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Review

Paneth Cell, Gut Microbiota Dysbiosis and Diabetes Mellitus

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Abstract: Around 500 million adults in the world have diabetes mellitus, and the incidence is increasing. Over 90% of type 2 diabetes mellitus cases are associated with dysbiosis of the microbiota of the gut, chronic systemic inflammation, mitochondrial dysfunction and destruction of the β-cells of the pancreas. Paneth cells are found in the entire length of the small intestine in humans and play a key role in its innate immunity. Deficient function of Paneth cells predisposes the intestine to gastrointestinal and extra-gastrointestinal diseases, which include inflammatory bowel disease. This manuscript reviews the roles of the Paneth cells in the innate immunity of the small intestine, the link between dysbiosis and dysfunction of Paneth cells and the influence of dysbiosis in the pathogenesis of diabetes mellitus. The manuscript also reviews some strategies currently used to try to reverse dysbiosis and its consequences.

Keywords: chronic inflammation; diabetes mellitus; dysbiosis; mitochondrial dysfunction; oxidative stress; Paneth cells

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1. Introduction

The gastrointestinal tract (GIT) is the largest organ and the most hostile area in the body, as it is the most significant region of the body in contact with the external environment. The majority of immune active cells are in the GIT, and it is the area where antigens are sent for processing by the immune system regardless of the portal of entry [1]. The region of the small intestine in the GIT is even more perilous because of its long length and because it is lined by a thin mono-layered epithelial layer, which has to perform the dual functions of absorption of nutrients and acting as a barrier against harmful pathogens [2]. The nutritious environment in the lumen of the small intestine is habitable to numerous potentially harmful species of bacteria, parasites, viruses and fungi [3,4].

The intestinal epithelial cells (IECs), junctional proteins and microbiota are responsible for the innate immunity of the small intestine [3,5–7]. Among the IECs that participate in the innate immunity of the small intestine are the absorptive enterocytes, goblet cells, Paneth cells, enteroendocrine cells, tuft cells and microfold cells (M-cells) [2,8]. The surface IECs and junctional proteins form a continuous layer, which prevents the translocation of microorganisms and their products from the lumen of the small intestines.

Most of the IECs possess pathogen recognition receptors, which they use to continuously sample the lumen of the small intestine for pathogens [6,7,9]. The IECs secrete antimicrobials whenever they detect pathogens. Some of the substances that the IECs use to regulate the microbiota of the gut are the antimicrobial peptides, proteins, secretory

immunoglobulins (IgA) and mucins [10,11]. Human α-defensin 5 (HD-5) is the most voluminous and potent antimicrobial that is secreted by the Paneth cells [11–15]. Paneth cells regulate the microbiota in the lumen of the small intestine [6,16–18]. Human α-defensin 5 can kill bacteria, parasites, fungi and some viruses [6,19,20]. Maintenance of normal microbiota in the lumen of the small intestine is critical for the structural integrity and regulation of mitotic activities of the crypt-based leucine-rich repeat-containing G-protein coupled receptor 5-expressing intestinal stem cells ($Lgr5^+$ ISCs) [12,21,22]. An alteration in the function of the IECs, including the Paneth cells, may lead to a change in the composition of the microbiota, known as dysbiosis [23–25]. Common causes of dysbiosis of the gut microbiota include change in diet, high-fat diet intake, the use of broad-spectrum antibiotics and bowel resection or bypass surgery [26].

Dysbiosis either leads to an excess of pathogenic organisms or a relative decrease in the proportion of beneficial species of bacteria and viruses. Dysbiosis leads to inflammation of intestinal epithelium and increased permeability and translocation of microorganisms and/or their products [7,27–29]. Dysbiosis also induces an increase in the production of pro-inflammatory cytokines, among them interleukin-6 (IL-6) [28,30–32]. Additionally, dysbiosis of the gut microbiota may lead to an increase in the production of reactive oxygen species (ROS) or reactive nitrogen species (RNS) by the resident bacteria [31,33,34].

Dysbiosis, increased gut permeability of the intestinal epithelium, translocation of bacteria, local inflammation, endotoxemia, chronic systemic inflammation and mitochondrial dysfunction are seen in some of the patients who have inflammatory bowel disease (IBD) [35], rheumatoid arthritis [36], obesity and metabolic syndromes [29,37–41]. In addition, dysbiosis, persistent systemic inflammation, mitochondrial dysfunction and increased oxidative stress are the typical findings in individuals who have diabetes mellitus (DM) regardless of the subtype [42–52].

The incidence of DM is increasing worldwide, and around 500 million adults globally have type 2 DM [46]. Diabetes mellitus is the leading cause of cardiovascular disease, blindness and chronic kidney dysfunction in adults [44,53–55]. Diabetes mellitus is also a major risk factor for lower limb amputation [47,56,57]. The following and subsequent sections of the manuscript review the role of Paneth cells and other IECs in the innate immunity of the small intestine, the influence of dysbiosis in the pathogenesis of DM and its complications and some of the treatment strategies used in the management of DM that target dysbiosis.

2. Methods

We elected to write a narrative review because of the recent increase of interest in the study of Paneth cells and the role of dysbiosis in DM, and few randomised or observational studies have been conducted. The majority of the publications are narrative reviews. The PubMed database was used to search for articles that have been published on Paneth cells. The search was limited to full-text articles. The search terms included innate immunity and the small intestine, Paneth cells, Paneth cells and gut immunity, Paneth cells and gut microbiota, Paneth cells and diabetes mellitus, diabetes mellitus and dysbiosis and Paneth cells, dysbiosis and diseases. An additional search was performed for articles covering subthemes including classification of diabetes mellitus, subtypes of diabetes mellitus, treatment of diabetes mellitus and complications of diabetes mellitus. From articles published in the last 10 years, older articles that have been cited at least 100 times were selected. The review prioritised publications based on work done in humans. The search started in January 2023 and repeated periodically until the end of 25 March 2023 to pick up new publications. The review ultimately included 233 articles, 74% (172) of which were published in the last 5 years.

3. Innate Immunity of the Small Intestine

The small intestine has a huge surface area that is further enhanced by villi and microvilli to facilitate the digestion and absorption of nutrients. The expanded surface

area of the small intestine increases the likelihood of exposure to pathogens in the lumen. The small intestine must balance the need for nutrient absorption with the ability to ward off pathogens [58]. The majority of the immune cells in the body reside in the mucosa-associated tissues and the mesenchymal tissues of the gastrointestinal tract (GIT) [59]. The gut-associated lymphoid tissues (GALT) play a vital role in the development of the immunity of the entire body, as most of the antigens that get into the body are transported to the GIT for processing by its innate immunity before being delivered to the adaptive immunity [30,59,60].

