Anti-diabetics and antimicrobials: Harmony of mutual interplay

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Abstract

Diabetes is one of the four major non-communicable diseases, and appointed by the world health organization as the seventh leading cause of death worldwide. The scientists have turned over every rock in the corners of medical sciences in order to come up with better understanding and hence more effective treatments of diabetes. The continuous research on the subject has elucidated the role of immune disorders and inflammation as definitive factors in the trajectory of diabetes, assuring that blood glucose adjustments would result in a relief in the systemic stress leading to minimizing inflammation. On a parallel basis, microbial infections usually take advantage of immunity disorders and propagate creating a pro-inflammatory environment, all of which can be reversed by antimicrobial treatment. Standing at the crossroads between diabetes, immunity and infection, we aim in this review at projecting the interplay between immunity and diabetes, shedding the light on the overlapping playgrounds for the activity of some antimicrobial and anti-diabetic agents. Furthermore, we focused on the anti-diabetic drugs that can confer antimicrobial or anti-virulence activities.

Key Words: Diabetes; Immune disorders; Anti-diabetics; Antimicrobials; Anti-virulence

Core Tip: Understanding the mutual interplay between diabetes and microbial infection is necessary to control both and to avoid a lot of serious complications that may happen in such clinical conditions. Repurposing of approved drugs and investigation of their new application represents a promising approach for maximizing treatment outcomes.

In this review, we shed light on the overlapping areas of efficacy between anti-diabetics and antimicrobials.

INTRODUCTION

Diabetes is a chronic metabolic disorder associated with high blood glucose levels. Diabetes is a lifelong condition which requires proper monitoring and change in the patient's diet and routine habits. The world health organization reported an increase in the incidence of diabetes over the last decades worldwide that affected all social, economic and ethnic backgrounds. The universal prevalence of diabetes has nearly doubled since 1980 to 2014, rising from 4.7% to 8.5% in the adult population, and expected to rise to 10.4% in 2040[1]. This alarming uprise in the statistics of diabetes is owed to the global shift towards urban habits generally characterized by unbalanced diet, stress and reduced physical activity. Before the coronavirus disease 2019 (COVID-19) pandemic 650 million adults (13% of the world's adult population) were obese and it was estimated that 19.7% of the world's population will be obese by the year of 2030 [2]. The COVID-19 pandemic has been associated with increased risk of obesity and associated health hazards mainly diabetes. The global application of quarantine requirements forced billions of people into a new life style of isolation where people are forced to spend more time indoors with minimum physical activities and limited contact with others. The quarantine related frustration pushed people to consume larger amounts of high sugar foods which is reflected as higher incidence of obesity[3, 4]. Moreover, many studies have outlined the role of obesity and diabetes as important risk factors in COVID-19 infections[5,6].

Diabetes is commonly divided into two major categories depending on the age of onset and the pathophysiological cascade of events giving rise to diabetes; type I diabetes (T1DM), also known as juvenile diabetes, is characterized by the inability of pancreas to secrete insulin due to damage of β-cells mostly caused by an autoimmune disorder. The onset of T1DM appears usually in childhood and requires lifelong insulin injections. On the other hand, type II diabetes (T2DM) is characterized by insulin resistance that can be accompanied by reduced insulin secretion from the pancreas. T2DM is more common than T1DM, its onset appears in adulthood and its treatment involves diet control, medications for control of blood glucose level and eventually insulin injection is required in late stages[7].

