

Roles of the gut in the metabolic syndrome: an overview

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The metabolic syndrome is a cluster of risk factors (central obesity, hyperglycaemia, dyslipidaemia and arterial hypertension), indicating an increased risk of diabetes, cardiovascular disease and premature mortality. The gastrointestinal tract is seldom discussed as an organ system of principal importance for metabolic diseases. The present overview connects various metabolic research lines into an integrative physiological context in which the gastrointestinal tract is included. Strong evidence for the involvement of the gut in the metabolic syndrome derives from the powerful effects of weight-reducing (bariatric) gastrointestinal surgery. In fact, gastrointestinal surgery is now recommended as a standard treatment option for type 2 diabetes in obesity. Several gut-related mechanisms that potentially contribute to the metabolic syndrome will be presented. Obesity can be caused by

hampered release of satiety-signalling gut hormones, reduced meal-associated energy expenditure and microbiota-assisted harvest of energy from nondigestible food ingredients. Adiposity *per se* is a well-established risk factor for hyperglycaemia. In addition, a leaky gut mucosa can trigger systemic inflammation mediating peripheral insulin resistance that together with a blunted incretin response aggravates the hyperglycaemic state. The intestinal microbiota is strongly associated with obesity and the related metabolic disease states, although the mechanisms involved remain unclear. Enterorenal signalling has been suggested to be involved in the pathophysiology of hypertension and postprandial triglyceride-rich chylomicrons; in addition, intestinal cholesterol metabolism probably contributes to atherosclerosis. It is likely that in the future, the metabolic syndrome will be treated according to novel pharmacological principles interfering with gastrointestinal functionality.

Keywords: body weight, chylomicrons, energy expenditure, food intake, glycaemia, metabolism.

Introduction

We are presently experiencing a paradigm shift related to the treatment of metabolic diseases. New clinical guidelines, endorsed by 45 professional societies around the world, propose that gastrointestinal surgery should be considered as a standard treatment option for type 2 diabetes [1]. This is remarkable because the gastrointestinal tract is seldom discussed as an organ system of principal importance for metabolic control. Dysregulated metabolism is often instead ascribed to disturbances in other metabolically active organs and tissues such as liver, pancreas, adipose tissue and the musculature. It is noteworthy that the gastrointestinal tract is the body's principal nutrient provider and that a considerable amount of evidence exists demonstrating gut-initiated direct and anticipatory metabolic control of distant organs. The aim of the present review is to connect the various trends in basic and clinical metabolic research into an integrative physiological context

including the gastrointestinal tract. This overview is based on a huge scientific literature, and therefore it is not possible to provide a comprehensive review of all areas of research (full details have only been given for areas in which recent reviews are lacking).

Bariatric and metabolic surgery

The most striking evidence for the involvement of the gut in the metabolic syndrome emanates from the effects of weight-reducing (bariatric) gastrointestinal surgery [2, 3]. Bariatric surgery was originally based on two general principles: restricting the capability for food intake (e.g. gastric bands creating a resistance for luminal flow) and creating malabsorption by bypassing a portion of intestine (e.g. gastric bypass). The first bariatric operations were based on intestinal resections and were performed in the 1950s by the Swedish surgeon Viktor Henrikson at the Sahlgrenska Hospital in Gothenburg [4]. Later, intestinal bypass without resection was used. This procedure caused malabsorption that

indeed reduced body weight but also induced severe side effects. Since then, the surgical techniques have been developed considerably and are based nowadays on minimally invasive laparoscopic approaches with very low perioperative risk and an average mortality of 0.3%, thus comparable to a routine cholecystectomy [5]. Laparoscopic adjustable gastric banding is a modern version of a strict restrictive operation (Fig. 1, right). Following this operation, the patient remains hungry but cannot eat large meals. However, many 'food intake-restricted' patients adapt by increasing the number of (small) meals with easily swallowable, high-energy content resulting in a less optimal weight reduction [6, 7]. Gastric banding is therefore performed less often than other procedures. Today, the predominant procedures are Roux-en-Y gastric bypass and vertical sleeve gastrectomy (Fig. 1, left and middle). Of interest, neither of these procedures is regarded as particularly restrictive or malabsorptive (although some micronutrients must be substituted). Instead, it appears that the gut-brain signalling becomes influenced, in turn driving the individual to an improved eating behaviour [8]. After a gastric bypass, the swallowed food arrives directly in the jejunum, whereas the secretions of the bypassed stomach and duodenum (including bile and pancreatic secretions) enter more distally in the small intestine. This anatomical re-routing of ingested nutrients in relation to the digestive factors results (in most cases) in a powerful weight loss being sustained over a long period [9]. A multitude of mechanisms are activated resulting in reduced hunger and enhanced satiation as well as altered food preferences. For example, nutrient loading of the hindgut (ileum) and simultaneous unloading of

the foregut will change the liberation of gut hormones and the associated gut-brain signalling. Furthermore, bypassing the stomach removes an important decontamination system allowing a differential distribution of intraluminal microbiota as well as the intraluminal conversion of biliary acids [10, 11]. After a sleeve gastrectomy, the anatomical route for food is preserved but the reservoir capacity of the stomach is markedly reduced (Fig. 1, middle). Compared to gastric bypass, the mechanisms of action following sleeve gastrectomy are less well studied. As with gastric bypass, after sleeve gastrectomy, ingested food is rapidly delivered to the distal small intestine activating the hindgut mechanisms; however, there are significant differences between these procedures particularly related to gastroduodenal functions [12].

In addition to weight loss, bariatric surgery improves the associated dysmetabolic conditions as well as end organ diseases and mortality rate [9, 13]. Some metabolic improvements, particularly glycaemic stabilization and blood pressure reduction, occur almost instantly and are partly weight loss independent, indicating a direct influence on metabolic control by the gastrointestinal intervention. The term 'metabolic surgery' has therefore been established to emphasize that the primary purpose of a procedure is not weight reduction *per se*, but rather metabolic improvements, particularly resolution of type 2 diabetes [14].

Noncommunicable diseases and the metabolic syndrome

The prevalence of obesity and diabetes has increased dramatically during the last three decades, and the

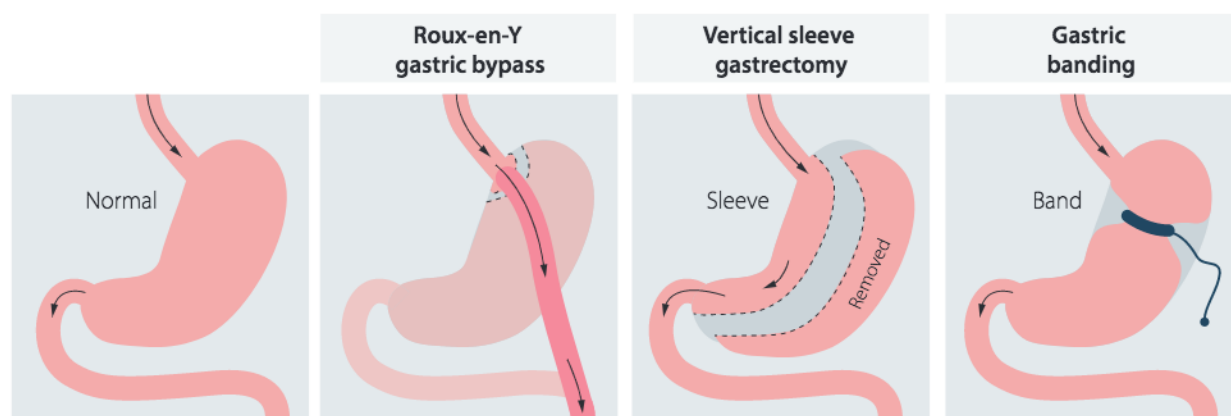


Fig. 1 The principal bariatric procedures.