A healthy life depends on maintaining the small intestine's structural integrity and normal physiological function. Both the structural integrity and normal physiological function of the small intestine are dependent on the continuous generation of new IECs by the Lgr5$^+$ ISCs to replace senescent ones [2,61–64]. A combination of the surface epithelial cells and junctional proteins provides a continuous physical barrier that is augmented by mucins [5,7]. The microbiota of the gut is also critical for the development and sustenance of the innate immunity of the small intestine [65–70]. Bacteria compete among themselves to maintain a healthy balance, while some of the viruses in the lumen of the small intestines are bacteriophages and take part in the control of potentially pathogenic bacteria [7,27,71].

3.1. Intestinal Epithelial Cells and Innate Immunity

Almost all the IECs play a critical role in the innate immunity of the small intestine. Although all of them except the Paneth cells have a short lifespan of around 3–5 days, they are replaced quickly following their death. Regular replacement of the surface IECs ensures an intact physical barrier. Antimicrobial peptides and proteins that are secreted by the intestinal epithelial cells (IECs) are responsible for most of the chemical defence. Antimicrobial peptides are the most effective weapons against an overgrowth of pathogens and the subsequent bridge of the innate immunity of the small intestine [14,16,72,73].

3.1.1. The Role of Paneth Cells in the Innate Immunity of the Small Intestine

Paneth cells are among the derivatives of the Lgr5$^+$ ISCs in the small intestine and the small intestine's major source of antimicrobial peptides and proteins [62]. Paneth cells control the microbiota in the lumen of the small intestine and the proximal parts of the large bowel. The antimicrobial peptides from Paneth cells bathe and sterilise the area where the rapidly dividing and highly vulnerable Lgr5$^+$ ISCs are found [2,64,73].

Matured Paneth cells are found at the base of the intestinal crypt of Lieberkühn in the entire small intestine from the duodenum to the terminal ileum [74,75]. Paneth cells start appearing in the small and large intestines of embryos at the end of 12 weeks, and their number increases significantly in the small intestine after 36 weeks [73,76]. The adult colon contains few, if any, Paneth cells. Goblet cells and other cells, instead of Paneth cells, are responsible for the antimicrobial activities in the colon [76]. Metaplastic Paneth cells may appear in the colon and other sites in patients who have, for example, IBD [77]. The number of Paneth cells increases during childhood and a full complement for an individual is reached later in life [78]. Each intestinal crypt in an adult ultimately contains around 5–15 Paneth cells [79]. The number of Paneth cells per intestinal crypt is, however, variable, as their density increases downwards. The highest density of Paneth cells in a healthy state is found in the ileum [80].

The HD-5 is responsible for most of the antimicrobial activities in the small intestine [13,14,74,81]. The other antimicrobial peptides and proteins that are secreted by the Paneth cells include human α-defensin 6 (HD-6), lysozyme and phospholipase [13,82]. Although the other IECs such as the absorptive enterocytes, goblet cells and tuft cells survey and regulate the gut microbiota, Paneth cells are the most critical for innate immunity in the small intestine, as they secrete the largest amount of the most potent antimicrobial peptides and proteins [16,78]. In addition, the localisation of matured Paneth cells at the base of the intestinal crypts ensures the maximal concentration of antimicrobial peptides for the defence of the highly active but most vulnerable Lgr5 ISCs [78] (Figure 1).

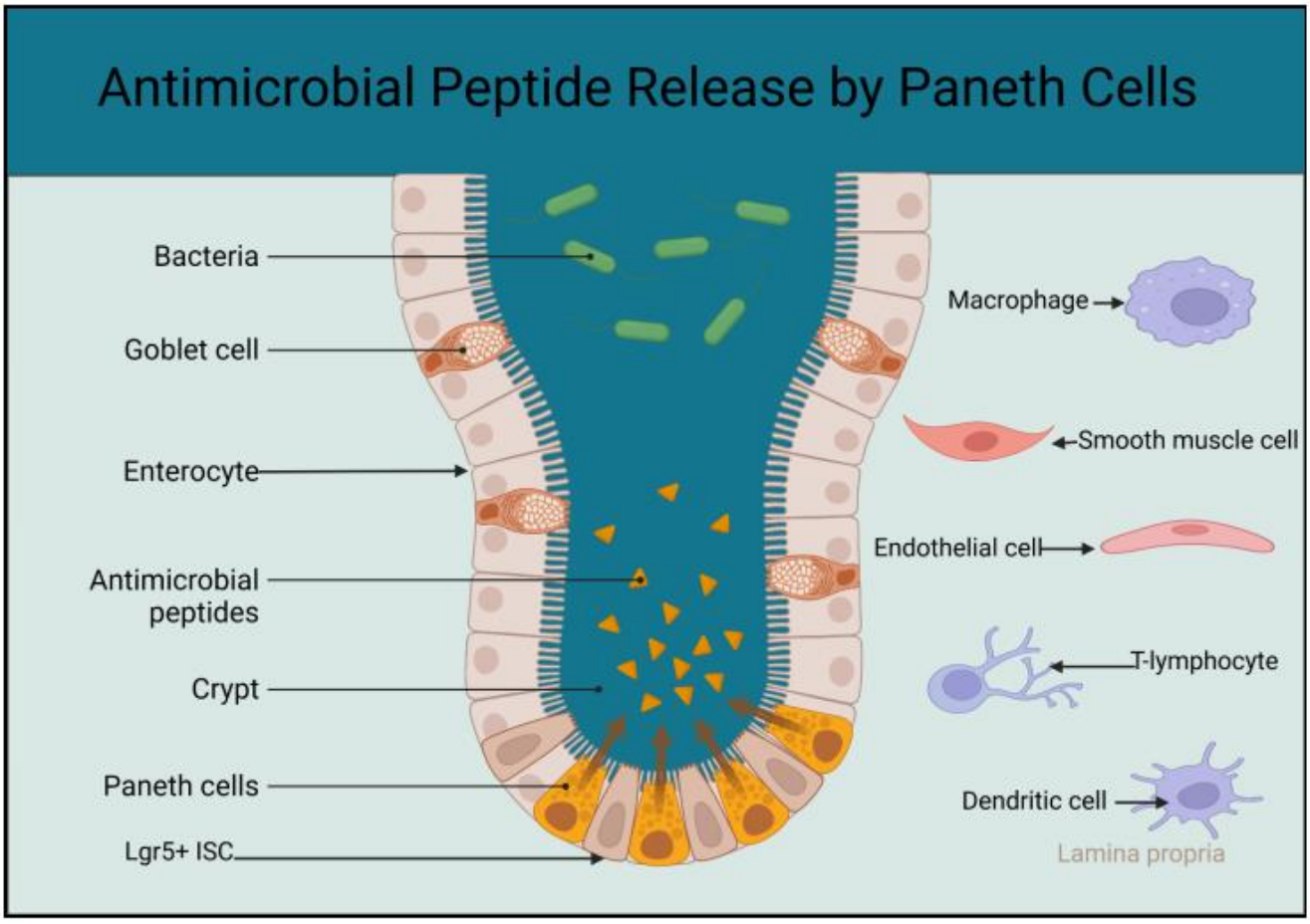

Figure 1. Schematic diagram showing the localisation of matured Paneth cells at the base of the intestinal crypt and higher concentration of antimicrobial peptides at the stem cell zone. The sketch also includes cells in the lamina propria that interact with the Paneth cells to support and regulate activities of the $Lgr5^+$ ISCs (created using BioRender.com accessed on the 25 April 2023).