The delay in diagnosis and treatment of diabetes can lead to irreversible damage to many of the body organs; some of the complications of diabetes include neuropathy, retinopathy, nephropathy, cardiovascular diseases, peripheral insufficiency, and diabetic foot ulcers. Failure to control diabetes can eventually lead to life threatening complications like kidney failure, lower limbs gangrene, heart attacks and stroke[8]. Some of the most distinguished complications of diabetes include: Immunodeficiency, high risk of infection and longer recovery period, all of which represent lifelong companions of diabetic patients. The most frequent infections in diabetic patients are respiratory tract infections, urinary tract infections, skin and soft tissues infections, diabetic foot ulcers, otitis and periodontal infections[9]. Many mechanisms were proposed for the reasons behind the high risk of contracting infection in diabetic individuals like the high blood glucose level, the lower-than-normal pH in body fluids [9,10], in addition to poor vascularity of peripheral tissues[11], all of which support pathogenic infestation. However, the most profound factor is the impaired immune functions. The relation between microbes and diabetes is bidirectional. In other words, the high blood glucose levels complicate infections and also some microbial infections can contribute to the etiology of diabetes[12-16]. The undeniable role of inflammation in both diabetes and infection have been extensively portrayed, which lead to the conclusion that the use of anti-inflammatory agents can represent a rationale treatment approach for better control of diabetes or even delaying its complications. Generally, anti-inflammatory agents are essential members in any anti-diabetic regimen; non-

steroidal anti-inflammatory drugs and salicylates are commonly prescribed anti-inflammatory agents for better control of the diabetes associated inflammation[17].

As diabetics are immunocompromised chronic patients and are more susceptible to microbial infections, exploring antimicrobial activities of approved anti-diabetic agents may be highly appreciated by clinicians. Preferential selection of anti-diabetic agents that have additional antimicrobial activities for diabetic patients can offer multiple advantages, including antimicrobial protection enhancement and decreasing the treatment costs[18-21]. In this work we intend to discuss the multiple facets of the relation between infection and diabetes. We shed the light on the interplay between immunity, diabetes and microbial infections, discussing the influence of diabetes on worsening of microbial infections. Additionally, the antimicrobial agents that can harbor anti-diabetic activities were discussed, with special interest in the anti-diabetic drugs which have antimicrobial activities, enhance immune responses or mitigate microbial virulence (Figure 1).

DIABETES AND IMMUNITY INTERPLAY

The interplay between immune-dysfunction and diabetes has a deep complicated background that exceeds our full understanding. The question whether immune-dysfunction is the cause or the effect of diabetes was always questioned. It is widely accepted that an immune disorder is responsible for T1DM *via* T cell-mediated selective destruction of pancreatic β-cells[15]. The activation of such destructive autoimmune behavior is based on a genetic factor in addition to a triggering environmental event[22]. Meta-analysis of genomic data has identified the genetic loci related to high risk of T1DM, the most prevailing are haplotypes in human leukocyte antigen class II, other common risk loci include mutations in *INS*-gene leading to preproinsulin misfolding and polymorphisms in Protein tyrosine phosphatase, non-receptor type (PTPN-22), interleukin-2 (IL-2), renalase (RNLS) and *CTLA-4* genes[9,15,23]. The presence of a single or multiple risk loci would lead to an unfortunate sequence of immunological reactions starting by loss of tolerance to pancreatic islets β-cell antigens, the production of anti-diabetic islet antibodies from plasma B-cells and the active involvement of autoreactive CD4- and CD8-T cells, eventually leading to steady rate damage in pancreatic β-cells[24]. This steady autoimmune destructive pattern remains hidden from the individual up until a critical damage limit is reached in the pancreatic islets after which hyperglycemia prevails and external insulin dependence becomes crucial[25]. During the prolonged silent preclinical period, early detection and reversal of the disease is possible by screening for the genetic risk loci, circulating anti-islet autoantibodies, and auto-reactive CD4 and CD8-T cells[15,25,26]. The presence of high-risk genetic loci only presents a predisposing factor to the disease; as a matter of fact, an individual carrying a high-risk gene could enjoy a delay in the onset of symptoms if he was lucky enough to escape the triggering factors associated with T1DM[22,27]. The triggering event can be an alteration in gut microbiota, obesity, a dietary factor like gluten or early introduction of cow's milk in infancy, toxins or a viral infection especially by dsRNA virus[28-31]. It is widely conceived that such events could trigger abnormal immunogenicity of β-cells and the loss of tolerance to pancreatic islets β-cell antigens which marks the onset of the autoimmune response[22, 24,27].