associated macrovascular and microvascular diseases such as stroke, myocardial infarction and chronic kidney disease have become a huge burden on affected individuals and healthcare systems. The World Health Organisation (WHO) recently stated that noncommunicable diseases (NCDs) constitute a steadily expanding global health challenge [15]. NCDs are defined as chronic diseases with generally slow progression that are not passed from person to person (at least this is the current belief based on present knowledge). Based on annual premature mortality data, the WHO has identified four main types of NCDs: cardiovascular disease and diabetes which together account for the majority of annual deaths (19 million) followed by cancer (8.2 million) and respiratory diseases (1.5 million). Use of tobacco and alcoholic beverages, unhealthy diets and physical inactivity has been considered important in relation to NCDs, not least by being modifiable. Furthermore, the NCDs are associated with the metabolic syndrome, which is defined as a cluster of metabolic/physiological risk factors (central obesity, hyperglycaemia, dyslipidaemia and arterial hypertension). The presence of the metabolic syndrome indicates increased risk of diabetes, as well as cardiovascular disease and premature mortality [16]. The definition of the metabolic syndrome has shifted somewhat over the years. Furthermore, its clinical usefulness as a composite indicator in relation to each individual component is debated [17–19]. Nevertheless, the metabolic syndrome has been of great importance by constituting a basis for lifestyle changes and for pharmaceutical interventions targeting each component of the syndrome. For example, antihypertensive, blood lipid-modulating and glycaemia-stabilizing treatments have indeed improved cardiovascular morbidities and the related mortality [20]. However, targeting risk factors is not usually curative, strongly arguing that the source of the dysmetabolic pathogenesis is situated ‘upstream’ of the clinical signs.

Does the gut have a role in metabolic regulation?

Energy homeostasis consists of two principal functional states: the interdigestive/postabsorptive catabolic state and the digestive/absorptive anabolic state. The switch between these two metabolic conditions is intimately related to meal ingestion and digestion/absorption and, therefore, dependent on the functional state of the gastrointestinal tract. As the gastrointestinal tract is also the port of entry for water and salts, the gut is important for another fundamental area of

metabolism: fluid and electrolyte homeostasis. This in turn determines nutrient transport to the various cell communities and their metabolic capacity. From this perspective, it is intuitive that the gut has a role in metabolic control at the level of the organism, but the mechanisms involved have only been partly explored.

The enigmatic associations between metabolic risk factors and end organ diseases have created a huge scientific literature, and it is not possible to provide full details here. However, some features should be mentioned in the context of the roles of the gut. The modern postindustrial lifestyle has created certain requirements on the metabolism. It is often proposed that humans developed for hunting and gathering and that our ancestors underwent positive selection for genes that favoured energy storage to survive harsh periods. It follows that the human genotype is prepared for episodes with low food intake and high physical activity, the latter needed for moving into more ‘energy-rich’ surroundings. This ‘thrifty gene hypothesis’ is probably an oversimplification, and there may be selection pressures also in relation to migration of our early ancestors from the African continent to various climate zones adding to a ‘drifty genotype’ [21]. Although these speculations may be controversial, it appears plausible that evolution has resulted in a human genotype that favours overconsumption of energy when available, to counteract anticipated starvation periods. Such a genotype can thus be the principal cause of today’s obesity epidemic [22]. The time course of the increased prevalence of obesity and associated morbidity coincides with the sedentary lifestyle that we have developed during only the last 25–30 years with physical inactivity now being a strong risk factor for obesity and related diseases [23]. Modern living provides an almost unrestricted availability of energy-rich food, and in this environment the thrifty genotype will be a strong driver for overeating, without a concomitant energy need (Fig. 2). As mentioned above, the pathophysiological role of the gut is intuitive: an increased meal frequency forces the energy balance into the anabolic state characterized by intestinal digestion/absorption with high insulin blood levels, whereas the catabolic state with physical activity becomes less common and short lasting.

Low-grade inflammation

Metabolic disturbances accompanying a sedentary lifestyle can be mimicked by overfeeding an

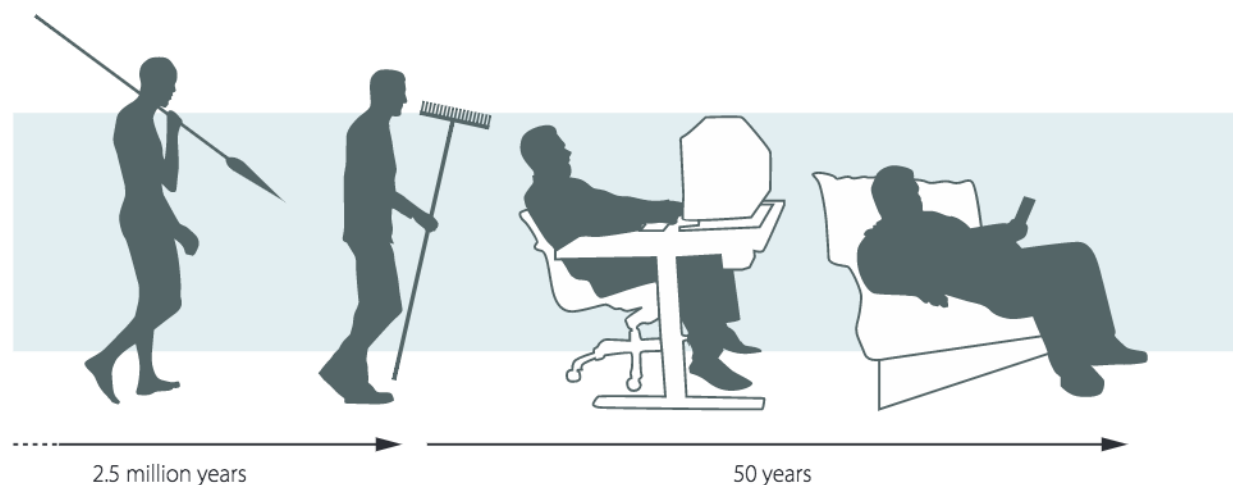


Fig. 2 Human evolution is characterised by a balance between physical activity and energy intake. The thrifty gene hypothesis proposes that the ability to overeat when food was available was beneficial in periods with a lack of food. Because of today's sedentary lifestyle with unrestricted food consumption, the 'thrifty genotype' has resulted in unbalanced overeating. This in turn has created an unhealthy anabolic state with obesity and metabolic disturbances.

