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Review

Iron Reshapes the Gut Microbiome and Host Metabolism

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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 appoximately 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).[4-6] Of these types of bacteria the most common phyla within the human gut is that of Bacteroidetes and Firmicutes.[7,8]

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.[9] This includes nutrient extraction through the use of bacterial derived digestive enzymes and vitamin synthesis.[10,11] A delicate equilibrium between gut bacteria, the intestinal epithelial barrier, and host immunity to maintain mutalism or commensalism. A disruption in this host barrier/immune-microbe equilibrium can result in a change in the composition of the micorbial communites that is signaificantly different from normal variation in the micobiome, which is often called dysbiosis.[12] 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,[13] rhematoid arthritis,[14] Parkinsons,[15] osteoporosis,[16] susceptibilty to infectious disease[17] and metabolic disease.[18]

While many of the roles of the gut microbiome have yet to be elucidated, several beneficial effects have been discovered.[7,8] The gut microbiome plays an important role in digestion and vitamin synthesis.[19] 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*.[20-23] 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.[24,25] 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.[26,27]

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.[28,29] 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.[30] 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.[31] Other studies have also found that both age[32] and gender[33-35] 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.[36,37] 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.[38,39]

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

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co-variation.[40] 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.[41] 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.[42] Recently studies have suggested that diet may have a more substantial impact on the gut microbiome than genetic factors[43] and can significantly influence and alter its composition.[44,45] This mainly depends on macronutirents such as fat and carbohydrate content,[44,46] but also on metals such as iron, copper and zinc.[47-51]

GUT MICROBIOME AND DIET

Diet is an important factor that can rapdily alter the composition of the gut microbiota, and since mammals are constantly eating, diet continiously shapes the alpha and beta diversity of intestinal bacterial communities.[44,52] 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.[53] Studies demonstrate that diet can have both acute and long-term effects on the composistion of the gut microbiome. The impact of single dietary compounds and widely used dietary patterns like vegetarian, Mediterrean, and Western diets on gut bacteria and host health have been assessed in humans.[54]

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.[55] 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.[56-58] 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.[59] 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.[60-62] 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 micobial 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.[53,63] 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

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trimethylamine N-oxide and secondary bile acids.[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.[65] In the absence of global microbal 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 charasteristic gut microbial profile.[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.[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.[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.[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 *Prevotella* and *Lachnospira*.[66] Similarly, in an interventional trial using overweight and obese individuals, Mediterranean diet increased the presence of the butyrate producer *Faecalibacterium prausnitzii*,[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.[74] The characteristic bacterial profile associated with the Western diet can be linked to its low complex carbohydrate content. Bacterial clades of the species *Prevoltella copri*, involved in carbohydrate metabolism, are underrepresented in Westernized populations, mainly attributed to diet.[73] In addition, microbes associated with polysaccharide degradation of porphyran present in edible seaweed species is scarce in Western diets.[75] As well, there is a reduced abundance of *Prevotella* and *Xylanibacter* bacteria involved in cellulose and xylan hydrolysis in children fed Western diets compared to fiber-rich diets.[76] In a cross-sectional study of 517 community-dwelling men, greater adherence to a Western diet positively correlated with bacterial families *Veillonellaceae* and *Mogibacteriaceae*, and genera like *Ruminococcus* which degrade resistant starches in refined grain products, without any significant changes in bacterial phyla.[77,78] Gut bacteria inversely associated with adherence to the Western diet included relative abundances of orders *Clostridiales* and *Streptophyta*, family *Anaeroplasmataceae*, and genera *Coprococcus*, *Faecalibacterium*, *Haemophilus*, *Lachnospira*, *Paraprevotella*, and *Prevotella.* In addition, decreased bacterial diversity is also associated with consumption of a Western diet when compared to hunter-gatherer or rural farming populations.[76,79-82] 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.[82] Altogether, these results demonstrate the Western diet can impact microbial profile and diversity, largely attributed to its low complex carbohydrate content.

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Dietary components associated with these diets, specifically fiber, fat, and sugar, can affect the gut microbiota and host health, which have been reviewed elsewhere.[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.[83] Fiber supplementation in both healthy and specific patient populations enhance the abundance of *Bifidobacterium* spp. and *Lactobacillus* spp. when compared to lower fiber diets or placebo.[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.[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.[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.[44,89] Women supplemented with dietary omega-3 polyunsaturated fatty acids increased both the microbial alpha diversity and increased relative abundance of the *Lachnospiraceae* family, independent of fiber intake.[90] In addition, mice fed saturated fats gained weight, were insulin resistant, had incrased 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.[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.[92-94] This lean phenotype observed in germ-free mice devoid of gut bacteria is largely attributed to defective nutrient absorption.[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.[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.[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 *Firmicutes* and the *Bacteroidetes* and the relative proportion of these 2 phyla may protect or predispose the host to obesity.[96,97] Metagenomic studies have demonstrated that the proportion of *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.[98-100] In particular changes in Firmicutes phylum species *Blautia hydrogenotorophica*, *Coprococcus catus*, *Eubacterium ventriosum*, *Ruminococcus bromii*, and *Ruminococcus obeum* were strongly associated with development of obesity.[34] While studies have shown that increases in Firmicutes are associated with obesity and increases in Bacteroidetes have been associated with weight loss,[97,102] other studies have contradicted these findings.[40,102-104]