On the other hand, T2DM etiology involves weaker dependence on genetic factors and more correlation to life style factors[32]. The genetic risk factors predisposing to T2DM were outlined by genome-wide association studies as polymorphisms in *TCFL2*, *ABCC8*, *CAPN10*, *PPAR*, *CDNKN2A/B*, *CDKAL1*, and *IGF2BP2* genes[33]. How- ever, the genetic susceptibility factor plays little role in the development of T2DM and again immunity related disorders play the leading role in the pathogenesis of the disease[9]. T2DM is generally characterized by a chronic low grade of inflammation arising from the immune response to hyperglycemia, aging, obesity and stress[7,34]. A growing mass of evidence suggests the involvement of both innate and adaptive immune-responses in the inflammatory trajectory of T2DM. The diabetes related dysfunctions in adaptive immunity include decreased γδ-T cell function, increased inflammatory T-helper phenotypes, decreased regulatory T-cells, and impaired B-cells function[7,35-37]. On the other hand, T2DM innate response defects come with altered neutrophil function, increased pro-inflammatory M1 macrophages, abnormal natural killer cell phenotypes, and increased inflammatory dendritic cells[7,35,36,38]. It should be noted that systemic inflammation is less projected in T1DM due to stimulated production of IL-10 from dendritic cells which is reflected as low incidence of insulin resistance[7,
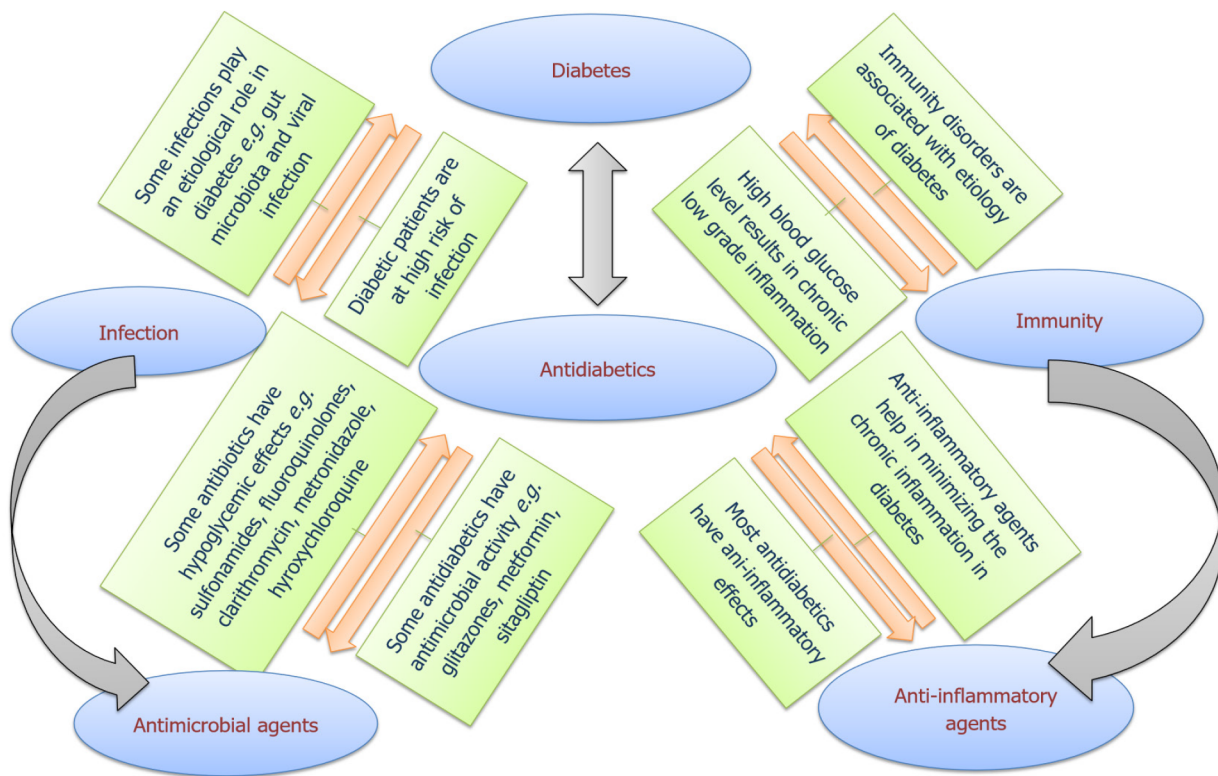
Figure 1 Interplay between diabetes, infection and immunity.

