proteins such as Lcn2 and calprotectin which should limit iron availability, *Salmonella Thyphimurium* is able to overcome these conditions by the production of Lcn2 evasive or “stealth” siderophores. As these siderophores are not bound by Lcn2 this allows for the growth of pathogenic bacteria, but suppresses growth of species such as commensal Enterobacteriaceae, which produce siderophores that are recognized by Lcn2.

The principal conclusions arising from this review article are summarized in the accompanying Figs. 2 and 3. Specifically, the illustration in Fig. 2 highlights the main concept of iron-mediated modification of the gut microbiome being a potentially important determinant of metabolic consequences in the host. Fig. 3 depicts the various ways in which iron overload or deficiency can occur and subsequently re-shape the gut microbiome and alter barrier function. The impact of these changes on the host is dictated via cross talk mediated by gut-derived factors as shown in the figure. Ultimately, the clinical manifestation of this is the syndrome of dysmetabolic iron overload.

**Fig. 3.** Illustration of interplay between iron and microbiome. There are various ways in which iron overload or deficiency can occur (top-right). These scenarios can re-shape the gut microbiome and alter barrier function. Subsequently, cross talk mediated by gut-derived factors and peripheral metabolic tissues in the host are amended. The clinical manifestation of this is the syndrome of dysmetabolic iron overload. DIOS, dysmetabolic iron overload syndrome; SCFA, short chain-fatty acid.
CONCLUSIONS

The gut microbiome is now well recognized as a driver of metabolic health status. Well established yet less recognized is the strong correlation between iron overload or deficiency with adverse cardiometabolic outcomes. As indicated in this review, it is now understood that iron can have important effects on reshaping gut microbiome composition and on gut barrier function. For example, excess levels of iron can enhance the prevalence of pathogenic bacteria. The consequences of these changes are likely to be partly responsible for the association of iron status with MetS. This is an intriguing area of research which holds much promise and further studies are poised to add new mechanistic knowledge and identify suitable interventions.

REFERENCES

1. Jia W, Li H, Zhao L, Nicholson JK. Gut microbiota: a potential new territory for drug targeting. Nat Rev Drug Discov 2008;7:123-129. PubMed | CrossRef
2. Gomes AC, Bueno AA, de Souza RG, Mota JF. Gut microbiota, probiotics and diabetes. Nutr J 2014;13:60. PubMed | CrossRef
3. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. PLoS Biol 2016;14:e1002533. PubMed | CrossRef
4. Wu GD, Lewis JD, Hoffmann C, Chen YY, Knight R, Bittinger K, et al. Sampling and pyrosequencing methods for characterizing bacterial communities in the human gut using 16S sequence tags. BMC Microbiol 2010;10:206. PubMed | CrossRef
5. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, et al. Diversity of the human intestinal microbial flora. Science 2005;308:1635-1638. PubMed | CrossRef
6. Flint HJ, Duncan SH, Scott KP, Louis P. Interactions and competition within the microbial community of the human colon: links between diet and health. Environ Microbiol 2007;9:1101-1111. PubMed | CrossRef
7. Imbert M, Blondeau R. On the iron requirement of lactobacilli grown in chemically defined medium. Curr Microbiol 1998;37:64-66. PubMed | CrossRef
8. Weinberg ED. The Lactobacillus anomaly: total iron abstinence. Perspect Biol Med 1997;40:578-583. PubMed | CrossRef
9. Wu ZA, Wang HX. A systematic review of the interaction between gut microbiota and host health from a symbiotic perspective. SN Compr Clin Med 2019;1:224-235. CrossRef
10. Martens EC, Kelly AG, Tauxin AS, Brumer H. The devil lies in the details: How variations in polysaccharide fine-structure impact the physiology and evolution of gut microbes. J Mol Biol 2014;426:3853-3865. PubMed | CrossRef
11. Derrien M, Veiga P. Rethinking diet to aid human-microbe symbiosis. Trends Microbiol 2017;25:100-112. PubMed | CrossRef
12. Petersen C, Round IL. Defining dysbiosis and its influence on host immunity and disease. Cell Microbiol 2014;16:1024-1033. PubMed | CrossRef
13. Nishida A, Inoue R, Inatomi O, Bamba S, Naito Y, Andoh A. Gut microbiota in the pathogenesis of inflammatory bowel disease. Clin J Gastroenterol 2018;11:140. PubMed | CrossRef
14. Scher JU, Abramson SB. The microbiome and rheumatoid arthritis. Nat Rev Rheumatol 2011;7:569-578. PubMed | CrossRef

https://e-jla.org  https://doi.org/10.12997/jla.2021.10.2.160
15. Sun MF, Shen YQ. Dysbiosis of gut microbiota and microbial metabolites in Parkinson’s disease. Ageing Res Rev 2018;45:53-61.

16. Hao ML, Wang GY, Zuo XQ, Qu CJ, Yao BC, Wang DL. Gut microbiota: an overlooked factor that plays a significant role in osteoporosis. J Int Med Res 2019;47:4095-4103.

17. Honda K, Litman DR. The microbiome in infectious disease and inflammation. Annu Rev Immunol 2012;30:759-795.

18. Chen X, Devaraj S. Gut microbiome in obesity, metabolic syndrome, and diabetes. Curr Diab Rep 2018;18:129.

19. Baothman OA, Zamzami MA, Taher I, Abubaker J, Abu-Farha M. The role of gut microbiota in the development of obesity and diabetes. Lipids Health Dis 2016;15:108.

20. Ferreira RB, Gill N, Willing BP, Antunes LC, Russell SL, Croxen MA, et al. The intestinal microbiota plays a role in Salmonella-induced colitis independent of pathogen colonization. PLoS One 2011;6:e20338.

21. Sprinz H, Kundel DW, Dammin GJ, Horowitz RE, Schneider H, Formal SB. The response of the germfree guinea pig to oral bacterial challenge with Escherichia coli and Shigella flexneri. Am J Pathol 1961;39:681-695.

22. Zachar Z, Savage DC. Microbial interference and colonization of the murine gastrointestinal tract by Listeria monocytogenes. Infect Immun 1979;23:168-174.