Paneth cells are pyramidal in shape. They have a broader base where their nucleus is situated [82]. Paneth cells are among the secretory derivatives of the $Lgr5^+$ ISCs, and their cytoplasm contains several organelles, which include the endoplasmic reticulum and Golgi apparatus. The apical area of Paneth cells has eosinophilic granules that contain, among other constituents, HD-5, HD-6, lysosome, growth factors, Wnt signals and cytokines [74,82]. Paneth cells release their constituents after the detection of pathogens through their pathogen recognition receptor system. Paneth cells continually sample the microbiota in the lumen of the small intestine to prevent dysbiosis [82–84]. Paneth cells also secrete antimicrobial peptides and other products following a stimulus from the brain via the cholinergic system. The mere sight or smell of food may also lead to the activation of the Paneth cells. Additionally, Paneth cells sample the composition of nutrients in the food following ingestion [7] (Figure 2).

Some of the antimicrobial proteins and peptides secreted by the Paneth cells are stored as zymogens in the cytoplasmic granule and are activated just before release [82]. Once activated, HD-5 can kill all bacteria, fungi and parasites and some viruses [85]. Paradoxically, HD-5 can enhance proliferation of certain viruses [12,82]. Human defensin 5 is lipophilic and kills pathogenic bacteria by creating pores on the cell membrane, which increases the permeability, thus making the bacteria swell up and subsequently burst [12,17,19]. Human α-defensin 6 does not have anti-microbiocidal activity but is able to create nanonets around pathogens, thus trapping and containing them [84] (Figure 3).

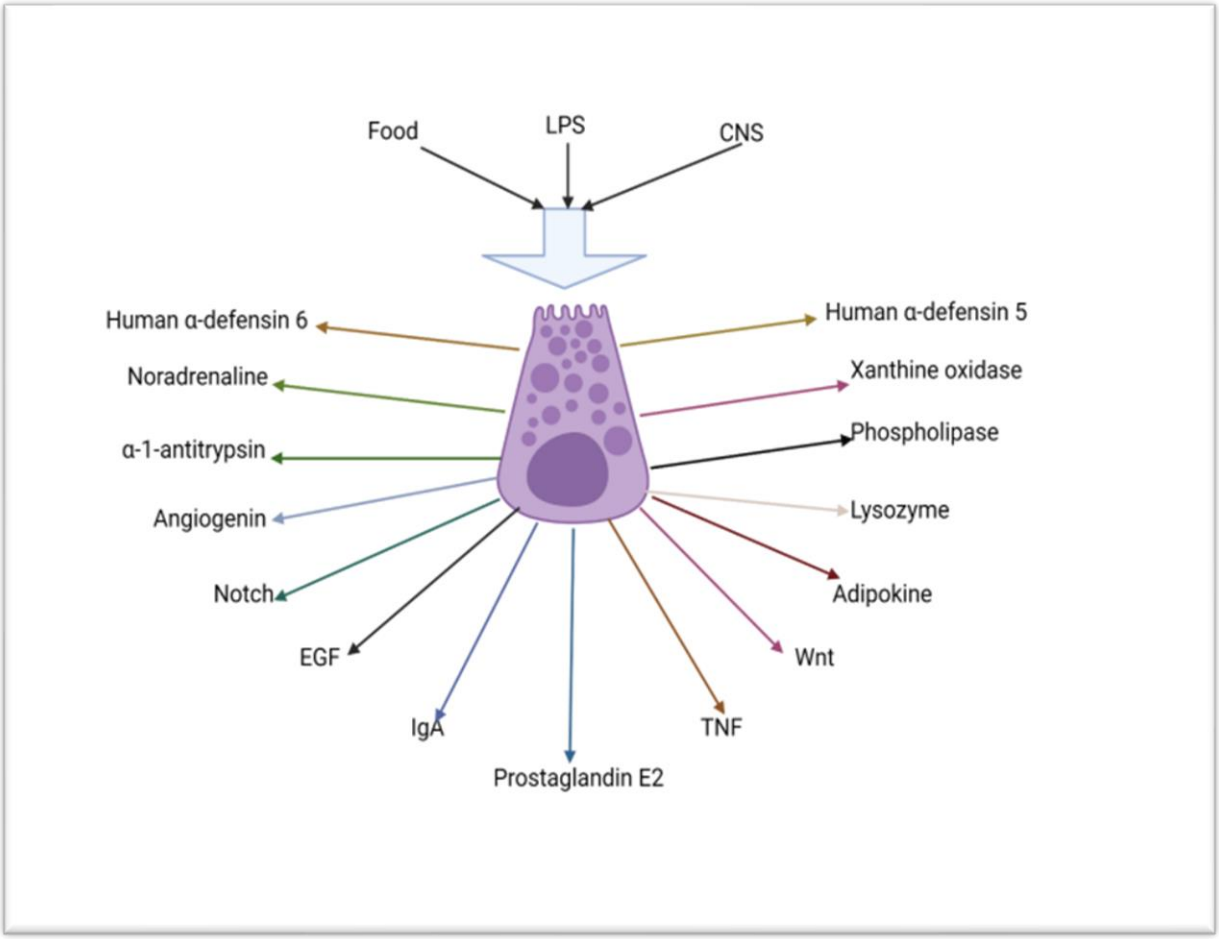

Figure 2. Schematic diagram depicting the mechanism of stimulation and some of the substances that are secreted by the Paneth cell (created using BioRender.com 9 of April 2023). LPS = lipopolysaccharide, CNS = central nervous system, Notch = neurogenic locus notch homolog protein 2, EGF = epidermal growth factor, IgA = IgA immunoglobulin, TNF = tumour necrosis factor, Wnt = wingless/integrated.

Lysozyme and IgA, also secreted by the Paneth cells, add to the antimicrobial activities in the lumen of the small intestine [80]. The other functions of the Paneth cells that are critical for the maintenance of robust innate immunity in the small intestine include the regulation of proliferation and differentiation of the Lgr5$^+$ ISCs, metabolic support of the Lgr5$^+$ ISCs and liaison with cells involved in adaptive immunity [2,12,59,60,62,83,85,86]. Abnormality in the number or function of Paneth cells is seen in numerous diseases, including viral infections [80], necrotising enterocolitis [76], prolonged use of total parental nutrition [87], starvation [88], Crohn's disease [15,77,83,89–91], smoking [90] and ageing [8]. A change in the total number of Paneth cells or a deterioration in the quality of their function may also occur during chronic HIV infections [92].