experimental animal. Rodents with or without known genetic aberrations fed a high-fat diet are therefore frequently used in biomedical research. Energy overload not only causes the 'physiological' subcutaneous and visceral fat depots to expand, but lipids also accumulate in tissues that normally do not store fat (so-called ectopic fat deposition). Peripheral insulin resistance is a key abnormality that has been proposed to be fundamental and can initiate a chain of pathophysiological events. However, the primary mechanisms that reduce peripheral insulin sensitivity are not completely understood, but there is a strong association with low-grade systemic inflammation [24]. A common hypothesis, therefore, is that when the adipose tissue becomes hypertrophic, it secretes proinflammatory factors (adipokines) that cause leucocyte infiltration, in turn releasing cytokines that induce insulin resistance and consequently hyperglycaemia, i.e. type 2 diabetes [25, 26]. Long-term hyperglycaemia 'exhausts' the insulin-producing beta cells, eventually resulting in reduced endogenous insulin production [27]. The negative effects of long-term hyperglycaemia are sometimes termed glucotoxicity and act in concert with lipotoxicity, i.e. negative influences on the pancreatic beta cells from increased blood levels of free fatty acids [27]. But why does the hypertrophic adipose tissue become inflammatory in the first place? Is it an inborn adipokine property or are external factors involved? The 'leaky epithelium hypothesis' proposes that reduced intestinal mucosal barrier

capacity, induced by a fatty 'western diet', allows bacterial endotoxin from intestinal microbiota to penetrate into the mucosal tissue and reach the circulation [28, 29]. The endotoxaemia in turn triggers the systemic proinflammatory signalling cascade leading to peripheral insulin resistance and hyperglycaemia as well as effects on other organs, such as nonalcoholic fatty liver disease [29, 30]. The translocation of endotoxin into the circulation has, however, recently been questioned. Significant endotoxaemia has not always been confirmed and this could be because once endotoxin penetrates into the intestinal mucosa it can activate a local host defence response. This, in turn, initiates proinflammatory cascade signalling to metabolically active tissues on distance [31] (Fig. 3). A recent experimental study provides strong support for the notion that systemic metabolic aberrations are initiated at the level of the gut mucosa. Anti-inflammatory agents usually used to treat inflammatory bowel disease (IBD) improve diet-induced metabolic aberrations [32]. These results provide evidence for the gut immune system as the trigger of obesity-related insulin resistance, but also suggest novel therapeutic principles involving anti-inflammatory drugs, diet and prebiotics or probiotics [33].

Important gastrointestinal features

Before considering the potential roles of the gut in the metabolic syndrome, important gastrointestinal

Fig. 3 An energy-rich diet causes the intestinal epithelium to become more permeable to microbial macromolecules (endotoxin) and initiates a proinflammatory cascade reaction. The 'leaky' intestinal mucosa can thus provide a link between diet and the systemic low-grade inflammatory state that drives peripheral insulin resistance.

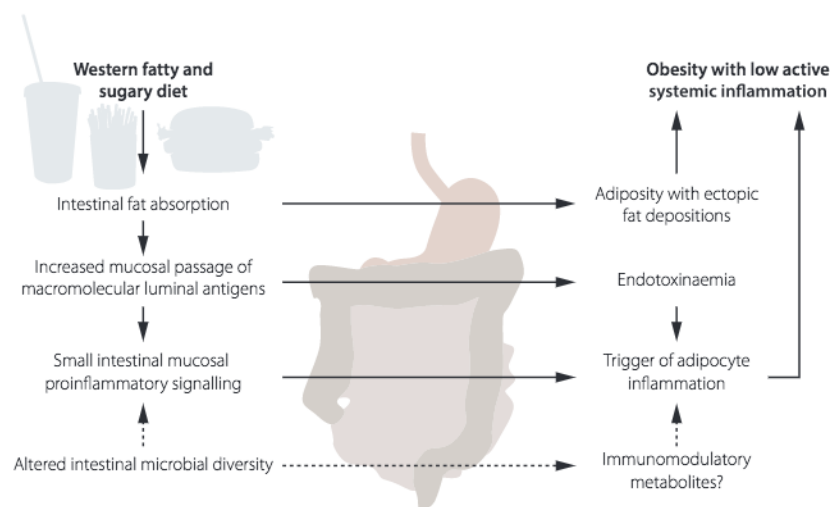


Table 1 Gastrointestinal features of importance for systemic metabolic control

- The gastrointestinal tract consists of several organs in series with huge variability in mucosal surface reflecting differential functionality
- Macronutrient digestion/absorption involves coordinated mechanical, chemical, immunological and biological actions
- Several nutrient-sensing principles mediate signalling to extra-intestinal tissues
- Recirculation of bile acids also involves systemic metabolic regulation
- The properties of the gastrointestinal mucosal barrier are dynamic and sensitive to diet
- The intestinal microbiota is part of a lifelong symbiotic relationship and altered microbial diversity has the potential to influence the host's metabolism

features will be discussed in the light of recent research (briefly summarized in Table 1). However, due to space constraints, the potential effects of different diets on health and disease cannot be presented in detail. The primary function of the gut is to supply the body with energy, building elements and water/electrolytes. Humans are *omnivores*, meaning that the digestive system has the capability to assimilate energy from macronutrients (i.e. carbohydrates, fat and proteins) of most food types, independent of origin (plant or animal).

Several organs in series

Basically, the gastrointestinal tract is composed of a two-layered muscular tube with the inside covered by a mucosa. However, the

gastrointestinal tract is not one organ, but several organs positioned in series. The stomach and large bowel are primarily volume reservoirs with small surface areas. Of interest, because of the retardation of luminal bulk flow and its portion-wise exit ('gastric emptying' and 'bowel evacuation'), both these organs are 'bioreactors', although with opposite functions (Fig. 4, left). Furthermore, because of the antimicrobial hydrochloric acid and nitric oxide in the stomach, the gastric and small intestinal interior contains a very low number of living microbes [34, 35]. By contrast, the large intestinal lumen offers optimized conditions for living microorganisms, clearly with a symbiotic purpose to extract energy and essential elements from the luminal bulk leftover after small intestinal digestion/absorption [36, 37]. The small intestine (duodenum, jejunum and ileum), on the other hand, performs the mechanochemical degradation of macronutrients during gradual transport in the aboral direction [38]. This process is due to coordinated activities in the wall musculature orchestrated by the local enteric nervous system and endocrine factors [39, 40]. The gut musculature is also active between meals. High-activity fronts of propulsive motility move distally from the gastric antrum in a cyclic fashion termed interdigestive migrating motility complexes. This type of gastrointestinal motility is also coordinated by the enteric nervous system, with the purpose of regularly clearing the empty intestinal lumen of cellular debris and microorganisms [41].