23. Kamada N, Kim YG, Sham HP, Vallance BA, Puente JL, Martens EC, et al. Regulated virulence controls the ability of a pathogen to compete with the gut microbiota. Science 2012;336:1325-1329.

24. Quince C, Ijaz UZ, Loman N, Eren AM, Saulnier D, Russell J, et al. Extensive modulation of the fecal metagenome in children with Crohn’s disease during exclusive enteral nutrition. Am J Gastroenterol 2015;110:1718-1729.

25. Andoh A, Kuzuoka H, Tsujikawa T, Nakamura S, Hirai F, Suzuki Y, et al. Multicenter analysis of fecal microbiota profiles in Japanese patients with Crohn’s disease. J Gastroenterol 2012;47:1298-1307.

26. Liang D, Leung RK, Guan W, Au WW. Involvement of gut microbiome in human health and disease: brief overview, knowledge gaps and research opportunities. Gut Pathog 2018;10:3.

27. Mohajeri MH, Brummer RJ, Rastall RA, Weersma RK, Harmsen HJ, Faas M, et al. The role of the microbiome for human health: from basic science to clinical applications. Eur J Nutr 2018;57:1-14.

28. Brooks AW, Priya S, Blekhman R, Bordenstein SR. Gut microbiota diversity across ethnicities in the United States. PLoS Biol 2018;16:e2006842.

29. Tasnim N, Abulizi N, Pither J, Hart MM, Gibson DL. Linking the gut microbial ecosystem with the environment: Does gut health depend on where we live? Front Microbiol 2017;8:1935.

30. Deschasaux M, Bouter KE, Prodan A, Levin E, Groen AK, Herrera H, et al. Depicting the composition of gut microbiota in a population with varied ethnic origins but shared geography. Nat Med 2018;24:1526-1531.

31. He Y, Wu W, Zheng HM, Li P, McDonald D, Sheng HF, et al. Regional variation limits applications of healthy gut microbiome reference ranges and disease models. Nat Med 2018;24:1532-1535.

32. Galkin F, Mamoshina P, Aliper A, Putin E, Moskalev V, Gladyshev VN, et al. Human gut microbiome aging clock based on taxonomic profiling and deep learning. iScience 2020;23:101199.

33. Haro C, Rangel-Zúñiga OA, Alcalá-Díaz JF, Gómez-Delgado F, Pérez-Martínez P, Delgado-Lista J, et al. Intestinal microbiota is influenced by gender and body mass index. PLoS One 2016;11:e0154090.

34. Kasai C, Sugimoto K, Moritani I, Tanaka J, Oya Y, Inoue H, et al. Comparison of the gut microbiota composition between obese and non-obese individuals in a Japanese population, as analyzed by terminal
restriction fragment length polymorphism and next-generation sequencing. BMC Gastroenterol 2015;15:100.

35. Suzuki Y, Ikeda K, Sakuma K, Kawai S, Sawaki K, Asahara T, et al. Association between yogurt consumption and intestinal microbiota in healthy young adults differs by host gender. Front Microbiol 2017;8:847.

36. Vatanen T, Franzosa EA, Schwager R, Tripathi S, Arthur TD, Vehik K, et al. The human gut microbiome in early-onset type 1 diabetes from the TEDDY study. Nature 2018;562:589-594.

37. Bokulich NA, Chung J, Battaglia T, Henderson N, Jay M, Li H, et al. Antibiotics, birth mode, and diet shape microbiome maturation during early life. Sci Transl Med 2016;8:343ra82.

38. Santos-Marco JA, Haro C, Vega-Rojas A, Alcala-Diaz JF, Molina-Abril H, Leon-Acuña A, et al. Sex differences in the gut microbiota as potential determinants of gender predisposition to disease. Mol Nutr Food Res 2019;63:e1800870.

39. Levy G, Solt I. The human microbiome and gender medicine. Gend Genome 2018;2:123-127.

40. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, et al. A core gut microbiome in obese and lean twins. Nature 2009;457:480-484.

41. Goodrich JK, Waters JL, Poole AC, Sutter JL, Koren O, Blekhman R, et al. Human genetics shape the gut microbiome. Cell 2014;159:789-799.

42. Dąbrowska K, Witkiewicz W. Correlations of host genetics and gut microbiome composition. Front Microbiol 2016;7:1357.

43. Gomez A, Sharma AK, Mallott EK, Petrzolkova KJ, Jost Robinson CA, Yeoman CJ, et al. Plasticity in the human gut microbiome defies evolutionary constraints. MSphere 2019;4:e00271-19.

44. Singh RK, Chang HW, Yan D, Lee KM, Ucmak D, Wong K, et al. Influence of diet on the gut microbiome and implications for human health. J Transl Med 2017;15:73.

45. Voreades N, Kozil A, Weir TL. Diet and the development of the human intestinal microbiome. Front Microbiol 2014;5:494.

46. Rajoka MS, Shi J, Mehwish HM, Zhu J, Li Q, Shao D, et al. Interaction between diet composition and gut microbiota and its impact on gastrointestinal tract health. Food Sci Hum Well 2017;6:121-130.

47. Medeiros P, Bolick DT, Roche JK, Noronha F, Pinheiro C, Kolling GL, et al. The micronutrient zinc inhibits EAEC strain 042 adherence, biofilm formation, virulence gene expression, and epithelial cytokine responses benefiting the infected host. Virulence 2013;4:624-633.

48. Dostal A, Baumgartner J, Riesen N, Chassard C, Smuts CM, Zimmermann MB, et al. Effects of iron supplementation on dominant bacterial groups in the gut, faecal SCFA and gut inflammation: a randomised, placebo-controlled intervention trial in South African children. Br J Nutr 2014;112:547-556.

49. Dostal A, Lacroix C, Pham VT, Zimmermann MB, Del’homme C, Bernalier-Donadille A, et al. Iron supplementation promotes gut microbiota metabolic activity but not colitis markers in human gut microbiota-associated rats. Br J Nutr 2014;111:2135-2145.