3.1.2. Absorptive Enterocytes, Goblet Cells, Tuft Cells, M-Cells and Junctional and Innate Immunity of the Small Intestine

Goblet cells augment the antimicrobial defence by secreting mucous made up of mucins, water and trefoil factors. MUC2 is the major constituent of the mucus and helps to form a carpet of mucus that maintains a higher concentration of antimicrobial peptides in the area adjacent to the surface of the IECs [74]. Secretory mucus is an essential nutrient for some commensal organisms. The absorptive enterocytes are the most abundant IECs [2].

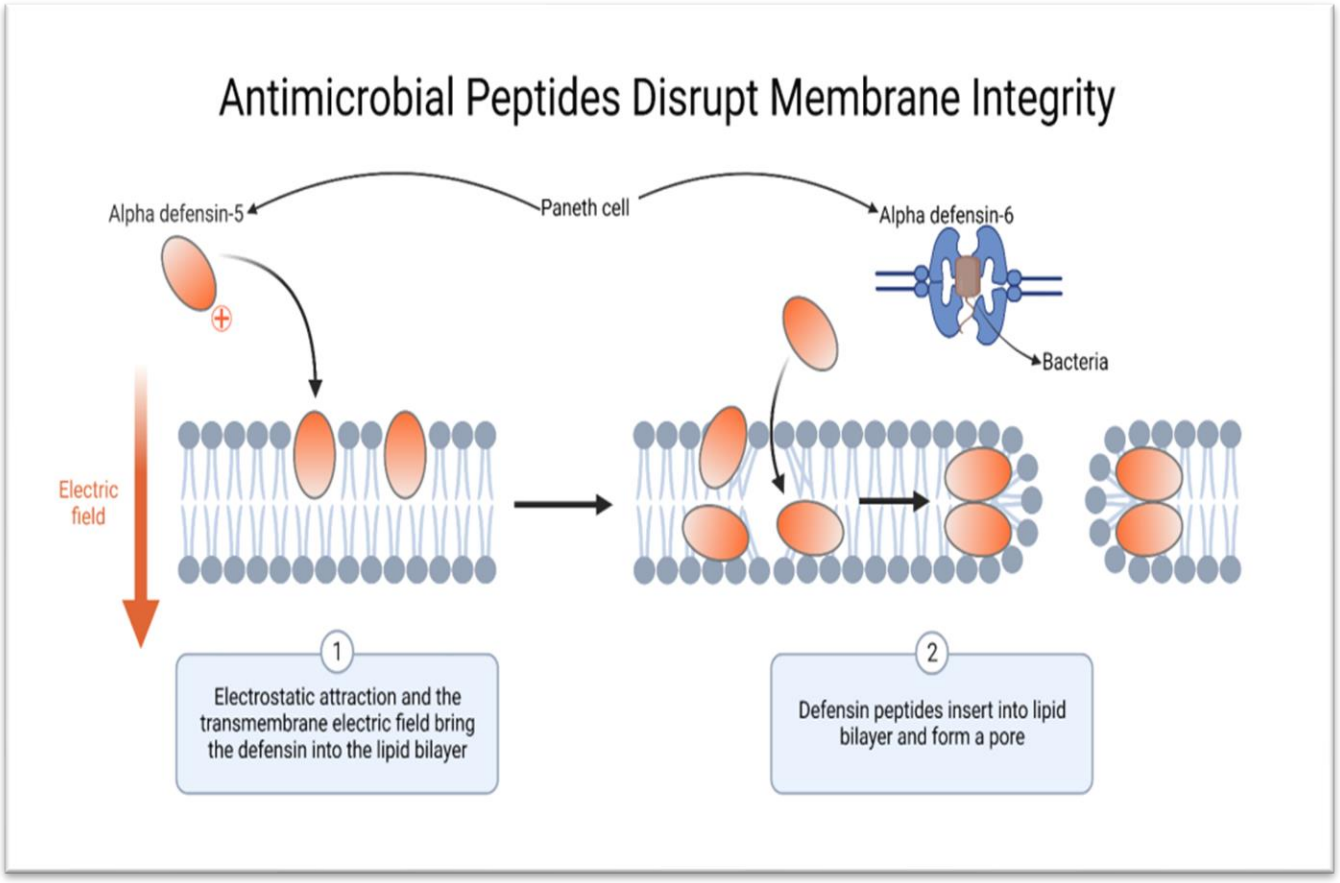

Figure 3. Schematic diagram showing the mechanism of action of HD-5 and HD-6. HD-5 kills bacteria and other microorganisms by creating pores on the cell membrane, while HD-6 forms nanonets to entrap pathogens (created using BioRender.com on 9 of February 2023).

Absorptive enterocytes have pathogen recognition receptors, which they use to sample the contents in the lumen of the small intestine and therefore participate in innate gut defence [9]. Like any other epithelial cell throughout the body, the absorptive enterocytes secrete β-defensin and not HD-5 or HD-6. Other IECs that participate in the regulation of the microbiota in the lumen of the small intestine are the tuft cells and the M-cells [58,93–96]. The tuft cells sample the gut microbiota like the Paneth cells but to a limited extent [96–98]. Secretions from the tuft cells are limited to cytokines [99]. Tuft cells have not been shown to secrete antimicrobial peptides, growth factors or catecholamines [99]. The junctional proteins also add to the innate immunity of the small intestine [5,7,27].

3.2. Gut Microbiota and Innate Immunity in the Small Intestine

The gut lumen contains numerous species of bacteria, viruses, fungi, parasites and archaea [100]. Around 10^{14} bacteria reside in the colon, but the small intestine contains fewer microorganisms [78]. Colonisation of the gut starts in utero and increases during childbirth [101,102]. Further changes in the gut microbiota composition occur during breastfeeding and weaning [101,102]. The normal gut flora of an individual is established during early childhood or adolescence. Once established, the gut microbiota is involved in the regulation of the physiological function and innate immunity of the small intestine [101,103]. The gut microbiota also influences the proliferation and differentiation of the $Lgr5^+$ ISCs and assists with the digestion of food [28]. Some of the commensals in the microbiota help process nutrients such as vitamins and short-chain fatty acids (SCFAs) like acetate and butyrate [3,28]. Complex dietary fibres would be difficult to digest and absorb without the assistance of commensal bacteria [3,28].

Certain species of bacteria help sustain the prevailing anti-inflammatory state to prevent damage to the intestinal epithelium, increased permeability, translocation of endotoxins and chronic systemic inflammation [32]. The other roles of the commensal organisms include preventing excessive production of ROS or RNS [30]. Furthermore, some of the commensal bacteria in the microbiota possess quorum sensors and secrete bacteriocins to kill the pathogenic species [70]. In addition, several species of bacteria can influence the cells involved in adaptive immunity in the lamina propria of the small intestine [30]. Several bacteria can modulate the hormonal milieu in the GIT and the entire body by participating in the microbiota-gut-brain axis. In return, commensal organisms depend on the nutrients in the diet, residue following digestion of nutrients and mucins secreted by goblet cells [104].