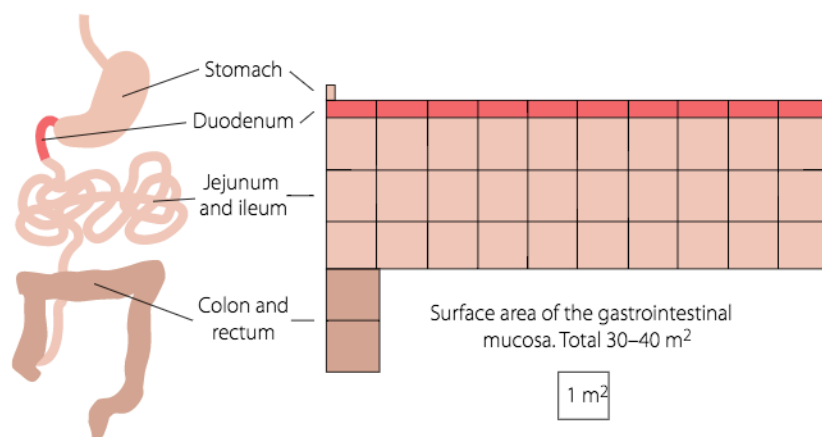


Fig. 4 The gastrointestinal tract consists of several organs in series. The complex geometry of the mucosa results in marked surface area enlargement (modified from [42]).

The geo-anatomical perspective

The gastrointestinal tract is usually regarded as a tube of a certain length. However, the geometrical anatomy *in vivo* is very variable, and from a functional perspective it might be better to consider the gut as a surface. Compared to the serosal side of the gut, the mucosal area is enlarged due to the presence of folds, villous structures and microvilli. The total area of the gastrointestinal surface has long been believed to be comparable to that of a tennis court, corresponding to 180–200 m², or even larger [42]. This is probably a considerable overestimation because, after re-calculating the geometrical enlargement factors, we recently estimated that the total mucosal luminal surface of an adult human gut is 30–40 m² of which 95% belongs to the small intestine where the motility-dependent exposure of the luminal contents is greatest. Therefore, even if much smaller than previously believed, the area of the gut mucosa is still more than 15-fold greater than that of the skin. Additionally, the total length from the teeth to the anal sphincter has been recalculated [42]; the *in vivo* value is of the order of 3.5 m, thus only ~40% of the postmortem values usually stated in textbooks. A geo-anatomical presentation of the human gastrointestinal tract based on the distribution of luminal surface is shown in Fig. 4 (right).

Extended role for bile acids

Hepatopancreatic secretions are closely integrated with the gastrointestinal tract in the digestive process. A generalized role for bile acids in metabolic regulation, including interactions with luminal microbiota, has recently been highlighted [43].

According to the classical view, bile acids are released into the gut lumen in association with a meal and act as detergents forming micelles with digested fat and cholesterol, to aid intestinal lipid absorption. In the more distal intestine, bile acids are modified by luminal microbiota and reabsorbed to return to the liver via the portal circulation: the enterohepatic recirculation. During the last decade, it has become evident that bile acids in the systemic circulation influence various tissues by interaction with the nuclear receptor farnesoid X receptor (FXR) and the G protein-coupled bile acid receptor TGR5 [43, 44]. In this way, bile acid synthesis in the liver is inhibited via FXR directly, or via FXR-mediated release of the hormone fibroblast growth factor 19 (FGF19) [45]. Furthermore, during enterohepatic recirculation, a fraction of the bile acids will be shunted to the systemic circulation and reach most cells in the body and therefore have potential to influence energy turnover at all biological levels [44].

The host defence perspective

In addition to ingested nutrients, the mucosal surface is exposed to potentially noxious factors such as microorganisms, toxins and drugs, as well as to endogenous aggressive digestive factors. It follows that the mucosa allows the passage of nutrients and fluid essential for metabolism, but prevents entrance of potentially harmful factors through various (dynamic) lines of defence based on physical, chemical and immunological actions. Luminal digestive factors including gastric acidity and pancreatic proteolytic enzymes are important as a luminal barrier by eliminating living pathogens. A second line of defence is the mucus gel of

mucins and water covering the mucosa constituting a pre-epithelial barrier. The mucus is thickest in the stomach and colon and is generally organized into two layers: one more loosely adherent and one more firmly attached mucus layer [46]. In the stomach and large intestine, the mucus layer is mainly composed of MUC5ac and MUC2 mucins, respectively [47]. The small intestinal mucosa has a generally loose mucus type dominated by MUC2 mucins. The layer is relatively thin and permeable allowing the luminal nutrient solution to make contact with the small intestinal epithelium for nutrient end-digestion and absorption. By contrast, the epithelium-adherent mucus of the stomach and the colon is rather impermeable to macromolecules and microbes, but allows movement of ions and water [47]. Furthermore, the surface mucus both in the stomach and first part of the duodenum is constantly supplied with bicarbonate from the mucosa providing a pre-epithelial neutralizing zone against the acidic lumen [48]. One enigma has been how the stomach can acidify the luminal contents despite the presence of an alkaline mucus layer. It is now known that the acid from the parietal cells in the mucosal crypts is ejected into the lumen through short-lasting channels within the mucus [49].

The colon, the other reservoir organ of the gut, harbours huge amounts of living microbes that are prevented from direct contact with the epithelium by the impermeable adherent mucus layer [50]. The surface cell layer itself acts as a third line of defence: the epithelial barrier. The gastrointestinal epithelium consists of a single layer of cylinder-shaped, polarized cells. The majority of these are nutrient-transporting enterocytes and mucus-producing goblet cells. The surface epithelial cells are connected with each other via tight junction proteins, restricting the paracellular passage of antigenic macromolecules [51]. These intercellular junctional protein complexes are in turn connected to mechanoactive cytoskeleton elements of the enterocytes. Paracellular permeability, and thus the passage of macromolecules and solutes, can be regulated in the short term by conformational changes in the junctional and cytoskeleton proteins and in the longer term depending on protein expression. Specialized small intestinal epithelial (Paneth) cells can secrete antimicrobial peptides from the crypt regions for innate host defence [52]. The crypts also contain stem cells that replicate at a very high rate, resulting in cell turnover that is amongst the highest in the body and leading to

complete renewal of the intestinal surface epithelium within one to a couple of days [53]. Furthermore, the gut hosts the largest population of immunological cells in the body [36]. Specialized M cells in the epithelium as well as dendritic cells beneath the surface epithelium participate in antigen presentation to the numerous immunocytes residing in the submucosa and in regional lymph nodes, in turn activating innate as well as adaptive immune reactions both locally and systemically [54].