50. Tan G, Cheng Z, Pang Y, Landry AP, Li J, Lu J, et al. Copper binding in IscA inhibits iron-sulphur cluster assembly in Escherichia coli. Mol Microbiol 2014;93:629-644.

51. Lopez CA, Skaar EP. The impact of dietary transition metals on host-bacterial interactions. Cell Host Microbe 2018;23:737-748.

52. Smits SA, Leach J, Sonnenburg ED, Gonzalez CG, Lichtman JS, Reid G. Seasonal cycling in the gut microbiome of the Hadza hunter-gatherers of Tanzania. Science 2017;357:802-806.
53. Gentile CL, Weir TL. The gut microbiota at the intersection of diet and human health. Science 2018;362:776-780.

54. Dahl WJ, Rivero Mendoza D, Lambert JM. Diet, nutrients and the microbiome. Prog Mol Biol Transl Sci 2020;171:237-263.

55. Craig WJ. Nutrition concerns and health effects of vegetarian diets. Nutr Clin Pract 2010;25:613-620.

56. Dinu M, Abbate R, Gensini GF, Casini A, Sofi F. Vegetarian, vegan diets and multiple health outcomes: a systematic review with meta-analysis of observational studies. Crit Rev Food Sci Nutr 2017;57:3640-3649.

57. Lee Y, Park K. Adherence to a vegetarian diet and diabetes risk: a systematic review and meta-analysis of observational studies. Nutrients 2017;9:603.

58. Pilis W, Stec K, Zych M, Pilis A. Health benefits and risk associated with adopting a vegetarian diet. Rocz Panstw Zakl Hig 2014;65:9-14.

59. Trefflich I, Jabakhanji A, Menzel J, Blaut M, Michelsen A, Lampen A, et al. Is a vegan or a vegetarian diet associated with the microbiota composition in the gut? Results of a new cross-sectional study and systematic review. Crit Rev Food Sci Nutr 2020;60:2990-3004.

60. Panda S, El khader I, Casellas F, López Vivancos J, García Corn M, Santiago A, et al. Short-term effect of antibiotics on human gut microbiota. PLoS One 2014;9:e95476.

61. Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. Proc Natl Acad Sci U S A 2011;108 Suppl 1:4554-4561.

62. Imhann F, Vich Vila A, Bonder MJ, Lopez Manosalva AG, Koonen DP, Fu J, et al. The influence of proton pump inhibitors and other commonly used medication on the gut microbiota. Gut Microbes 2017;8:351-358.

63. Lin IC, Bergey M, Sonnad SS, Serletti JM, Wu LC. Management of the ptotic or hypertrophic breast in immediate autologous breast reconstruction: a comparison between the wise and vertical reduction patterns for mastectomy. Ann Plast Surg 2013;70:264-270.

64. Tomova A, Bukowsky AJ, Rembert E, Yonas W, Alwarith J, Barnard ND, et al. The effects of vegetarian and vegan diets on gut microbiota. Front Nutr 2019;6:47.

65. De Angelis M, Ferrocino I, Calabrese FM, De Filippis F, Cavallo N, Siragusa S, et al. Diet influences the functions of the human intestinal microbiome. 2020;10:4247.

66. De Filippis F, Pellegrini N, Vannini L, Jeffery IB, La Storia A, Laghi I, et al. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. Gut 2016;65:1812-1821.

67. Salas-Salvadó J, Bulló M, Estruch R, Ros E, Covas MI, Ibarrola-Jurado N, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. Ann Intern Med 2014;160:1-10.

68. Widmer RJ, Flammer AJ, Lerman LO, Lerman A. The Mediterranean diet, its components, and cardiovascular disease. Am J Med 2015;128:229-238.

69. Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. Am J Clin Nutr 2010;92:1189-1196.

70. Pastori D, Carnevale R, Nocella C, Novo M, Santulli M, Cammisotto V, et al. Gut-derived serum lipopolysaccharide is associated with enhanced risk of major adverse cardiovascular events in atrial fibrillation: effect of adherence to Mediterranean diet. J Am Heart Assoc 2017;6:e005784.

71. García-Mantrana I, Selma-Royo M, Alcantara C, Collado MC. Shifts on gut microbiota associated to Mediterranean diet adherence and specific dietary intakes on general adult population. Front Microbiol 2018;9:890.
72. Meslier V, Laiola M, Roager HM, De Filippis F, Roume H, Quinquis B, et al. Mediterranean diet intervention in overweight and obese subjects lowers plasma cholesterol and causes changes in the gut microbiome and metabolome independently of energy intake. Gut 2020;69:1258-1268.

73. Zhou L, Zhang M, Wang Y, Dorfman RG, Liu H, Yu T, et al. *Faecalibacterium prausnitzii* produces butyrate to maintain Th17/Treg balance and to ameliorate colorectal colitis by inhibiting histone deacetylase 1. Inflamm Bowel Dis 2018;24:1926-1940.

74. Zinöcker MK, Lindseth IA. The western diet-microbiome-host interaction and its role in metabolic disease. Nutrients 2018;10:365.

75. Hehemann JH, Correc G, Barbeyron T, Helbert W, Czjzek M, Michel G. Transfer of carbohydrate-active enzymes from marine bacteria to Japanese gut microbiota. Nature 2010;464:908-912.

76. De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc Natl Acad Sci U S A 2010;107:14691-14696.

77. Shikany JM, Demmer RT, Johnson AJ, Fino NF, Meyer K, Ensrud KE, et al. Association of dietary patterns with the gut microbiota in older, community-dwelling men. Am J Clin Nutr 2019;100:1003-1014.

78. Whisner CM, Maldonado J, Dente B, Krajmalnik-Brown R, Bruening M. Diet, physical activity and screen time but not body mass index are associated with the gut microbiome of a diverse cohort of college students living in university housing: a cross-sectional study. BMC Microbiol 2018;18:210.

79. Schnorr SL, Candela M, Rampelli S, Centanni M, Consolandi C, Basaglia G, et al. Gut microbiome of the Hadza hunter-gatherers. Nat Commun 2014;5:3654.