More than 80% of the bacteria in a healthy adult human belong to the Firmicutes and Bifidobacterium phyla [105]. Changing diet, use of antibiotics, chronic illness and excisional or bypass surgery in the GIT may lead to dysbiosis [106,107]. Dysbiosis may involve the entire length or certain niches along the GIT. Dysbiosis commonly leads to a reduction in the diversity of the microbial species and the dominance of pathogenic organisms like the Bacteroides [3,27,30,32,78]. Dysbiosis not only involves bacteria but may also include the virome [100]. Dysbiosis and the emergence of pathogenic species may lead to an increase in the production of ROS [108]. High levels of ROS in the lumen of the gut can damage the intestinal epithelium [108]. Concomitantly, pathogenic gram-negative or gram-positive bacteria may initiate an inflammatory response by releasing pro-inflammatory lipopolysaccharides or peptidoglycan, respectively [32,109] (Figure 4).

Inflammation of the epithelium of the small intestine increases its permeability, leading to the translocation of bacteria and their products [29]. Ongoing translocation of bacteria and endotoxins causes endotoxaemia and chronic systemic inflammation [4]. Chronic systemic inflammation creates an environment that is obesogenic and diabetogenic [106]. Chronic systemic inflammation also increases the generation of ROSRNS from mitochondria in tissues and organs throughout the body [34,78]. Some cells in organs throughout the body such as the β-cells of the islets of Langerhans in the pancreas have a limited capacity to neutralise reactive species, which can perpetuate the damage to their mitochondria [30].

The high level of glucose in the blood and tissues creates a mismatch between the aerobic glycolysis and the oxygen-dependent tricarboxylic acid cycle, which increases the production of ROS and RNS [42,45,109]. Chronic inflammation also impairs mitophagy in the mitochondria and affects the ability of the mitochondria to recycle and preserve essential constituents through either fusion or fission [48]. Dysbiosis, increased ROS production, increased gut permeability, translocation of bacteria and chronic systemic inflammation are the pathological basis of common non-communicable diseases like obesity [110], depression [111], cancer [110,112,113] and DM [108,114,115]. Over 90% of individuals who have DM are obese [101]. The adipokines from the adipose tissue in individuals who are obese sustain and worsen the inflammatory process [39,113].

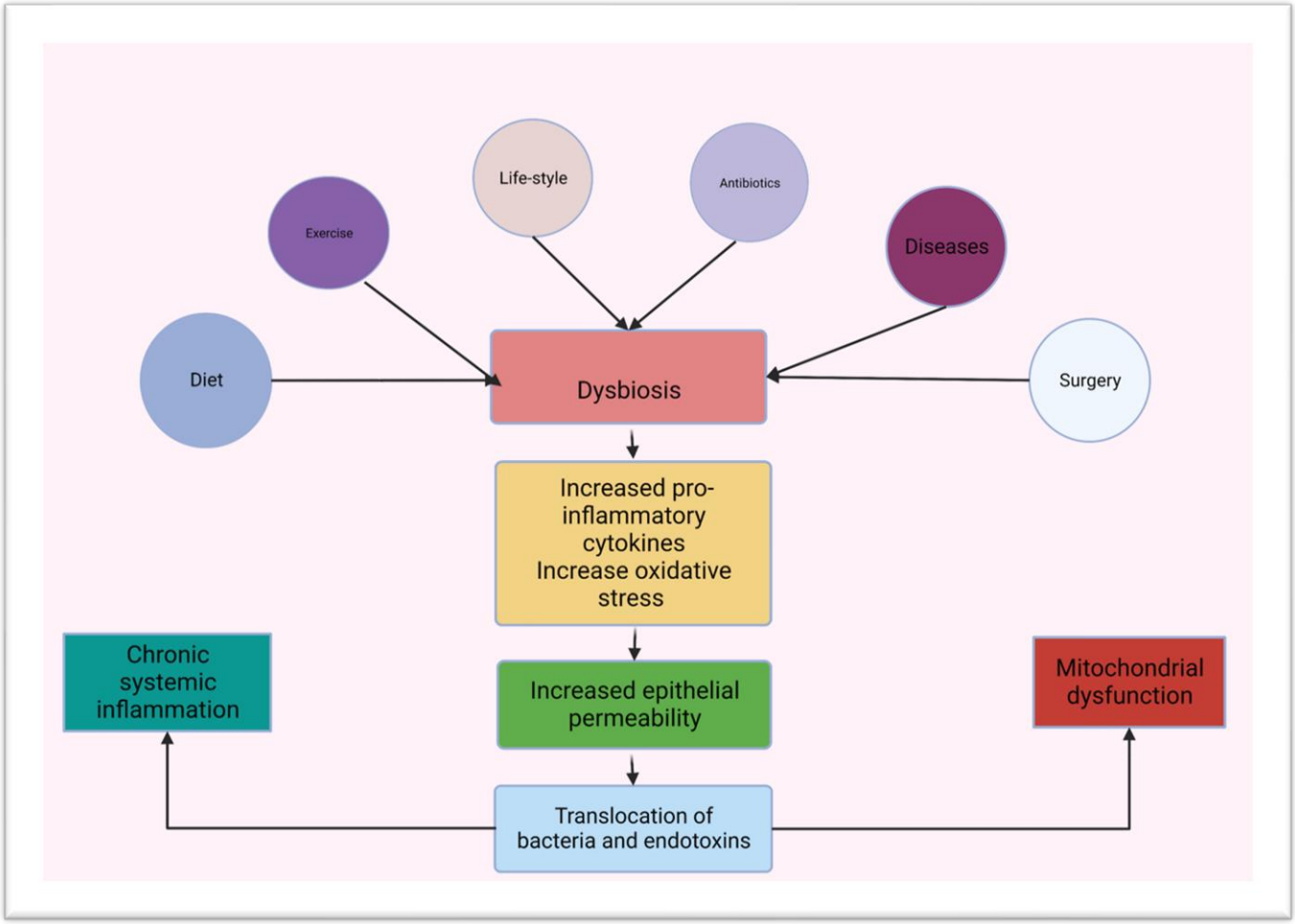

Figure 4. Schematic diagram showing predisposing factors for dysbiosis and a link between dysbiosis, chronic inflammation and mitochondrial dysfunction (created using BioRender.com on the 3 of March 2023).

4. Diabetes Mellitus

Over 400 million adults in the world have DM [78]. The increase in the prevalence of DM is more rapid in low- and middle-income countries (LMICs) worldwide. The common forms of DM are type 1 DM and type 2 DM [19]. The other types of DM are pancreatogenic DM (Typec 3c) [116], gestational DM (GDM) [117], neonatal DM (NDM) [118], post-transplant DM (PTDM) [119] and human immunodeficiency virus (HIV) infection associated DM [63]. Gestational DM is usually transient as opposed to HIV-associated DM which persist during treatment with ARVs [120,121].