36]. Moreover, an autoimmune response characterized by circulating autoantibodies has been increasingly recognized in many T2DM patients[35,36,38]. However, the autoimmune pathway differs in T1DM compared to T2DM, since autoimmunity in T2DM patients is more related to obesity-activated chronic inflammatory responses and β-cells fatigue[36,38].

MICROBIAL INFLUENCE ON DIABETES

Imbalance in gut microbiota and diabetes

The gut microbiota represents an ecosystem of trillions of inhabitants that co-exist in our gastrointestinal track in perfect balance with other body systems, actively engaging in a mutually beneficial relationship[39,40]. The formation of the gut microbiota starts in infancy and continues to develop and diversify throughout our lifetime[41]. The complex and dynamic population of the gut microbiota includes bacteria, fungi, protists, archaea, and viruses with bacteria comprising the vast majority in the gut population[42]. The composition of the gut microbiota is subjected to continuous alterations and development depending on age, diet, geographical distribution, infection history, antimicrobial treatments, medication regimen, stress and physical activity among many other parameters[43,44], leading to huge composition variability between individuals in a pattern that can resemble fingerprint uniqueness[45]. Indeed, the gut microbiota plays an undeniable role in many metabolic and immune related disorders *e.g.*, metabolic syndrome, diabetes, inflammatory bowel diseases and obesity[46-48]. However, the exact contribution of gut microbiota to the pathophysiology of diabetes is widely variable due to the individual variations on the matter. That being said, a handful of gut microbiota members have shown repeated signals in multiple researches, where the results suggested some bacterial genus to impact protective effects against T2DM *e.g. Bifidobacterium, Lactobacillus*, *Bacteroides, Roseburia*, *Faecalibacterium*, *Clostridium* cluster IV and subcluster XIVa and *Akkermansia*[49], such members were suggested as probiotics treatment with high association to improved glucose homeostasis and protection against T2DM, bearing in mind the importance of species-dependent variation in the result outcomes[49,50].

The suggested mechanisms for the protective effect of these bacterial groups against T2DM involves multiple pathways; observations have recorded an increase in the anti-

inflammatory cytokines IL-10 and IL-22, enhanced T regulatory cell function, increased transforming growth factor-beta (TGF-β), suppressed intestinal inflammation, decreased gut permeability and increased insulin sensitivity[49]. On the other hand, other bacterial genera were repeatedly associated with impaired glucose homeostasis and increased risk of obesity and diabetes *e.g.*, *Ruminococcus*, *Fusobacterium*, *Blautia* and *Firmicutes*[49,51,52]. The involved mechanisms are not clearly elucidated; however, some studies suggested that the introduction of a dietary factor like gluten, unbalanced high fat diet or the reduction in gut pH can significantly increase the pro-diabetic bacterial population at expense of the balance and diversity in the gut microbiota[14], with many observations relating these effects to increased pro-inflammatory cytokines and induction of antigen-specific T cells-initiated destruction of the pancreatic β-cells in T1DM[14,16], increased bowel permeability[53], endotoxemia[54,55], and altered metabolism of bile acids[56,57]. Moreover, the shift in balance in the gut microbiota can lead to overgrowth of bacteria that has an increased capacity to harvest energy from the diet, such members of microbiota can boost energy uptake from diet by hydrolysing the undigested plant polysaccharides (cellulose, xylan and pectin) thus contributing to higher risk of obesity and subsequently higher risk of T2DM[58,59].