80. Clemente JC, Pehrsson EC, Blaser MJ, Sandhu K, Gao Z, Wang B, et al. The microbiome of uncontacted Amerindians. Sci Adv 2015;1:e1500183.

81. Obregon-Tito AJ, Tito RY, Metcalf J, Sankaranarayanan K, Clemente JC, Ursell LK, et al. Subsistence strategies in traditional societies distinguish gut microbiomes. Nat Commun 2015;6:6505.

82. Martinez I, Stegen JC, Maldonado-Gómez MX, Eren AM, Siba PM, Greenhill AR, et al. The gut microbiota of rural papua new guineans: composition, diversity patterns, and ecological processes. Cell Reports 2015;11:527-538.

83. Macfarlane GT, Macfarlane S. Bacteria, colonic fermentation, and gastrointestinal health. J AOAC Int 2012;95:50-60.

84. So D, Whelan K, Ross M, Morrison M, Holtmann G, Kelly JT, et al. Dietary fiber intervention on gut microbiota composition in healthy adults: a systematic review and meta-analysis. Am J Clin Nutr 2018;107:965-983.

85. Kamarul Zaman M, Chin KF, Rai V, Majid HA. Fiber and prebiotic supplementation in enteral nutrition: a systematic review and meta-analysis. World J Gastroenterol 2015;21:5372-5381.

86. Martinez I, Kim J, Duffy PR, Schlegel VL, Walter J. Resistant starches types 2 and 4 have differential effects on the composition of the fecal microbiota in human subjects. PLoS One 2010;5:e15046.

87. Do MH, Lee E, Oh MJ, Kim Y, Park HY. High-glucose or -fructose diet cause changes of the gut microbiota and metabolic disorders in mice without body weight change. Nutrients 2018;10:761.

88. Jang C, Hui S, Lu W, Cowan AJ, Morschel RJ, Lee G, et al. The small intestine converts dietary fructose into glucose and organic acids. Cell Metab 2018;27:351-361.e3.

89. Coelho OG, Cândido FG, Alfenas RC. Dietary fat and gut microbiota: mechanisms involved in obesity control. Crit Rev Food Sci Nutr 2019;59:3045-3053.
90. Menni C, Zierer J, Pallister T, Jackson MA, Long T, Mohney RP, et al. Omega-3 fatty acids correlate with gut microbiome diversity and production of N-carbamylglutamate in middle aged and elderly women. Sci Rep 2017;7:11079.

PUBMED | CROSSREF

91. Caesar R, Tremaroli V, Kovatcheva-Datchary P, Cani PD, Bäckhed F. CROSsalk between gut microbiota and dietary lipids aggravates WAT inflammation through TLR signaling. Cell Metab 2015;22:658-668.

PUBMED | CROSSREF

92. Bäckhed F, Mancheester IK, Semenkovich CF, Gordon JL. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. Proc Natl Acad Sci U S A 2007;104:979-984.

PUBMED | CROSSREF

93. Rabot S, Membrez M, Bruneau A, Gérard P, Harach T, Moser M, et al. Germ-free C57BL/6J mice are resistant to high-fat-diet-induced insulin resistance and have altered cholesterol metabolism. FASEB J 2010;24:4948-4959.

PUBMED | CROSSREF

94. Ding S, Chi MM, Scull BP, Rigby R, Schwerbrock NM, Magness S, et al. High-fat diet: bacteria interactions promote intestinal inflammation which precedes and correlates with obesity and insulin resistance in mouse. PLoS One 2010;5:e12191.

PUBMED | CROSSREF

95. Bäckhed F, Ding H, Wang T, Hooper LV, Kohoky G, Nagy A, et al. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci U S A 2004;101:15718-15723.

PUBMED | CROSSREF

96. Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, Nageshwar Reddy D. Role of the normal gut microbiota. World J Gastroenterol 2015;21:8787-8803.

PUBMED | CROSSREF

97. Chakraborti CK. New-found link between microbiota and obesity. World J Gastrointest Pathophysiol 2015;6:110-119.

PUBMED | CROSSREF

98. Rahat-Rozenbloom S, Fernandes J, Gloor GB, Wolever TM. Evidence for greater production of colonic short-chain fatty acids in overweight than lean humans. Int J Obes 2014;38:1525-1531.

PUBMED | CROSSREF

99. Shortt C, Hasselwander O, Meynier A, Nauta A, Fernández EN, Putz P, et al. Systematic review of the effects of the intestinal microbiota on selected nutrients and non-nutrients. Eur J Nutr 2018;57:25-49.

PUBMED | CROSSREF

100. Jumpertz R, Le DS, Turnbaugh PJ, Trinidad C, Bogardus C, Gordon JI, et al. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. Am J Clin Nutr 2011;94:58-65.

PUBMED | CROSSREF

101. Turnbaugh PJ, Ley RE, Mahowal MA, Magrini V, Mardis ER, Gordon JL. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 2006;444:1027-1031.

PUBMED | CROSSREF

102. Stephens RW, Arhire L, Covasa M. Gut microbiota: from microorganisms to metabolic organ influencing obesity. Obesity (Silver Spring) 2018;26:801-809.

PUBMED | CROSSREF

103. Schwieritz A, Taras D, Schäfer K, Beijer S, Bos NA, Donus C, et al. Microbiota and SCFA in lean and overweight healthy subjects. Obesity (Silver Spring) 2010;18:190-195.

PUBMED | CROSSREF

104. Million M, Lagier JC, Yahav D, Paul M. Gut bacterial microbiota and obesity. Clin Microbiol Infect 2013;19:305-313.

PUBMED | CROSSREF

105. Vrieze A, Van Nood E, Holleman F, Salojärvi J, Kootte RS, Bartelsman JF, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology 2012;143:913-916.e7.

PUBMED | CROSSREF

106. Barreto FM, Colado Simão AN, Morimoto HK, Battisti Lozovoy MA, Dichi I, Helena da Silva Miguelina L. Beneficial effects of Lactobacillus plantarum on glycemia and homocysteine levels in postmenopausal women with metabolic syndrome. Nutrition 2014;30:939-942.