4.1. Pathogenesis of Diabetes Mellitus

Diabetes mellitus is due to either absolute or relative insulin deficiency. The majority of DM cases are, however, due to the combination of absolute deficiency and resistance to its action [7,55,115,120,122–126]. In most cases, DM starts with dysbiosis and is sustained by chronic inflammation, mitochondrial dysfunction, oxidative stress, continuing destruction of β-cells of the pancreas and obesity [42,44,49,55,100,106,125–128]. Rarely, malignancy of the pancreas may present as DM [116]. The diagnosis of DM relies on the level of fasting, random or stimulated blood glucose [117,119]. Other tests useful for diagnosing DM are the level of glycosylated haemoglobin or circulating exosomes [41,127,129].

4.1.1. Type 2 Diabetes Mellitus

Over 90% of individuals with DM have type 2 DM [126,130]. Type 2 DM was previously deemed to be solely due to insulin resistance; however, insulin deficiency is involved in its pathogenesis, perhaps later during its progression as the pancreatic β-cell mass gets destroyed [44,49]. Over 90% of individuals with type 2 DM are overweight or obese, and the common association of DM with obesity has led to the coining of the term "diabesity" [101]. Like obesity, type 2 DM starts with dysbiosis of the gut bacteriome and virome, increased permeability of the epithelium of the small intestine, translocation of bacteria and endotoxins, systemic inflammation and increased production of ROS or RNS [56,100]. Patients with type 2 DM are in a state of chronic inflammation [126,130]. The ROS and RNS produced during ongoing systemic inflammation damage the β-cells of the pancreas and lead to their diminution, which adds to the insulin resistance that occurs due to chronic systemic inflammation [122].

4.1.2. Type 1 Diabetes Mellitus

Around 5% of the individuals with DM have type 1 DM, but its prevalence is increasing [130]. A feature of type 1 DM is absolute insulin deficiency, which follows destruction of β-cells of the pancreas by autoantibodies. Like type 2, type 3c, GDM, HIV and post-transplant DM, dysbiosis of the gut microbiota precedes its onset [30,100,129]. Individuals with type 1 DM are prone to ketoacidosis and other complications that occur in patients with type 2 DM, like retinopathy and nephropathy [42].

4.1.3. Pancreatogenic (Type 3c) Diabetes Mellitus

Type 3c DM follows non-selective destruction of the parenchyma of the pancreas and commonly seen in chronic pancreatitis [63]. Other predisposing conditions for type 3c are acute pancreatitis, pancreatic cancer, cystic fibrosis, pancreatic resection and haemochromatosis [116,130]. Dysbiosis of the gut microbiota also plays a role in the pathogenesis of type 3c DM [131]. Type 3c DM is difficult to treat, as the diabetes is brittle due to the combination of glucagon and pancreatic polypeptide deficiency, hepatic insulin resistance and exocrine insufficiency [131].

4.1.4. Gestational Diabetes Mellitus

Gestational diabetes mellitus affects up to 25% of pregnancies and starts during the second or third trimester of pregnancy, and women who are older and/or obese are at increased risk [117,132–134]. The other risk factors of GDM are a family history of type 2 DM and a previous history of GDM [117]. Gestational diabetes mellitus results from insulin resistance caused by the hormones that released from the placenta [120]. Dysbiosis of the gut microbiota is also involved in the pathogenesis of GDM [99,133,134]. Women with GDM are at high risk of an adverse outcome and may later develop type 2 DM, but GDM should disappear, and the blood glucose normalises following delivery [117].

4.1.5. Human Immunodeficiency Virus Infection and Antiretroviral Drug-Associated Diabetes Mellitus

Dysbiosis of the gut microbiota is commonly seen in individuals with chronic HIV disease regardless of treatment status [57,64,104,135–139]. Individuals who have HIV are likely to have Paneth cells that are either dysfunctional or exhausted [92]. The dysbiosis of the gut microbiota persists even during treatment with ARV drugs [38,140–144]. Individuals who have chronic HIV disease are in a state of chronic systemic inflammatory state, with elevated oxidative stress, insulin resistance, obesity, mitochondrial dysfunction and destruction of the beta cell mass [38,138,143,144]. The dysbiosis and chronic systemic inflammation that develop in chronic HIV disease explain the high prevalence of obesity, cancers, thromboembolic disease, dyslipidaemia and DM [68]).

4.1.6. Post-Transplant Diabetes after Solid Organ Transplant

Post-transplant diabetes (PTDM) after solid transplantation is a common condition. Its incidence varies from 10–40%, depending on the definition [145–149]. The mechanism of development of PTDM differs based on the organ transplanted. New-onset diabetes after a liver transplant has a different mechanism than other solid organ transplants [145,147,149]. Post-transplantation diabetes is defined as the development of increased blood sugar levels during fasting times above 7 mmol/L, abnormal oral glucose tolerance test of 2 h >11 mmol/L, random glucose greater than 11 mmol/L, elevated glycated glucose (HbA1c) over 6.5% or a need for hypoglycaemic agents after transplantation in the absence of pre-existing diabetes [148]. Metabolic derangements of increased elevated triglycerides, hypertension, obesity and insulin resistance accompany it [149]. Metabolic derangement confers an increased risk for cardiovascular morbidity and mortality affecting survival after organ transplantation compared to non-diabetic organ transplant recipients [150]. The pathophysiology for PTDM is multifactorial, includes reduced insulin secretion, and increased insulin resistance in the peripheral circulation. The pathophysiology involves multiple drug groups, like corticosteroids, calcineurin inhibitors (CNIs) and mammalian target of rapamycin (mTOR) inhibitors. The mechanism relates to the high doses of steroids required to maintain the recipient graft function. Like in the other types of DM, in patients post organ transplant, PTDM is associated with dysbiosis of the gut microbiota [149]. Although Paneth cells are resilient, they sometimes become dysfunctional following solid organ transplant [77].

4.1.7. Maturity Onset Diabetes of the Young

Maturity onset diabetes of the young (MODY) makes up around 2% of DM patients and has more than 22 subtypes [52]. It is frequently confused with type 1 DM and type 2 DM [52]. The diagnostic criteria of MODY include the age of onset below 45 years, evidence of normal beta cell function and absence of antibodies against β-cells of the pancreas [150]. MODY is peculiar, as it does include insulin deficiency or resistance, and the presumed reason for its development is a high set point for stimulating insulin receptors [150]. Table 1 contains a summary of the classification, predisposing factors, influence of dysbiosis and underlying pathology of MODY and the other types of DM.