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Fecal transplantation from lean human donors to obese recipients led to a significant improvement in insulin sensitivity in the obese recipients.[105] Intriguingly, microbiota transplantation studies in germ-free murine models showed that the efficient energy extraction traits of obese-type gut flora are transmissible.[101] Furthermore both human and animal model studies of obesity and MetS have shown that supplementation with *Lactobacillus* can improve glucose tolerance.[106-108] In patients with MetS changes in the gut microbiome have been linked to a genetic variant in the apolipoprotein A5 gene.[109] The human gut is populated by at least 10^{13} microorganisms, mostly anaerobic bacteria.[3] 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.[110]

Importantly, the microbiota contains factors, including unknown molecules, that are positioned to influence host metabolism.[108] 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[111-113]; 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.[114] Research on this topic is extremely important since it was estimated that in North America more than 25% of the population suffer from MetS[115] and this is associated with serious and extensive comorbidity.[116] A prevalence of mild iron overload in MetS patients is well established by the presence of non-transferrin-bound iron in serum[117,118] and by the correlation of hyperferritinemia,[119,120] and hepatic iron overload[121] 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.[122] 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.[123] 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.[124] In particular, dietary iron levels in the intestinal lumen modify the microbiota

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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.[125]	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.[126]	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.[127]	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.[128]	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
Chuansumrit et al.[129]	Clinical trial	Subjects with NTDT (n=10)	Patients prescribed iron chelator deferasirox (10 mg/kg/day) for 6 months	Trend of improving insulin sensitivity and beta cell function (reduced fasting glucose)
Lainé et al.[130]	Randomized controlled trial	Nondiabetic dysmetabolic iron overload syndrome patients (n=274)	Patients randomly assigned lifestyle and diet advice with or without bloodletting for 1 year	Iron depletion by bloodletting was associated with weight gain; did not improve glycemia, hepatic measures (i.e., ALT, AST, fibrosis score, fatty liver index, GGT) and enhanced IR
Adams et al.[131]	Randomized controlled trial	Non-alcoholic fatty liver disease patients (n=74)	Patients randomly assigned lifestyle and diet advice with or without phlebotomy for 6 months	Iron reduction by phlebotomy does not improve hepatic steatosis MRI measures, ALT, cytokeratin-18 (liver injury marker), or IR
Valenti et al.[132]	Randomized controlled trial	NAFLD and hyperferritinemia patients (n=38)	Patients randomly assigned lifestyle advice with or without phlebotomy for 2 years	Phlebotomy improved steatosis grade, liver enzyme levels (ALT, AST, GGT)
Beaton et al.[133]	Phase II prospective clinical trial	NAFLD patients (n=31)	Phlebotomy treatment occurred biweekly/ monthly for 6 months	Phlebotomy improved NAFLD-liver disease score compared to baseline
Houschyar et al.[134]	Randomized controlled trial	Patients with MetS (n=64)	Patients randomly assigned to iron reduction by phlebotomy vs. control; metabolic measures taken after 6 weeks	Phlebotomy lowered blood pressure, improved glycemic control (i.e., HbA1c, blood glucose) and cardiovascular risk (lowered LDL/HDL ratio, heart rate)

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.

composition.[111,113] 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[135] and since iron is commonly used in supplements this can also increase the variability of iron intake.[136,137] Also, higher male predisposition to heart and liver disease in MetS patients with higher iron stores, was reported.[138,139] 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.[140] 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,[141,143] but have not always been successful.[144] It should also be noted that iron deficiency is a frequent finding after prolonged morbid obesity and can likewise contribute to T2DM and HF.[139,142,145,146] Thus, previous work has shown a bidirectional relationship between iron and glucose homeostasis or cardiomyopathy, suggesting a balance of optimal iron level is critical.[139,142]

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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.[147] A study with thalassemia major patients showed an increased risk for diabetes, heart disease and MetS, particularly amongst women.[148,149] 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[150-152] 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.[150] 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.[141-143] Important cellular mechanisms via which iron accumulation leads to metabolic disease have been characterized, principally mitochondrial dysfunction.[153] Indeed, boosting mitochondrial function can be beneficial.[154] 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.[155] 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.[156] Interestingly, men are at higher risk of developing hemochromatosis.[157] These patients exhibit a high frequency of diabetes with evidence for both destruction of pancreatic β cells and insulin resistance.[158] Several mechanisms have been shown to potentially contribute to various clinical metabolic manifestations in hemochromatosis,[159] 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.[160] 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.[161] 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.[161] 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.