PUBMED | CROSSREF

107. Lee E, Jung SR, Lee SY, Lee NK, Paik HD, Lim SI. Lactobacillus plantarum strain Ln4 attenuates diet-induced obesity, insulin resistance, and changes in hepatic mRNA levels associated with glucose and lipid metabolism. Nutrients 2018;10:643.

PUBMED | CROSSREF
108. Uchinaka A, Azuma N, Mizumoto H, Nakano S, Minamiya M, Yoneda M, et al. Anti-inflammatory effects of heat-killed *Lactobacillus plantarum* L-137 on cardiac and adipose tissue in rats with metabolic syndrome. Sci Rep 2018;8:8156.

109. Lim MY, You HI, Yoon HS, Kwon B, Lee JY, Lee S, et al. The effect of heritability and host genetics on the gut microbiota and metabolic syndrome. Gut 2017;66:1031-1038.

110. Sommer P, Sweeney G. Functional and mechanistic integration of infection and the metabolic syndrome. Korean Diabetes J 2010;34:71-76.

111. Paganini D, Zimmermann MB. The effects of iron fortification and supplementation on the gut microbiome and diarrhea in infants and children: a review. Am J Clin Nutr 2017;106:1688S-1693S.

112. Chiappe M, Giannelli G. Immune cells and microbiota response to iron starvation. Front Med (Lausanne) 2018;5:109.

113. Yilmaz B, Li H. Gut microbiota and iron: the crucial actors in health and disease. Pharmaceuticals (Basel) 2018;11:98.

114. Rask-Madsen C, Kahn CR. Tissue-specific insulin signaling, metabolic syndrome, and cardiovascular disease. Arterioscler Thromb Vasc Biol 2012;32:2052-2059.

115. Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among U.S. adults. Diabetes Care 2004;27:2444-2449.

116. Sperling LS, Mechanick JI, Neeland II, Herrick CJ, Després JP, Ndumele CE, et al. The CardioMetabolic Health Alliance: working toward a new care model for the metabolic syndrome. J Am Coll Cardiol 2015;66:1050-1067.

117. Lee DH, Liu DY, Jacobs DR Jr, Shin HR, Song K, Lee IK, et al. Common presence of non-transferrin-bound iron among patients with type 2 diabetes. Diabetes Care 2006;29:1090-1095.

118. Aljwaid H, White DL, Collard KJ, Moody AJ, Pinkney JH. Non-transferrin-bound iron is associated with biomarkers of oxidative stress, inflammation and endothelial dysfunction in type 2 diabetes. J Diabetes Complications 2015;29:943-949.

119. Bozzini C, Girelli D, Olivieri O, Martinelli N, Bassi A, De Matteis G, et al. Prevalence of body iron excess in the metabolic syndrome. Diabetes Care 2005;28:2064-2063.

120. Fernández-Real JM, Ricart-Engel W, Arroyo E, Balançà R, Casamitjana-Abella R, Cabrero D, et al. Serum ferritin as a component of the insulin resistance syndrome. Diabetes Care 1998;21:62-68.

121. Mendler MH, Turlin B, Moirand R, Jouanolle AM, Sapey T, Guyader D, et al. Insulin resistance-associated hepatic iron overload. Gastroenterology 1999;117:1155-1163.

122. Deugnier Y, Bardou-Jacquet É, Lainé F. Dysmetabolic iron overload syndrome (DIOS). Presse Med 2017;46:e306-e311.

123. Sachinidis A, Doumas M, Imprialos K, Stavropoulos K, Katsumiordou A, Athyros VG. Dysmetabolic iron overload in metabolic syndrome. Curr Pharm Des 2020;26:1019-1024.

124. Buret AG, Motta JP, Allain T, Ferraz I, Wallace JL. Pathobiont release from dysbiotic gut microbiota biofilms in intestinal inflammatory diseases: a role for iron? J Biomed Sci 2019;26:1.

125. Ortiz-Flores AE, Martínez-García MA, Nattero-Chávez L, Álvarez-Blasco F, Fernández-Durán E, Quintero-Tobar A, et al. Iron overload in functional hyperandrogenism: in a randomized trial, bloodletting does not improve metabolic outcomes. J Clin Endocrinol Metab 2021;dgaa978.
126. Behboudi-Gandevani S, Abtahi H, Saadat N, Tohidi M, Ramezani Tehrani F. Effect of phlebotomy versus oral contraceptives containing cyproterone acetate on the clinical and biochemical parameters in women with polycystic ovary syndrome: a randomized controlled trial. J Ovarian Res 2019;12:78.

127. Baye E, Utkopec I, de Courten MP, Kurdiya T, Krumpolec P, Fernández-Real JM, et al. Carnosine supplementation reduces plasma soluble transferrin receptor in healthy overweight or obese individuals: a pilot randomised trial. Amino Acids 2019;51:73-81.

128. Suárez-Ortegón MF, Ensaldo-Carrasco E, Shi T, McLachlan S, Fernández-Real JM, Wild SH. Ferritin, metabolic syndrome and its components: a systematic review and meta-analysis. Atherosclerosis 2018;275:97-106.

129. Chuansumrit A, Pengpis P, Mahachoklertwattana P, Sirachainan N, Poomthavorn P, Sungkarat W, et al. Effect of iron chelation therapy on glucose metabolism in non-transfusion-dependent thalassaemia. Acta Haematol 2017;137:20-26.

130. Lainé F, Ruivard M, Loustaud-Ratti V, Bonnet F, Calès P, Bardou-Jacquet E, et al. Metabolic and hepatic effects of bloodletting in dysmetabolic iron overload syndrome: a randomized controlled study in 274 patients. Hepatology 2017;65:465-474.

131. Adams LA, Crawford DH, Stuart K, House MJ, St Pierre TG, Webb M, et al. The impact of phlebotomy in nonalcoholic fatty liver disease: a prospective, randomized, controlled trial. Hepatology 2015;61:1555-1564.