4.2. Complications of Diabetes Mellitus

Diabetes mellitus affects water, electrolytes, carbohydrates, lipid and protein metabolism. Individuals with DM are prone to acute and chronic complications [46,157–159]. Acute complications include hypoglycaemia, hyperglycaemia, ketoacidosis, infection and infestations [53,160–163]. The most common reason for the admission of DM patients is diabetic foot sepsis (DFS) [53,162]. Diabetic foot sepsis follows foot ulceration and is responsible for more than 60% of non-traumatic amputations in the civilian population [53,164]. Dysbiosis of the gut increases the risk of acute complications of DM and peri-operative complications [165–167]. Nephropathy, retinopathy, neuropathy, cardiac diseases and peripheral arterial occlusive disease are among the complications of DM [2,5,42,45,47,168–172].

Individuals with DM are likely to be obese, which adds to the risk of developing cardiovascular complications [101]. In addition, DM patients are at a high risk of left-sided stenotic heart lesions, which could be due to the increased production of advanced glycated products and oxidative stress [173,174]. Diabetes mellitus paradoxically protects against the development of aortic aneurysms [173].

Table 1. Classification, predisposing factors, influence of dysbiosis and underlying pathology in various types of diabetes mellitus.

Type of Diabetes Mellitus	Prevalence	Predisposing Factor(s)	Influence of Dysbiosis	Underlying Pathology
Type 1 DM [52,115,151].	5%	Genetic Autoimmunity.	Yes	Absolute insulin deficiency.
Type 2 DM [52,152–156].	90%	Genetic. Obesity. High fat diet. High calorie diet. Sedentary lifestyle.	Yes	Insulin resistance. Insulin deficiency.
Type 3c DM [116,131,155].	8–16%	Acute pancreatitis. Chronic pancreatitis. Haemochromatosis. Cystic fibrosis. Pancreatic cancer.	Yes	Exocrine insufficiency. Reduced incretin secretion. Insulin deficiency. Glucagon deficiency. Pancreatic polypeptide deficiency. Hepatic insulin resistance.
Neonatal diabetes mellitus [118].	1 in 90,000	Genetic	Unknown.	Abnormal function of β-cells. Anatomical anomaly of pancreas.
Post-transplant associated diabetes mellitus [119].	10–40% of posttransplant patients	Steroids. Immunosuppressive drugs.	Yes	Insulin resistance. Insulin deficiency.
Gestational diabetes mellitus [132].		Family history. Older age. Obesity. Smoking.	Yes	Insulin resistance.
HIV and ARV-associated DM [136,138,139].		Antiretroviral drugs. Systemic inflammation.	Yes	Insulin resistance.
Maturity onset diabetes of the young [150].	2%	Genetic	Unknown.	High set point of insulin receptors.
Drug-induced DM [156].		Type, dose and duration of treatment.	Unknown.	Insulin resistance.

One of the factors that increases the risk of chronic complications of DM is the quality of glycaemic control, which is assessed by checking the level of glycosylated haemoglobin (HbA1c) and/or exosomes [127]. An HbA1c level above 6.5% signifies poor DM control. Individuals with DM are also at increased risk of perioperative complications if their HbA1c is above 6.5% [163]. The presence of pre-operative DM, amongst other factors, cumulatively adds significantly to the likelihood of mortality. The patients with DM exhibit higher pre-operative inflammation level and worse pre-operative renal function than those without DM.

The extent of vascular endothelial damage and dysbiosis also influences the development of complications of DM [175]. Other chronic complications of DM driven by dysbiosis and high oxidative stress are cognitive impairment, stroke, autonomic heart dysfunction, cardiomyopathy and hepatic steatosis [175–177]. Autonomic dysregulation of the GIT tract, opportunity infection and infestations in the GIT and development of colorectal and other malignancies are additional complications of longstanding DM [160,178,179]. Diabetes mellitus causes villous atrophy and an increase in the number of Paneth cells in the intestinal crypt of the small intestine.

The prevalence of surgical site infections in DM varies widely from centre to centre, with estimates of 0.06% to 12.5% following coronary artery bypass [180–183]. Although the causes are multifactorial, with significant risk factors of age, body mass and CABG as index procedures, Listewnik, in a series of 5152 patients undergoing median sternotomy, found diabetes to be one of the independent risk factors (OR: 2.4; $p < 0.004$) for sternal dehiscence [181].

Hyperglycaemia is frequent in patients undergoing cardiac surgery on cardio-pulmonary bypass support. The release of stress hormones, catecholamines and other routine pharma-

cological agents used in the peri-operative period can result in higher glucose levels [30,182]. High glucose levels in the peri-operative period are associated with an increase in post-operative morbidity and mortality [183]. Although the literature limited to non-randomised controlled studies is favouring an intensive glycaemic control in the peri-operative period, an intensive glycaemic control strategy has also not outright resulted in a reduction in adverse outcomes [182,184]. A properly designed randomised controlled trial study avoiding the shortcomings of previous studies could address these divergent opinions.

4.3. Management of Diabetes Mellitus

Management of DM is complex and should involve a multidisciplinary team (MDT) comprised of dieticians, endocrinologists, nurses, paediatricians and physicians [20,185]. The treatment choice for DM depends on the type and severity of DM. Options for treating DM include diet, exercise, lifestyle modifications, oral hypoglycaemic drugs and insulin. All options for the treatment of DM are suitable for type 2 DM, and their use is based on the severity of the DM and its response to treatment. Diet, lifestyle change and insulin are the mainstays of treatment for type 1 and type 3c as well as GDM. Oral hypoglycaemics include the biguanides, sulfonylureas, sodium-glucose cotransporter 2 inhibitors and thiazolidinediones. The non-insulin drugs influence either the secretion or sensitivity of insulin and the incretins [186].

4.3.1. Lifestyle Changes and Management of Diabetes Mellitus

Sedentary lifestyle, which includes excessive watching of television, is among the predisposing factors of DM. Non-pharmacological treatment of all forms of DM should include structured and supervised physical exercise [187] and an adequate amount of sleep [188]. The benefits of exercise in individuals with DM include correction of the dysbiosis, increased production of ketones [189], reduction of inflammation and priming the body to learn and develop mechanisms to deal with excessive oxidative stress [190].

4.3.2. Dietary Management of Diabetes Mellitus

Obesity and DM are less likely without the intake of excessive nutrients. Regular intake of a diet that is low in fibre and high in saturated fat and/or calories is both obesogenic and diabetogenic. A high-fat diet is also detrimental to the Paneth cells [23]. Dietary modification should therefore be a component of treating all forms of DM. Dietary management aims at optimal metabolic control by confirming a balance between food intake, physical activity and medication to avoid complications. In type 2 diabetes, the dietary goals include control of blood glucose, lipid levels and weight loss [191].

Because DM is a disease directly related to carbohydrate, lipid and protein metabolism, nutrition has always had an integral role in its management. Regulation of metabolic markers like blood glucose levels and blood pressure management constitute key aims of the nutritional management of diabetes. The other goals of nutritional management of DM are appropriate eating behaviour, social, cultural and psychological well-being; regular balanced meals with adequate energy and essential nutrients three times a day, no binge eating and balanced daily intakes with energy expenditure, and dietary intervention should also assist in the prevention of complications of DM.