The symbiotic perspective

The microbes residing in the gastrointestinal lumen, collectively termed the gut microbiota or intestinal microbiota, represents a field of research that has expanded enormously during recent years. The reason for such expansion is that the use of culturing-independent molecular methods (i.e. 16s rDNA sequencing or whole-genome sequencing/metagenomics) on faecal samples has established a new horizon regarding potential interactions with the host organism [55]. Traditionally, the medical community has been interested in intraluminal microbiota mainly because of associations with disease. It is also known that the microbiota exerts beneficial actions, for example by fuelling the colonic mucosa with short-chain fatty acids and extracting vitamins from nondigestible luminal contents discarded by the small intestine. However, the role of the gut microbiota in health and disease appears to be much more sophisticated. The distribution of microbes follows principally the luminal antimicrobial and promicrobial principles described above, with very low numbers in the gastroduodenojejunal parts, increasing in the ileum to reach huge numbers in the large bowel [36, 56]. It has been estimated that within the gut of a healthy adult human, there is approximately 1–1.5 kg of microbes, corresponding to around 10^{14} bacterial cells, thus 10 times the number of cells in the body [55, 57]. However, this was recently questioned after reviewing the available literature, and a more reasonable ratio between microbes and body cells of 1.3:1 has been proposed [58]. The dominating bacterial phyla in the human distal gut are *Firmicutes*, *Bacteroidetes*, *Proteobacteria* and *Actinobacteria*, and collectively these have been proposed to constitute a powerful ‘organ’ with the capacity to influence most physiological functions of the body [59, 60]. Indeed, there are now numerous reports linking the microbial profile to various pathological states such as morbid obesity,

diabetes, cardiovascular disease, cancer and even psychiatric disorders. However, most studies have investigated disease states in relation to the microbial conditions in faeces rather than the intraluminal conditions, and certainly not the juxtamucosal environment. It is clear that 99% of intestinal microbes are retained in the large intestine and this is an organ with a relatively small luminal surface of around 2 m² in an adult human, compared with 30 m² in the small intestine [42]. This has implications in terms of how to interpret the associations from a mechanistic perspective. It follows that there are very few (if any, if the mucus layer is intact) direct contacts between microbes and the mucosa *per se*, at least during normal conditions. On the other hand, microbial metabolites (gases and small molecules) can be absorbed by the colonic mucosa and have the potential to exert a functional impact by means of an endocrine mode of action or via conversion of bile acids [43, 61, 62]. To what extent an individual's microbial profile is the consequence of metabolism, or vice versa, remains to be established. Data supporting the latter have been obtained by introducing human microbiota into germ-free mice, showing for example that 'obesogenic bacteria' cause the mice to gain more body weight than control animals receiving microbes from slim subjects [63]. However, the microbial composition appears to remain constant in the adult human [64]. It is likely that the intestinal microbiota obtained during the neonatal period will be sustained

throughout life. Consequently, it has so far been difficult to demonstrate a maintained metabolic effect of prebiotic or probiotic treatments or even faecal transplantation [65].

The metabolic syndrome and the gut

The gastrointestinal tract can influence the metabolic syndrome through several physiological principles. Despite the possibility of overlap, each factor (central obesity, hyperglycaemia, hypertension and dyslipidaemia) is presented separately below, and several proposed pathophysiological mechanisms of importance for the metabolic syndrome are summarized in Fig. 5.

Central obesity and body weight control

The WHO has defined obesity as a body mass index [(BMI) i.e. body weight divided by height squared] of more than 30 kg m⁻², above which the prevalence of metabolic aberrations and of premature mortality increase in an almost linear fashion. It should be noted, however, that obesity in the context of body weight or BMI is not part of the definition of the metabolic syndrome [16]. Instead the term 'central obesity' is used, indicating that the fat distribution, particularly abdominal adiposity, is pivotal rather than body weight *per se*. Waist circumference, and particularly when related to body height, has been promoted as a better risk indicator than BMI as an

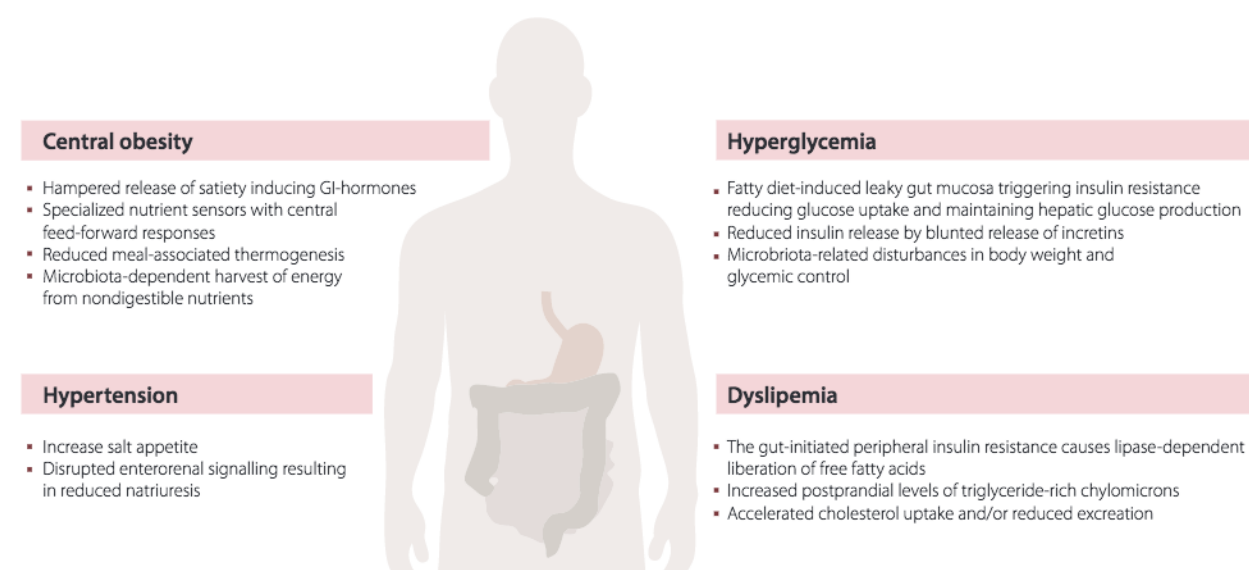


Fig. 5 Proposed pathophysiological mechanisms of importance for the metabolic syndrome. GI, gastrointestinal.

individual measure [66]. The reason that abdominal rather than, for example, subcutaneous adiposity is more closely associated with metabolic disease is not completely known but one hypothesis is that proinflammatory adipokine release is higher in adipocytes with a visceral location, contributing to initiation of peripheral insulin resistance [67]. As mentioned above, it has been proposed that a leaky intestinal epithelium can be a prerequisite for this condition, probably initiated by an energy-rich fatty diet [29]. It is interesting that after gastric bypass surgery, patients tend to avoid foods rich in fats and sugar [6, 68]. It can thus be speculated that the changed dietary composition 'tightens' the intestinal epithelium with a subsequent reduction in the passage of luminal microbial antigens triggering inflammation (see Fig. 3). The result will be improved insulin sensitivity, as well as weight loss.

Food intake and gut-brain signalling

Gastrointestinal mucosal nutrient sensing and neurohumoral signalling with feedback regulation on food intake, digestion and absorption have indeed long been known to exist. The first hormone to be described was secretin, a signalling factor released by the duodenojejunal mucosa that regulates the exocrine pancreas as reported by Bayliss and Starling in 1902. The discovery of secretin was the start of a new era in medicine of blood-borne signalling, nowadays termed endocrinology [69]. Numerous gastrointestinal factors with signalling capacity have since been described, and many of these interact directly with the central nervous system via the blood stream, but also indirectly through local activation of vagal and spinal afferents and/or the internal nervous system of the gut, the enteric nervous system [39]. Gastrointestinal endocrine factors can act separately or in concert with nerve-mediated mechanisms creating an impressive and complex basis for regulatory actions, not only within the gut itself but also with projections on distant tissues. Eating behaviour is partly regulated by peripheral signals from mechanical and nutrient neurohumoral sensing within the gut with final projections in the central nervous system [70, 71]. Ghrelin is a hormone released mainly from the stomach and is proposed to exert an orexigenic effect, including hunger sensation [72]. Under normal circumstances, meal intake suppresses ghrelin (and the associated hunger drive), and this mechanism might be dysfunctional in obese subjects. Ghrelin release has

been reported to be sensitive to gastric bypass surgery, but contradictory results have been reported regarding both physiological ghrelin release and the effect of bariatric surgery [73]. Today, the nature of ghrelin as a true 'hunger hormone' is seriously questioned. Instead, more sophisticated roles for ghrelin in appetite regulation have been proposed, for example operating within the food-reward system as well as in other addiction disorders [74].