132. Valenti L, Fracanzani AL, Dongiovanni P, Rovida S, Rametta R, Fatta E, et al. A randomized trial of iron depletion in patients with nonalcoholic fatty liver disease and hyperferritinemia. World J Gastroenterol 2014;20:3002-3010.

133. Beaton MD, Chakrabarti S, Levstik M, Speechley M, Marotta P, Adams P. Phase II clinical trial of phlebotomy for non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2013;37:720-729.

134. Houschyar KS, Lüdtke R, Dobos GJ, Kalus U, Broecker-Preuss M, Rampp T, et al. Effects of phlebotomy-induced reduction of body iron stores on metabolic syndrome: results from a randomized clinical trial. BMC Med 2012;10:54.

135. Schümann K. Safety aspects of iron in food. Ann Nutr Metab 2001;45:91-101.

136. Comerford KB. Recent developments in multivitamin/mineral research. Adv Nutr 2013;4:644-656.

137. Stoffel NU, Cercamondi CI, Brittenham G, Zeder C, Geurts-Moespot AJ, Swinkels DW, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. Lancet Haematol 2017;4:e524-e533.

138. Busserolles J, Mazur A, Gueux E, Rayssiguier Y. Metabolic syndrome in the rat: females are protected against the pro-oxidant effect of a high sucrose diet. Exp Biol Med (Maywood) 2002;227:837-842.

139. Chan YK, Sung HK, Sweeney G. Iron metabolism and regulation by neutrophil gelatinase-associated lipocalin in cardiomyopathy. Clin Sci (Lond) 2015;129:851-862.

140. Sanchez KK, Chen GY, Schieber AMP, Redford SE, Shokhirev MN, Leblanc M, et al. Cooperative metabolic adaptations in the host can favor asymptomatic infection and select for attenuated virulence in an enteric pathogen. Cell 2018;175:146-158.e15.

141. Wongjaikam S, Kumfu S, Chattipakorn SC, Fucharoen S, Chattipakorn N. Current and future treatment strategies for iron overload cardiomyopathy. Eur J Pharmacol 2015;765:86-93.
143. Rajpathak SN, Crandall JP, Wylie-Rosett J, Kabat GC, Rohan TE, Hu FB. The role of iron in type 2 diabetes in humans. Biochim Biophys Acta 2009;1790:671-681.

144. Murali AR, Gupta A, Brown K. Systematic review and meta-analysis to determine the impact of iron depletion in dysmetabolic iron overload syndrome and non-alcoholic fatty liver disease. Hepatol Res 2018;48:E30-E41.

145. Aigner E, Feldman A, Datz C. Obesity as an emerging risk factor for iron deficiency. Nutrients 2014;6:3587-3600.

146. Fernández-Real JM, McClain D, Manco M. Mechanisms linking glucose homeostasis and iron metabolism toward the onset and progression of type 2 diabetes. Diabetes Care 2015;38:2169-2176.

147. Taher AT, Weatherall DJ, Cappellini MD. Thalassaemia. Lancet 2018;391:155-167.

148. Abdulsada SH, Farag AH, Kamil H, Abdul-Rudha S, Hussein AA. Metabolic syndrome in Iraqi female patients with major β-thalassemia. Al-Mustansiriyah J Sci 2016;27:39-42.

149. Saki F, Bahadori R, Kashkooli NM, Jazayeri A, Ghahremani N, Omrani GH. Prevalence of metabolic syndrome in beta thalassemia major adolescents in southern Iran: a cross-sectional study. Int J Diabetes Dev Ctries 2019;39:444-450.

150. Azami M, Sharifi A, Norozi S, Mansouri A, Sayehmiri K. Prevalence of diabetes, impaired fasting glucose and impaired glucose tolerance in patients with thalassemia major in Iran: a meta-analysis study. Caspian J Intern Med 2017;8:1-15.

151. Li MJ, Peng SS, Lu MY, Chang HH, Yang YL, Jou ST, et al. Diabetes mellitus in patients with thalassemia major. Pediatr Blood Cancer 2014;61:20-24.

152. Gamberini MR, Fortini M, De Sanctis V, Gilli G, Testa MR. Diabetes mellitus and impaired glucose tolerance in thalassaemia major: incidence, prevalence, risk factors and survival in patients followed in the Ferrara Center. Pediatr Endocrinol Rev 2004;2 Suppl 2:285-291.

153. Levi S, Rovida E. The role of iron in mitochondrial function. Biochim Biophys Acta 2009;1790:629-636.

154. Hesselin MK, Schrauwen-Hinderling V, Schrauwen P. Skeletal muscle mitochondria as a target to prevent or treat type 2 diabetes mellitus. Nat Rev Endocrinol 2016;12:633-645.

155. Visitchanakun P, Saisorn W, Wongphoom J, Chatthanathon P, Somboonna N, Svasti S, et al. Gut leakage enhances sepsis susceptibility in iron-overloaded β-thalassemia mice through macrophage hyperinflammatory responses. Am J Physiol Gastrointest Liver Physiol 2020;318:G966-G979.

156. Pantopoulos K. Inherited disorders of iron overload. Front Nutr 2018;5:103.

157. Allen KJ, Gurrin LC, Constantine CC, Osborne NJ, Delatycki MB, Nicoll AJ, et al. Iron-overload-related disease in HFE hereditary hemochromatosis. N Engl J Med 2008;358:221-230.

158. Utzschneider KM, Kowdle KV. Hereditary hemochromatosis and diabetes mellitus: implications for clinical practice. Nat Rev Endocrinol 2010;6:26-33.

159. Fillebeen C, Lam NH, Chow S, Botta A, Sweeney G, Pantopoulos K. Regulatory connections between iron and glucose metabolism. Int J Mol Sci 2020;21:7773.

160. Sivaprakasam S, Ristic B, Mudaliar N, Hamood AN, Colmer-Hamood J, Wachtel MS, et al. Hereditary hemochromatosis promotes colitis and colon cancer and causes bacterial dysbiosis in mice. Biochem J 2020;477:3867-3883.