MICROBIAL INFECTIONS TRIGGER DIABETES

Many of the risk factors related to diabetes have been studied and identified like the genetic risk loci, obesity and stress among others. Nevertheless, the role of some microbial related events has been repeatedly outlined as potential triggers in both T1DM and T2DM. In the following segment we discuss examples of the identified microbial suspects in the etiology of diabetes.

One of the leading triggers of T1DM is believed to be an enterovirus infection by Coxsackievirus B (CVB), rotavirus, mumps or cytomegalovirus[60-62]. This idea was first conceived when an observation in the Finnish population, where the highest incidence of T1DM is reported, lead to linking the first signs of autoantibodies in genetically susceptible children to the seasonal pattern of enterovirus infections, especially by CVB-1[13,60]. Additionally, enteric infections by CVB-4 were repeatedly associated with pancreatic islets inflammation and infiltration mediated by β-cell specific autoantigens and subsequent β-cell apoptosis[62]. Another study has outlined the positive correlation between enterovirus (A) overpopulation in the gut and an autoimmune response in the pancreatic islets of genetically susceptible individuals [63]. Some enterovirus can directly infect the β-cells *via* targeting specific pancreatic receptors such as the poliovirus receptor and integrin αvβ3, hence initiating an inflammatory autoimmune response[64,65]. This effect was clearer in some individuals who suffer a chronic viral induced β-cell inflammation that can be detected by tracing enteroviral major capsid protein VP1, enteroviral RNA and the over-expression of the major histocompatibility complex-1[12,66,67].

The association between hepatitis C virus (HCV) and T2DM was repeatedly studied; it is known that some extra-hepatic manifestations of HCV are related to impaired glucose homeostasis, decreased glucose uptake and increased insulin receptor damage[68,69]. Molecular investigations into the underlying mechanisms have revealed that HCV core protein enhances the production of reactive oxygen species (ROS) in the mitochondria and endoplasmic reticulum of hepatocytes. The accumulating oxidative stress results in propagating hepatic cirrhosis and fibrosis with impairment in liver mediated glucose homeostasis[70]. HCV core protein also activates serine phosphorylation with subsequent deterioration of insulin receptor substrate (IRS)-1 and consecutive blocking of insulin signal propagation at the insulin receptors [68,71]. Additionally, the function of (IRS)-1 is further impaired due to degradation mediated by the inflammatory mediator tumour necrosis factor (TNF)-α[69,71]. Moreover, HCV induces gluconeogenesis, reduced glucose uptake and accumulation of lipid droplets *via* up-regulation of the enzymes glucose 6 phosphatase (G6P) and phosphoenolpyruvate carboxykinase 2 (PCK2), and down regulation of glucose transporters (GLUT)-2 and (GLUT)-4[68]. The preceding information leads to the general conclusion that treatment of HCV infection could impose improvement in glucose homeostasis and insulin resistance, that was indeed observed in patients receiving anti-HCV antiviral regimens as shall be discussed shortly.

In an epidemiological study, an inverse relationship has been established between the decreasing prevalence of helminth infections and the increasing prevalence of metabolic diseases as diabetes[9]. But the controversy about the influence of *Helico-*