A classical example of gut-brain communication is the release of the duodenojejunal hormone cholecystokinin (CCK) from enteroendocrine cells upon consumption of energy-rich (fatty) meals. This hormone acts on CCK-A receptors on gastric vagal afferents that signal via the brainstem to the hypothalamus. The response is a sensation of satiation and termination of food consumption [40]. Examples of other anorexigenic gastrointestinal hormones of interest are pancreatic polypeptide (PP), peptide tyrosine-tyrosine (PYY), glucagon-like peptide 1 (GLP-1) and oxyntomodulin which have various satiety-related targets in the central nervous system or act indirectly via vagal afferents [70, 75, 76]. The meal-induced release of the satiety hormones PYY and GLP-1 from enteroendocrine L cells is suppressed in obese individuals, suggesting that this mechanism may contribute to overeating. The finding that bariatric surgery enhances such hormonal responses as well as the associated satiation following food intake supports a causal relationship [77]. GLP-1 will be further described below in the context of its role as an incretin.

Similar to the key gastrointestinal peptide hormones, the plasma concentration of bile acids in response to meal ingestion also appears to be blunted in obese individuals and becomes normalized after gastric bypass [78]. It has been proposed that the bile acid-specific receptors in the intestinal mucosa are involved in the release of gastrointestinal hormones. Bile acids released into the duodenal lumen will combine with the ingested meal and follow the bulk solution and act via FXR and TGR5 on the mucosal enteroendocrine L cells located distally in the small intestine and in the colon. The L cells can be reached both from the luminal cavity and, via the enterohepatic circulation, also from the submucosal blood flow [79, 80]. Because the release of bile to the lumen is regulated in relation to fat intake, bile acids can function as an indirect messenger to the distal gut mucosa indicating not

only the magnitude of a luminal load but also its composition. The efficacy of this proximal-to-distal gut signalling on gut hormone-releasing cells is partly dependent on the ileocolonic microbial composition determining the degree of conversion from primary conjugated bile acids to absorbable secondary bile acids. Furthermore, recent research has demonstrated numerous specialized nutrient sensors, for example single-modality sensitive intestinal taste cells, that in parallel with metabolic regulation at the organ level probably also influence central feed-forward hedonic mechanisms and food intake behaviour [71]. However, many of these specific sensing mechanisms have so far only been tested at an experimental level and await confirmation in humans.

The gut and energy expenditure

The primary function of the gastrointestinal tract is to provide the body with energy for immediate use or for storage. In the resting state, the splanchnic organs receive about one-third of the cardiac output, most of which perfuses the gastrointestinal tract. This impressive blood flow increases even more in the postprandial state [81]. It has been a generally forgotten fact that the gastrointestinal organs themselves need energy for digestion and absorption [82]. Some of this energy is harvested directly from the absorbed nutrients; the magnitude in humans is not known but within veterinary medicine, it is estimated that the intestinal energy expenditure corresponds to around 20% of the ingested energetic content [83]. The 'thermic effect of food' and the related term 'diet-induced thermogenesis' indicate the increased energy expenditure that is observed following food intake [84]. The postprandially upregulated metabolism was long considered to be due to the digestive and absorptive processes and partly dependent on the type of macronutrients. In addition, meal-associated thermogenesis has been proposed to be mediated by insulin release and/or increased sympathetic tone targeting various distant thermogenic mechanisms in the body [85–87]. Recently, it was shown in rats that instillation of lipids into the duodenum activates vagal afferents that in turn activate thermogenesis via a gut-brain-brown adipose tissue reflex [88]. This is of interest because brown adipose tissue has been re-discovered in adult humans, thus it is possible that such a reflex is also operational in humans [89]. Interestingly, meal-associated thermogenesis becomes markedly

increased after gastric bypass surgery, indicating a role in the maintenance of weight reduction [10, 90, 91]. Following this operation, the food-receiving jejunal segment, i.e. the alimentary limb (also known as the Roux limb), is in a hyperproliferative state [92, 93]. To cover the energy needed for increased epithelial cell replication, glucose is harvested from digestion in the alimentary limb during food intake, and from the blood supply in the interdigestive period. The rate of glucose utilization in the Roux limb has been shown to be of a magnitude that reduces the plasma glucose concentration and thereby contributes to the improved glycaemic control observed after this type of surgery [12, 93, 94]. Magkos *et al.* confirmed this phenomenon, but also reported that mucosal utilization of glucose absorbed from luminal nutrients was of a magnitude that probably does not affect glycaemia [95]. This finding supports the notion that clearance of glucose from the blood mainly accounts for improved glycaemia, particularly in the interdigestive phase. Gastric bypass construction is indeed an artificial condition, but taken together data suggest that intestinal mucosal energy expenditure is a physiological variable that can influence both body weight and glycaemia. The gut microbiota is also energy demanding and consumes energy from the luminal contents thereby enhancing energy utilization [60]. A well-known example of enhanced energy utilization from the luminal contents is the conversion of indigestible fibres to short-chain fatty acids for use as an energy substrate in the colonic mucosa [37]. The microbiota produces numerous other metabolites, and which of these the host may utilize as substrates or regulatory factors in metabolism remains to be discovered. In line with this, altering the intra-intestinal microbial composition may influence the host's metabolism [63]. Moreover, data from studies of the effect of bariatric surgery show that the composition of the faecal microbiota changed after the operation and that transfer of this 'bariatric-type' microbiota to germ-free mice resulted in reduced fat deposition [96]. Cold exposure of mice was recently reported to be associated with gut mucosal adaptation including changes in the luminal microbial composition [97]. Following transplantation of the 'cold microbiota' to germ-free animals, insulin sensitivity improved and browning of the white adipose tissue was observed. In addition, the intestinal morphology changed towards that observed in the cold-exposed donor animals. The interpretation of these findings is that the cold microbiota transferred a

'message' from the donors to the new host to perform an adaptive thermogenic response [97]. This novel crosstalk between the gut and systemic energy expenditure is a good example of an intriguing area for future frontline research.

Hyperglycaemia

Glycaemic control relates to the maintenance of a stable blood glucose concentration and can serve as a good example of complex actions by the gastrointestinal system in metabolic homeostasis. Data are accumulating that show that the gastrointestinal tract contributes significantly to glucose homeostasis by activation of several pathways with different targets in turn determining the metabolic state of tissues and organs [98]. As described above, the gut influences appetite signalling and eating behaviour as well as the distribution of nutrients in the intestinal lumen to optimize digestion and absorption, all of which are important for counteracting hyperglycaemia [38]. In addition, a leaky gut mucosa induced by a fatty diet can be the trigger of moderate systemic inflammation driving insulin resistance (Fig. 3).