161. Gabrielsen JS, Gao Y, Simcox JA, Huang J, Thorup D, Jones D, et al. Adipocyte iron regulates adiponectin and insulin sensitivity. J Clin Invest 2012;122:3529-3540.
162. Symeonidis A, Marangos M. Iron and microbial growth. In: Priti R, editor. Insight and control of Infectious disease in global scenario. London: IntechOpen; 2012. p.289-330.

PUBMED | CROSSREF

163. Andrews SC, Robinson AK, Rodriguez-Quiñones F. Bacterial iron homeostasis. FEMS Microbiol Rev 2003;27:215-237.

PUBMED | CROSSREF

164. Golonka R, Yeoh BS, Vijay-Kumar M. The iron tug-of-war between bacterial siderophores and innate immunity. J Innate Immun 2019;11:249-262.

PUBMED | CROSSREF

165. Rocha ER, de Uzeda M, Brock JH. Effect of ferric and ferrous iron chelators on growth of Bacteroides fragilis under anaerobic conditions. FEMS Microbiol Lett 1991;68:45-50.

PUBMED | CROSSREF

166. Otto BR, Sparrius M, Verweij-van Vught AM, MacLaren DM. Iron-regulated outer membrane protein of Bacteroides fragilis involved in heme uptake. Infect Immun 1990;58:3954-3958.

PUBMED | CROSSREF

167. Carpenter C, Payne SM. Regulation of iron transport systems in Enterobacteriaceae in response to oxygen and iron availability. J Inorg Biochem 2014;133:110-117.

PUBMED | CROSSREF

168. Hoppe M, Oanning G, Hulthén L. Freeze-dried Lactobacillus plantarum 299v increases iron absorption in young females. Double isotope sequential single-blind studies in menstruating women. PLoS One 2017;12:e0189141.

PUBMED | CROSSREF

169. Skrypnik K, Bogdański P, Schmidt M, Suliburska J. The effect of multispecies probiotic supplementation on iron status in rats. Biol Trace Elem Res 2019;192:234-243.

PUBMED | CROSSREF

170. Andrews SC. Making DNA without iron - induction of a manganese-dependent ribonucleotide reductase in response to iron starvation. Mol Microbiol 2011;80:286-289.

PUBMED | CROSSREF

171. Utley JR. Pathophysiology of cardiopulmonary bypass: current issues. J Card Surg 1990;5:177-189.

PUBMED | CROSSREF

172. Hedestedt L, Gorton L, Pankratova G. Two routes for extracellular electron transfer in Enterococcus faecalis. J Bacteriol 2020;202: e00725-19.

PUBMED | CROSSREF

173. Mey AR, Wyckoff EE, Kanukurthy V, Fisher CR, Payne SM. Iron and fur regulation in Vibrio cholerae and the role of fur in virulence. Infect Immun 2005;73:8167-8178.

PUBMED | CROSSREF

174. Kramer J, Özkaya Ö, Kümmerli R. Bacterial siderophores in community and host interactions. Nat Rev Microbiol 2020;18:152-163.

PUBMED | CROSSREF

175. Grenier D, Tanabe S. Transferrin as a source of iron for Campylobacter rectus. J Oral Microbiol 2011;3:3.

PUBMED | CROSSREF

176. Zhang XH, Austin B. Haemolysins in Vibrio species. J Appl Microbiol 2005;98:1011-1019.

PUBMED | CROSSREF

177. Dekker Nitert M, Gomez-Arango LF, Barrett HL, McIntyre HD, Anderson GI, Frazer DM, et al. Iron supplementation has minor effects on gut microbiota composition in overweight and obese women in early pregnancy. Br J Nutr 2018;120:283-289.

PUBMED | CROSSREF

178. Alexeev EE, He X, Slupsky CM, Lönn erdal B. Effects of iron supplementation on growth, gut microbiota, metabolomics and cognitive development of rat pups. PLoS One 2017;12:e0179713.

PUBMED | CROSSREF

179. Perez-Lopez A, Behnsen J, Nuccio SP, Raffatellu M. Mucosal immunity to pathogenic intestinal bacteria. Nat Rev Immunol 2016;16:135-148.

PUBMED | CROSSREF

180. Sassone-Corsi M, Nuccio SP, Liu H, Hernandez D, Vu CT, Takahashi AA, et al. Microcins mediate competition among Enterobacteriaceae in the inflamed gut. Nature 2016;540:280-283.

PUBMED | CROSSREF

181. Cassat JE, Skaar EP. Iron in infection and immunity. Cell Host Microbe 2013;13:509-519.

PUBMED | CROSSREF
182. Parmanand BA, Kellingray L, Le Gall G, Basit AW, Fairweather-Tait S, Narbad A. A decrease in iron availability to human gut microbiome reduces the growth of potentially pathogenic gut bacteria; an in vitro colonic fermentation study. J Nutr Biochem 2019;67:20-27.

183. Phipps O, Al-Hassi HO, Quraishi MN, Kumar A, Brookes MJ. Influence of iron on the gut microbiota in colorectal cancer. Nutrients 2020;12:2512.

184. Fang S, Zhuo Z, Yu X, Wang H, Feng J. Oral administration of liquid iron preparation containing excess iron induces intestine and liver injury, impairs intestinal barrier function and alters the gut microbiota in rats. J Trace Elem Med Biol 2018;47:12-20.

185. Lönnerdal B. Excess iron intake as a factor in growth, infections, and development of infants and young children. Am J Clin Nutr 2017;106:1681S-1687S.

186. Zimmermann MB, Chassard C, Rohner F, N’goran EK, Nindjin C, Dostal A, et al. The effects of iron fortification on the gut microbiota in African children: a randomized controlled trial in Cote d’Ivoire. Am J Clin Nutr 2010;92:1406-1415.

187. Rivera-Chávez F, Mekalanos JJ. Cholera toxin promotes pathogen acquisition of host-derived nutrients. Nature 2019;572:244-248.

188. Li N, Zhang C, Li B, Liu X, Huang Y, Xu S, et al. Unique iron coordination in iron-chelating molecule vibriobactin helps *Vibrio cholerae* evade mammalian siderocalin-mediated immune response. J Biol Chem 2012;287:8912-8919.