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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.[162-164] Therefore, iron has been shown to be an important element required for the growth of some but not all gut bacteria including *Bacteroides* spp.[165,166] and *Enterobacteriaceae*,[167] whilst *Lactobacilli* species do not require iron for growth.[7,8] Interestingly, *Lactobacillus plantarum* 299v, and a probiotic (containing *Bifidobacterium bifidum* W23, *B. lactis* W51, *B. lactis* W52, *Lactobacillus acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *Lactococcus lactis* W19, and *L. lactis* W58) have been shown to increase host iron absorption.[168,169] 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),[170-173] 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 transcription 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.[164] 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.[174-176]

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.[177] 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.[177] In a study conducted to investigate the impact of iron supplementation on rat pups, no effect on growth or weight gain was observed.[178] 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*.[178] Similarly iron supplementation amongst South African children did not significantly alter the composition of the major bacterial groups, or faecal SCFA concentration.[48]

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

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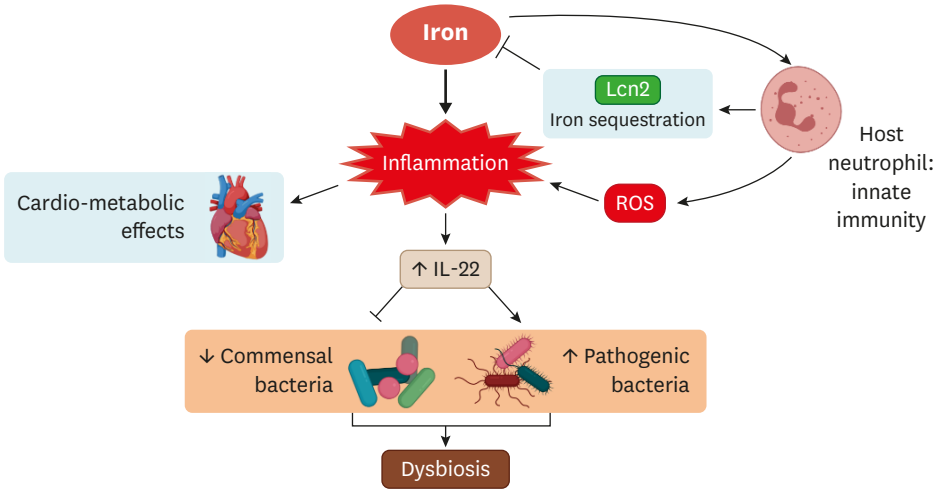

Fig. 1. Illustration of interplay between iron and inflammation. This figure depicts various ways in which interplay between iron and inflammation occur. In addition to directly causing inflammation, there is crosstalk with host innate immunity. This is predominantly mediated via neutrophil-derived Lcn2 which can sequester iron-laden bacterial siderophores. IL-22 is identified as an important mediator of dysbiosis in an inflammatory milieu. Lcn2, lipocalin-2; IL, interleukin; ROS, reactive oxygen species.

bacteria, alternatively intestinal inflammation can promote the colonization of pathogens.[179] One of the hallmarks of intestinal inflammation-induced dysbiosis (**Fig. 1**) is that of increased abunance of enterobacteria species. Due to the differing microbial profile in the inflammed 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.[180] 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.[181]

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.[140] 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.[140] However, in contrast, other studies have shown that decrease in iron availability is beneficial via reducing growth of potentially pathogenic gut bacteria.[182,183] Dietary iron supplementation has adverse effects such as inducing higher levels of pathogenic gut bacteria and the occurance of intestinal injury.[111,113,182,184,185] 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.[186]

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 illeal capillaries, leading to bacterial utilization for growth.[187] 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.[188] Cholera toxin also increases long-chain fatty acid and L-lactate

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metabolites within the lumen, which leads to the upregulation of *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 *Vibrio cholerae* through the acquisition of host-derived heme and fatty acids.[187]

Other bacterial species such as *Campylobacter jejuni* are also able to capture host iron and cause infection within the host. Infection with *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 it's survival.[189]