Also as described above, metabolism on the organism level has two general states: the fasting catabolic state in which energy is mobilized from endogenous stores such as hepatic glycogen deposition and adipose tissue, and the postprandial anabolic state in which energetic nutrients are absorbed from the digestive tract and circulated to the peripheral tissues for direct use or for insulin-mediated storage. The switch from energy catabolism to anabolism is a critical event and occurs instantly upon meal ingestion. During the interdigestive catabolic state, release of the key hormone insulin is determined mainly by the glucose concentration surrounding the pancreatic beta cells. However, following food intake, and already during the absorption phase when large amounts of glucose enter the portal circulation, the gut mucosa signals to the endocrine pancreas to release insulin and reduce glucagon release to prepare for an approaching glucose load. Such meal-associated anticipatory humoral mediators are termed incretins, i.e. gut hormones such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP1), and originate from enteroendocrine cells in the intestinal mucosa [99]. In particular, the GLP-1-mediated effects have been translated into pharmacological principles. Both

inhibition of the GLP-1-degrading enzyme dipeptidyl peptidase-4 (DPP4) and administration of GLP-1 analogues such as exenatide and liraglutide are used clinically to improve glycaemic control. In addition, weight control is influenced by GLP-1, which is indirectly important for glycaemic control. GLP-1 regulates gastric emptying and therefore intestinal substrate availability for subsequent glucose absorption [100]. GLP-1 also mediates satiety signalling, presumably executed within the gut via inhibition of gastroduodenal motility sensed by vagal afferents, but also directly on receptors in the central nervous system. These effects have clinical relevance because, for example, liraglutide given at an appropriate dose has been shown to reduce voluntary food intake and induce significant weight loss [76, 101]. Thus, the multiple actions of GLP-1 illustrate the complexity of gut-dependent regulation not only within the digestive organs but also with regard to distant organs and behaviour.

There is much experimental evidence to suggest how the gut directly influences glycaemic control. For example, in the absorbing phase, the portal glucose concentration is sensed by vagal afferents in the wall of the portal vein, in turn eliciting hypothalamus-mediated inhibition of food intake and, consequently, the carbohydrate load on the gut [102]. Another example of anticipatory glycaemic control is that the intestinal absorption of glucose via the enterocytic SGLT-1 transporter activates glucosensitive structures in epithelial taste cells associated with subepithelial afferent nerve endings that mediate an insulin-independent reduction of hepatic glucose production via the central nervous system and a vagal efferent limb [103]. It is noteworthy that the intestinal control of glycaemia is not related to glucose concentration alone; mucosal digestion and absorption of energetic macronutrients other than carbohydrates, particularly dietary fatty acids, also influence the vagal control of hepatic glucose release [104]. In addition, the microbial formation of short-chain fatty acids, mainly butyrate absorbed by the large bowel mucosa, has been suggested to exert regulatory impact via a gut-brain axis [105]. Furthermore, alterations in the intestinal microbiota are strongly associated with disturbed metabolic disturbances such as obesity and type 2 diabetes. However, how the microbiota, which is predominantly located within the large bowel, physiologically influences glycaemic control is yet not understood [98].

Hypertension

Hypertension is strongly associated with heart disease and stroke, and pharmacological lowering of blood pressure has indeed been a successful therapeutic strategy for the prevention of cardiovascular disease [106]. Both sodium retention and neurohumoral vasoconstriction are sensitive to weight reduction that consequently improves hypertension. This effect is independent of whether it is due to dieting and/or bariatric surgery and suggests strongly that the gut has a role in blood pressure control [107]. Restrictive bariatric surgery with gastric banding was associated with a transient weight loss-associated decrease in blood pressure [108]. By contrast, weight loss after gastric bypass was followed by a marked and sustained blood pressure reduction. Interestingly, gastric bypass was associated with an increased diurnal diuresis that was not attributed to weight loss or reduced dietary salt intake. Surprisingly, salt intake instead increased after gastric bypass despite the lowered blood pressure [108]. The mechanisms involved are still debated, but direct loading of the jejunum with ingested electrolytes appears to induce a postabsorptive volume expansion and release of natriuretic peptides resulting in increased diuresis [109–111]. The increased salt intake after gastric bypass can be either a compensation for the natriuresis and/or a change in salt appetite following the bypass of an upper gut sodium sensor, normally inhibiting salt appetite [108]. There is experimental evidence for the existence of such a gastric sodium/volume sensor with capacity to influence volume diuresis and natriuresis in association with food ingestion and/or drinking [112–115]. An important factor supporting anticipatory natriuresis is that a sodium load given intraluminally is more rapidly excreted by the kidneys than a similar intravenous load [116]. This phenomenon indicates a preabsorptive sensing mechanism in the upper gut that signals to the kidneys to increase diuresis in an anticipatory fashion, thus resembling the role of incretins in glycaemic control. A 'hot candidate' for mediating enterorenal natriuresis is the incretin GLP-1, but other peptide hormone (e.g. gastrin) have also been proposed to be involved including salt-sensitive taste cells in the gastrointestinal epithelium [115, 117, 118].

Thus, it can be speculated that there are two main mechanisms involving the gut in sodium handling and blood pressure control: (i) a

preabsorptive sodium/volume sensor in the upper gut (probably in the gastroduodenum) activating anticipatory renal sodium excretion and inhibiting salt appetite, and (ii) a volume sensor releasing natriuretic peptides located in the jejunum or at a postabsorptive site (probably a cardiac volume sensor). However, the role of the gut in hypertension is far from being completely understood, and more research is needed to clarify whether the proposed mechanisms of actions are involved.

Dyslipidaemia

Dyslipidaemia is an important risk factor for atherosclerosis with, for example, coronary artery disease as an end organ manifestation. A role for the gut in dyslipidaemia is intuitive as certain dietary changes might influence the condition and because gastrointestinal bariatric surgery is associated with significant improvements [3, 13]. Clinical assessments are routinely performed in the fasting state but it has been argued that the lipaemia in the absorption phase following meals is of more clinical relevance [119, 120]. It is of no surprise, therefore, that intestinal dependent postprandial lipaemia has gained considerable attention during recent years. It is beyond the scope of this review to discuss the complex interactions between the various types of lipoproteins resulting in vascular disease. Briefly, to enable circulation in the watery plasma, the blood-borne lipids, mainly triglycerides (triacylglycerol) and cholesterol, are encapsulated in a phospholipid membrane with a specialized protein structure, the apolipoprotein. These lipid-bearing particles, the lipoproteins, have differential appearances depending on the size and type of apolipoprotein. The apolipoprotein determines the functionality of the lipoprotein particle regarding for example binding to target tissues and activation of lipid-degradation enzymes. The predominant particle types are high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) and chylomicrons. The formation of lipoproteins can be divided roughly into a liver-dependent pathway (VLDL and HDL production) and an intestinal dependent pathway (chylomicron production). From the perspective of the gut, it is worth noting that the postprandially circulating triglyceride-rich chylomicrons constitute an independent risk factor for atherosclerosis, particularly in the insulin-resistant state [121, 122]. As described above, a leaky gut epithelium following

fatty meals can be the trigger for generalized insulin resistance (see Fig. 3). This suggests a fundamental role for the gut also in vascular disease, as insulin resistance in the adipose tissue results in disinhibition of hormone-dependent lipase, in turn resulting in a continuous release of free fatty acids which act as a substrate for the hepatic release of apolipoprotein B-100-containing VLDL. This will have pathogenic implications because high postprandial levels of circulating VLDL increases the rate of interaction with the meal-induced release of apolipoprotein B-48 chylomicrons, resulting in the formation of cholesterol ester-enriched small-sized lipoprotein remnants, some of which are highly atherogenic [123–125].