189. Askoura M, Youns M, Halim Hegazy WA. Investigating the influence of iron on *Campylobacter jejuni* transcriptome in response to acid stress. Microb Pathog 2020;138:103777.

190. Saha R, Saha N, Donofrio RS, Bestervelt LL. Microbial siderophores: a mini review. J Basic Microbiol 2013;53:303-317.

191. Behnsen J, Raffatellu M. Siderophores: more than stealing iron. mBio 2016;7:e01906-16.

192. Flo TH, Smith KD, Sato S, Rodriguez DJ, Holmes MA, Strong RK, et al. Lipocalin 2 mediates an innate immune response to bacterial infection by sequestering iron. Nature 2004;432:917-921.

193. Zhao H, Konishi A, Fujita Y, Yagi M, Ohata K, Aoshi T, et al. Lipocalin 2 bolsters innate and adaptive immune responses to blood-stage malaria infection by reinforcing host iron metabolism. Cell Host Microbe 2012;12:705-716.

194. Eller K, Schroll A, Banas M, Kirsch AH, Huber JM, Nairz M, et al. Lipocalin-2 expressed in innate immune cells is an endogenous inhibitor of inflammation in murine nephrotoxic serum nephritis. PLoS One 2013;8:e67693.

195. Bachman MA, Miller VL, Weiser JN. Mucosal lipocalin 2 has pro-inflammatory and iron-sequestering effects in response to bacterial enterobactin. PLoS Pathog 2009;5:e1000622.

196. Halaas O, Steigedal M, Haug M, Awuh JA, Ryan L, Brech A, et al. Intracellular *Mycobacterium avium* intersect transferrin in the Rab11’ recycling endocytic pathway and avoid lipocalin 2 trafficking to the lysosomal pathway. J Infect Dis 2010;201:783-792.

197. Holden VI, Lenio S, Kuick R, Ramakrishnan SK, Shah YM, Bachman MA. Bacterial siderophores that evade or overwhelm lipocalin 2 induce hypoxia inducible factor Iα and proinflammatory cytokine secretion in cultured respiratory epithelial cells. Infect Immun 2014;82:3826-3836.

198. Bachman MA, Lenio S, Schmidt L, Oyler JE, Weiser JN. Interaction of lipocalin 2, transferrin, and siderophores determines the replicative niche of *Klebsiella pneumoniae* during pneumonia. mBio 2012;3:e00224-11.
199. Jang Y, Lee JH, Wang Y, Sweeney G. Emerging clinical and experimental evidence for the role of lipocalin-2 in metabolic syndrome. Clin Exp Pharmacol Physiol 2012;39:194-199.

200. Taube A, Schlich R, Sell H, Eckardt K, Eckel I. Inflammation and metabolic dysfunction: links to cardiovascular diseases. Am J Physiol Heart Circ Physiol 2012;302:H2148-H2165.

201. Wang Y, Lam KS, Kraegen EW, Sweeney G, Zhang J, Tso AW, et al. Lipocalin-2 is an inflammatory marker closely associated with obesity, insulin resistance, and hyperglycemia in humans. Clin Chem 2007;53:34-41.

202. Choi KM, Lee JS, Kim EJ, Baik SH, Seo HS, Choi DS, et al. Implication of lipocalin-2 and visfatin levels in patients with coronary heart disease. Eur J Endocrinol 2008;158:203-207.

203. Law IK, Xu A, Lam KS, Berger T, Mak TW, Vanhoutte PM, et al. Lipocalin-2 deficiency attenuates insulin resistance associated with aging and obesity. Diabetes 2010;59:872-882.

204. Guo H, Jin D, Zhang Y, Wright W, Bazuline M, Brockman DA, et al. Lipocalin-2 deficiency impairs thermogenesis and potentiates diet-induced insulin resistance in mice. Diabetes 2010;59:1376-1385.

205. Fülöp P, Lőrincz H, Somodi S, Harangi M, Seres I, Paragh G. Associations of lipocalin 2 with markers of inflammation and oxidant status in obese non-diabetic patients. Atherosclerosis 2016;252:e69.

206. Ito M, Doi K, Takahashi M, Koyama K, Myojo M, Hosoya Y, et al. Plasma neutrophil gelatinase-associated lipocalin predicts major adverse cardiovascular events after cardiac care unit discharge. J Cardiol 2016;67:184-191.

207. Wu G, Li H, Fang Q, Jiang S, Zhang L, Zhang J, et al. Elevated circulating lipocalin-2 levels independently predict incident cardiovascular events in men in a population-based cohort. Arterioscler Thromb Vasc Biol 2014;34:2457-2464.

208. Latouche C, El Moghrabi S, Messaoudi S, Nguyen Dinh Cat A, Hernandez-Diaz I, Alvarez de la Rosa D, et al. Neutrophil gelatinase-associated lipocalin is a novel mineralocorticoid target in the cardiovascular system. Hypertension 2012;59:966-972.

209. Hemdahl AL, Gabrielsen A, Zhu C, Eriksson U, Kastrup J, et al. Expression of neutrophil gelatinase-associated lipocalin in atherosclerosis and myocardial infarction. Arterioscler Thromb Vasc Biol 2006;26:136-142.

210. Marques FZ, Prestes PR, Byars SG, Ritchie SC, Würtz P, Patel SK, et al. Experimental and human evidence for lipocalin-2 (neutrophil gelatinase-associated lipocalin [NGAL]) in the development of cardiac hypertrophy and heart failure. J Am Heart Assoc 2017;6:e005971.

211. Falke P, Elneihoum AM, Ohlsson K. Leukocyte activation: relation to cardiovascular mortality after cerebrovascular ischemia. Cerebrovasc Dis 2000;10:97-101.

212. Sung HK, Chan YK, Han M, Jahng JW, Song E, Danielson E, et al. Lipocalin-2 (NGAL) attenuates autophagy to exacerbate cardiac apoptosis induced by myocardial ischemia. J Cell Physiol 2017;232:2125-2134.