In order to obtain iron, many bacterial species produced compounds known as siderophores which bind iron and transport it inside the bacteria.[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[192-194] and acts via sequestering iron-laden siderophores, thereby preventing bacteria obtaining iron from the host.[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.[199-205] Lcn2 levels are also strongly associated with HF.[199,201,206-208] For example, Lcn2 is significantly augmented in patients with coronary heart disease and myocardial infarction.[202,209] In diabetic patients, increased Lcn2 has been correlated with cardiac hypertrophy and diastolic dysfunction.[210] Following an ischemic stroke event, measurements of Lcn2, within a few days after the

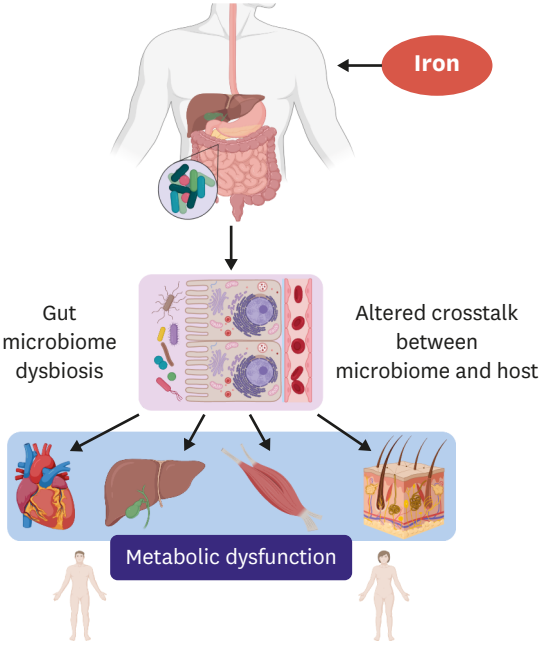

Fig. 2. Graphical abstract showing the link between iron and metabolic function. This illustration highlights the main concepts underlying the content of this article in which iron modifies the gut microbiome, leading to metabolic consequences in the host.

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event, can be used to stratify patients according to mortality risk during the following 4-year period.[211] Lcn2 content in the myocardium itself increases in HF, and after ischemia reperfusion from infiltrating neutrophils.[212] Furthermore, some pathogens have evolved systems to thrive in the inflamamed gut including limited metal (i.e., iron) resources.[181] 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 antimicrobioal proteins such as Lcn2 and calprotectin which should limit iron availability, *Samonella 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 surpresses growth of species such as commensal Enterobacteriacease, which produce siderophores that are recognized by Lcn2.[180]

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.

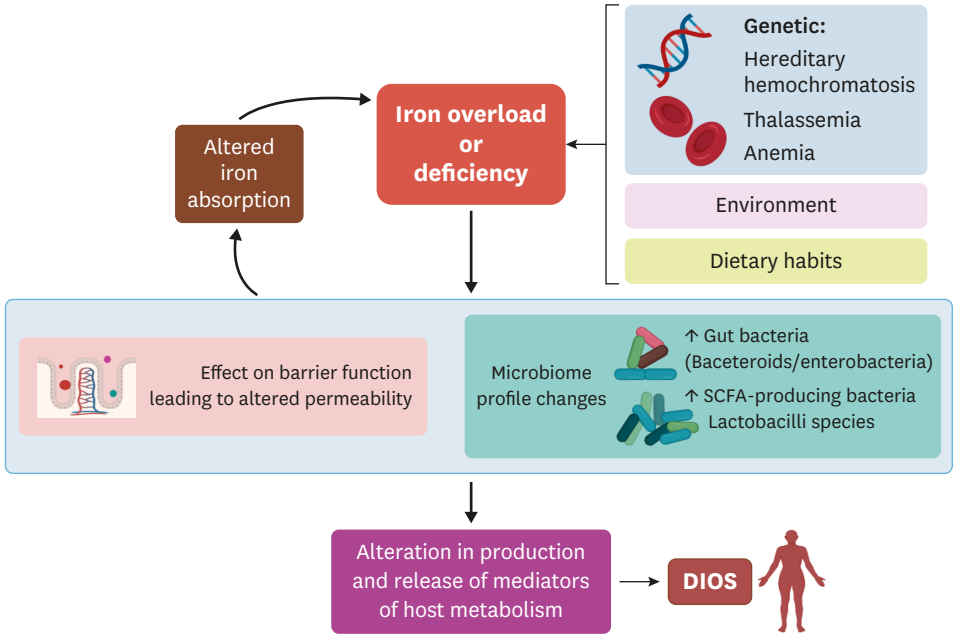

Fig. 3. Illustration of interplay between iron and microbiome. There are various ways in which iron overload or deficiency can occur (top-right). These scenarios can re-shape the gut microbiome and alter barrier function. Subsequently, cross talk mediated by gut-derived factors and peripheral metabolic 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.

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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.

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