Intestinal lipid uptake and metabolism

The intra-intestinal digestion of dietary fat by emulsification with bile salts and pancreatic lipase is ‘textbook knowledge’, as is the release of chylomicrons to the lymphatic drainage system and subsequent delivery to the venous blood via the thoracic duct. However, the detailed mechanisms of epithelial lipid absorption and intra-enterocytic chylomicron formation have long been unclear. It is therefore encouraging to note that understanding of the molecular machinery of absorption of monoglycerols and fatty acids from fat digestion, as well as of cholesterol and the intra-enterocytic handling with for example chylomicron formation, has improved considerably during recent years [126, 127]. One physiological feature is noteworthy: the lipids in a meal are to a certain degree kept within the enterocytes and the lamina propria until ingestion of the next meal and are then liberated as chylomicrons [127, 128]. Interestingly, the meal-associated high intramucosal glucose concentration appears to be a strong signal for release of intestinally stored fat [129]. This means that the postprandial lipaemia reflects the lipids ingested several hours previously and that glycaemia and intraluminal glucose loads are important. To what extent this phenomenon has clinical relevance, for example in relation to diabetes, remains to be investigated.

Targeting dyslipidaemia via the gut

Pharmacological reduction of cholesterol synthesis through the use of statins has been a successful anti-atherogenic therapeutic option, and today these agents are widely prescribed. The statins target HMG-CoA reductase which is a rate-limiting

step in the mevalonate pathway of cholesterol formation. It is interesting that when endogenous cholesterol biosynthesis is inhibited the intestinal cholesterol absorption increases, thus reducing the effect of statins on cholesterolaemia [130]. This and other findings suggest the presence of a regulated balance between *de novo* synthesis and the intestinal uptake of cholesterol. Not surprisingly the intestine has been promoted as a potential target for reducing the circulating pool of triglycerides and cholesterol [131]. The chylomicrons carry a substantial amount of cholesterol of which approximately 50% originates from bile, approximately 30% from dietary sources and the rest from enteric epithelial cells shed into the lumen [131]. Changes in the diet is a classical approach for reducing circulating cholesterol. However, the previously promoted restriction of cholesterol-rich foods (e.g. eggs and shrimps) appears to be of less clinical value except in cases with familial hypercholesterolaemia. The current US official recommendations are instead to reduce intake of saturated fats and increase the proportion of unsaturated fats [132]. Bile acid-/cholesterol-binding agents, such as cholestyramine, can be used to reduce the micellar mucosal exposure of cholesterol to the absorbing mucosa. Dietary plant sterols (phytosterols and phytostanols) have been shown to promote hypocholesterolaemia. As structural analogues, the phytosterols can compete with cholesterol in micelle formation [133]. Phytosterols may also activate the nuclear receptor LXR and the transcription of cholesterol efflux transporters, or even exert a statin-like action [131, 134]. Orlistat is a pancreatic lipase inhibitor, representing another pharmaceutical principle, that also interferes with micelle formation and subsequently reduces triglyceridaemia and improves the LDL/HDL ratio [135]. Furthermore, increased knowledge of the epithelial intracellular molecular handling of lipids has been translated into novel pharmaceutical principles. The triglyceride and cholesterol composition of chylomicrons can be targeted for example via actions on intracellular lipid-transporting proteins, on the esterification of cholesterol as well as on apolipoprotein transcription [127, 131]. Most of these actions are still being tested at the preclinical level but the cholesterol-uptake inhibitor ezetimibe is an example of an agent that is in clinical use [136]. The main pathway for cholesterol uptake by the intestinal mucosa is via the Niemann-Pick C1 Like 1 (NPC1L1) transporter located in the apical part of enterocytes. Ezetimibe blocks NPC1L1 with a

confirmed hypocholesterolaemic effect. However, the effect of ezetimibe as monotherapy was found to be partly balanced by an increase in endogenous cholesterol biosynthesis, and co-therapy with a statin is therefore more effective [137].

Emerging fields of gut metabolic science and potential clinical utility

The gastrointestinal tract plays a key role in systemic metabolic regulation during and some hours after each meal. The modern lifestyle of an unrestricted availability of high-energy foods with a low demand for physical activity means that the digestive/absorptive anabolic state predominates, resulting in overweight and obesity. Potential long-term pathophysiological effects vary in relation to genetic predisposition and environmental factors, including probably neonatal colonization of the gut microbiota. Several gastrointestinal influences on metabolism have been identified although only a few have so far been translated into clinically useful tools, good examples of which include orlistat, ezetimibe and GLP-1 analogues [135, 137, 138]. In addition, drugs used for treating diabetes also influence gastrointestinal functions. For example, metformin exerts several actions via the gut, including increased intestinal glucose utilization and GLP-1 release [139]. Insulin has been proposed to influence intestinal glucose transport via intra-enterocytic translocation of the GLUT2 transporter [140]. Furthermore, this mechanism is resistant to insulin in obese subjects but can be normalized by bariatric surgery in parallel with improved glycaemic control [94]. Interestingly, a recent study showed that intestinal epithelial T cells in obese subjects have a phenotype that secretes cytokines promoting enterocytic insulin resistance [141].

Concluding remarks

At present, research activity regarding the interactions between the immune system, the digestive organs (the gastrointestinal and hepatopancreatic tracts) and the intestinal microbiota is rapidly increasing. It must be noted, however, that basic scientific research is based mainly on rodent models and cell cultures, the relevance of which for human physiology and clinical conditions remains unknown. Few studies have validated the translation of rodent-based data to a human context in a 'head-to-head' fashion. Very recently, Hodge *et al.* demonstrated that nutritional agents which significantly improved weight and glycaemic

control in rodents lacked effect in humans [142]. Nevertheless, as energy homeostasis is a fundamental feature in evolution, mechanisms of action discovered in nonhuman models could certainly be of importance, but data must always be considered with scepticism. It can be expected that in the future, the metabolic syndrome will be prevented with novel pharmacological interventions affecting the crosstalk between the gut, its microbiota and the immune system. However, and perhaps even more importantly, a deeper understanding of the role of gut physiology in metabolism will also motivate effective preventive lifestyle measures both at the individual and society levels.

Conflict of interest statement

The author declares no conflicts of interest.

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