4.3.3. Nutritional Supplements and Management of Diabetes Mellitus

Diabetes mellitus is a heterogenous disease that is often difficult to manage [192,193]. Some of the treatments that are used in the treatment of patients with DM are probiotics [28,32,194,195], zinc supplementation [196,197], ketogenic diet [198] and high-fibre diet [198–200]. The use of glutamine and the other treatment options address some of the derangements that are involved in the pathogenesis of DM, which include dysbiosis, increased gut epithelium permeability, systemic inflammation, increased oxidative stress, mitochondrial dysfunction and the reduction of β-cells in the islets of Langerhans of the pancreas [100,106,108,133,154,175].

4.3.4. Ketogenic Diet and Management of Diabetes Mellitus

A ketogenic diet has low carbohydrates but very high fat in a combination that approaches close to a 1:4 carbohydrates-to-fat ratio [188,201–204]. A ketogenic diet is normocaloric but replaces glucose as the primary source of energy with ketones [201]. Unlike during starvation-induced ketosis, there are no restrictions of energy supply [203]. The carbohydrate intake per day is limited to around 50%, which amounts to less than 10% of the daily caloric need [201–203]. At least 70% of calories during the ketogenic diet are from fat, with 20% from proteins [203]. Examples of foods in a ketogenic diet include olive oil, spinach, broccoli, avocado and kidneys [188,203].

A ketogenic diet increases the formation of ketones like ß-hydroxybutyrate, acetoacetate and acetone, which is beneficial during the management of severe epilepsy that is resistant to medication [201,203]. Several studies have reported on the usefulness of the ketogenic diet in the management of DM, predominately type 2 DM [188,201,203,204]. Some of the benefits of a ketogenic diet include the reversal of the dysbiosis of the microbiota of the gut with the restoration of α-diversity, Firmicutes/Bacteroidetes ratio and SCFAs-producing species [201,203,204]. Additional benefits of a ketogenic diet are lowering systemic inflammation and reducing the daily insulin or oral treatment requirement [203]. The use of a ketogenic diet in patients with type 1 DM is limited because of the fear of induction of ketoacidosis [203]. Similarly, a combination of a ketogenic diet and sodium glucose cotransporter 2 inhibitors is not advisable, as it increases the risk of ketoacidosis [203].

4.3.5. Bariatric Surgery and Management of Diabetes Mellitus

Over 90% of individuals who have type 2 DM also have obesity [101]. Dysbiosis of the gut microbiota is the initial event in most cases of obesity and DM [106,126,205–207]. Obesity sustains the chronic systemic inflammation and oxidative stress responsible for the insulin deficiency and resistance in DM [200]. Medical treatment of DM, including insulin, ultimately fails. Among the indications for bariatric surgery is obesity with uncontrollable DM [206,207]. Uncontrollable DM is a justifiable indication of bariatric surgery even when the obesity is not morbid, provided the BMI is above 30 kg/m^2 [206]. A bariatric procedure may be restrictive or create a bypass of a significant part of the small intestine. The commonly performed bariatric procedures are sleeve gastrectomy, Roux-en-Y bypass and biliopancreatic diversion [207]. The benefits of bariatric surgery are moderation of dysbiosis and toning down systemic inflammation and oxidative stress. Although the biliopancreatic procedure is the most effective and recommended for extreme obesity, any bariatric procedure can lead to a complete remission of DM [206].

4.3.6. Other Options for the Treatment of Diabetes Mellitus

The other treatment modalities that are effective in the treatment of DM are faeces transplantation [208–210], antioxidants [211] and herbal medicines [125]. Isolated reports include the experimental use of cannabinoid receptor 2 agonists and synthetic HD-5 in managing type 2 DM [212], as well as islet cell transplant, stem cell therapy, pharmacological alteration of IECs to produce insulin and pancreas transplant [213–215]. The use of artificial intelligence (AI) has also led to an improvement in the management of DM [216,217]. Among the benefits of AI in management of DM is the ability to determine the insulin dose required using, as an example, the artificial pancreas [218]. Artificial intelligence is able to assist in the early detection of complications of DM by using, among others, the use of wearable or mobile technologies [219]. Table 2 lists the derangements associated with DM and available targeted treatment options.

Table 2. List of derangements associated with diabetes mellitus and targeted treatment options.

Derangement	Treatment Option
Insulin deficiency	Insulin. Islets cell transplant [213]. Pancreas transplantation [214]. Mesenchymal stem cell [218].
Insulin resistance	Exercise [192,219]. Lifestyle modification [219]. Oral hypoglycaemics. Insulin. Artificial pancreas [216]. Bariatric surgery [200,220].
Dysbiosis	High-fibre diet [199]. Low-fat diet [221]. Low-calorie diet [221]. Ketogenic diet [198]. Exercise [52,192,219]. Dietary supplements [221]. Probiotics [32,194,195]. Prebiotics [32,200]. Metformin [200,222]. Synbiotics [223]. Faecal transplantation [115,210]. Synthetic HD-5 [224]. Bariatric surgery [225–228].
Increased gut permeability	Diet [229]. Glutamine [230]. Herbal medicines [125,211,231]. Synthetic HD-5 [226].
Inflammation	Exercise [52]. Cannabinoids receptor agonists [212]. Faeces transplant [200,208–210].
Oxidative stress	Exercise [219]. Vitamin C [232]. Metformin [222]. Herbal medicines [231]. Ketogenic diet [205].
Pancreatic β-cell dysfunction	Mesenchymal stem cells [218]. Islet cell transplant [213]. Pancreas transplant [214].Stem cell therapy [233].

5. Limitations

Some of the limitations of this manuscript include that it is a narrative review and the search was limited to articles that were available through PUBMED and only focused on articles published in English. Unlike in systemic review and/or meta-analysis, there is no standardised way of searching for articles to be included in a narrative review. A narrative review is therefore susceptible to bias during selection of suitable publications. Furthermore, the quality of the studies is not relevant in narrative review. The majority of the studies and publications on Paneth cells and the influence of dysbiosis on DM have been published in the last 10 years. The authors performed an extensive search, and 74% of the articles cited were published within the last 5 years. The inherent weakness of a narrative review is that it is only meant to increase awareness and knowledge of a particular topic and not to support or refute a finding or management approach.

6. Conclusions

Diabetes mellitus is a heterogeneous disease that is complex to treat, and failure of medical treatment is common regardless of the treatment option selected. Paneth cells monitor and regulate the microbiota of the gut to prevent dysbiosis. Dysbiosis of the gut microbiota, increased permeability of intestinal epithelium, translocation of bacteria and endotoxins, chronic low-grade inflammation, mitochondrial dysfunction and excessive production of ROS and RNS drive the insulin deficiency or resistance and are involved in the pathogenesis of DM. The use of AI should extend beyond early diagnosis and detection of diabetes or its complications to better characterise the underlying pathology of DM, including the status of the Paneth cells.

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