bacter pylori (*H. pylori*) bacteria on diabetes is more interesting. *H. pylori*, Gram-negative bacteria, is the most common causative agent of peptic ulcer and chronic gastritis[72]. *H. pylori* infection persists in the gastric epithelium generating local and systemic inflammation induced by multiple mediators[73-76] in addition to molecular antigenicity which provokes autoimmune responses[77,78]. All of these abnormalities predispose to a storm of inflammatory manifestations that has been linked to multiple extra-gastrointestinal disorders such as diabetes, cardiovascular disease, metabolic syndrome, atherosclerosis, neurodegenerative disorders, idiopathic iron deficiency anemia and vitamin B12 deficiency[79]. The relation between *H. pylori* infection and diabetes was proposed and discussed multiple times with conflicting significances being presented. Multiple meta-analyses have established positive correlation between chronic *H. pylori* infections and T2DM with less significant correlation to T1DM[80,81]. The correlation was more obvious in studies performed on data from Asian, European and African cases, with contradictory results obtained from United States patients[80, 81]. There are two main proposed mechanisms for the diabetogenic effect of *H. pylori*: The diffuse inflammation stress induced by the infection and gastric hormones imbalance[82,83]. It can be expected that the pro-inflammatory environment caused by *H. pylori* would impact insulin receptors, leading to impaired insulin sensitivity. This hypothesis was confirmed in multiple studies that highlighted the positive correlation between *H. pylori* infections and insulin resistance[84,85]. Furthermore, one study reported that the presence of *H. pylori* antibodies was linked to 2.5 higher levels of insulin resistance[86]. *H. pylori* infection was also associated with higher incidence of chronic complications in T2DM patients, and associated with higher mean glycated hemoglobin (HbA1c), an indicator of chronic hyperglycemia in Prediabetic individuals [75]. On the other hand, it was reported that eradication of *H. pylori* by antibiotic treatment courses was not associated with improved insulin sensitivity[87]. In addition to the inflammatory pathways connecting *H. pylori* to T2DM, a parallel hormonal mechanism was proposed; *H. pylori* infection was reportedly associated with imbalance in secretion of the gastric hormones, with increased secretion of gastrin and decreased secretion of ghrelin, leptin and somatostatin[83,88,89]. The *H. pylori* induced imbalance in these hormones was associated with impaired insulin release from pancreatic islets, increased appetite and fat deposition[90-92]. More studies are required to clarify the exact pathways for *H. pylori* triggered insulin resistance and the interactions between gastric hormone imbalance and insulin release from the pancreatic islets, by which *H. pylori* interferes with insulin release from the pancreatic islets.

DIABETES PROMOTES MICROBIAL INFECTIONS

The evidence of bidirectional link between diabetes and viral, bacterial, fungal, and parasitic infectious agents has been proven and extensively documented[9,10,93,94]. This bidirectional link between diabetes and infection is governed by the inflammatory mediators that link inflammation process and diabetes vulnerability to infection[9,10, 23]. In other words, diabetes augments the outcome of microbial infections and vice versa (Figure 2). As a consequence of diabetes, immune alterations would lead to (1) Increased activity of ROS; (2) Increased production of the pro-inflammatory mediators TNF-α, INF-γ, IL-1β, IL-6, IL-8, IL-12 and IL-17; (3) Reduced protective effect of the anti-inflammatory mediators interferon-1, IL-2, IL-10 and IL-22; (4) Reduced expression of cathelicidins in macrophage leading to impaired bactericidal activity and chemotaxis; and (5) Reduced glutathione and non-enzymatic glycation of complement factor thus inhibiting its activation[7,9,35,36,38]. Such ramifications are responsible for impaired function of the first line antimicrobial defense, higher susceptibility to pathogens and delayed healing[7,35]. Long term hyperglycemia will cause advanced glycation end (AGE) products of proteins such as AGE-albumin which hinders trans-endothelial migration in macrophages[35].

Just as diabetes weakens both humoral and cellular immune responses, hyperglycemia can enhance the microbial virulence. Generally, diabetic patients with higher HbA_{1c} (> 6.5%) are at higher risk of hospital-acquired and community-acquired infections and sepsis[10,95,96]. Elevated HbA_{1c} represent a risk factor for bacteremia and sepsis in diabetic patients who suffer from urinary tract infections[96]. The increased susceptibility to *E. coli* infections is owed to glycation of *E. coli* fimbrial FimH adhesin which promotes the bacterial adhesion to urinary tract epithelial cells[97]. In periodontitis, diabetes enhances expression of IL-17 and increases pathogenicity of the oral microbiome[98]. In respiratory infections, the elevation of blood glucose in
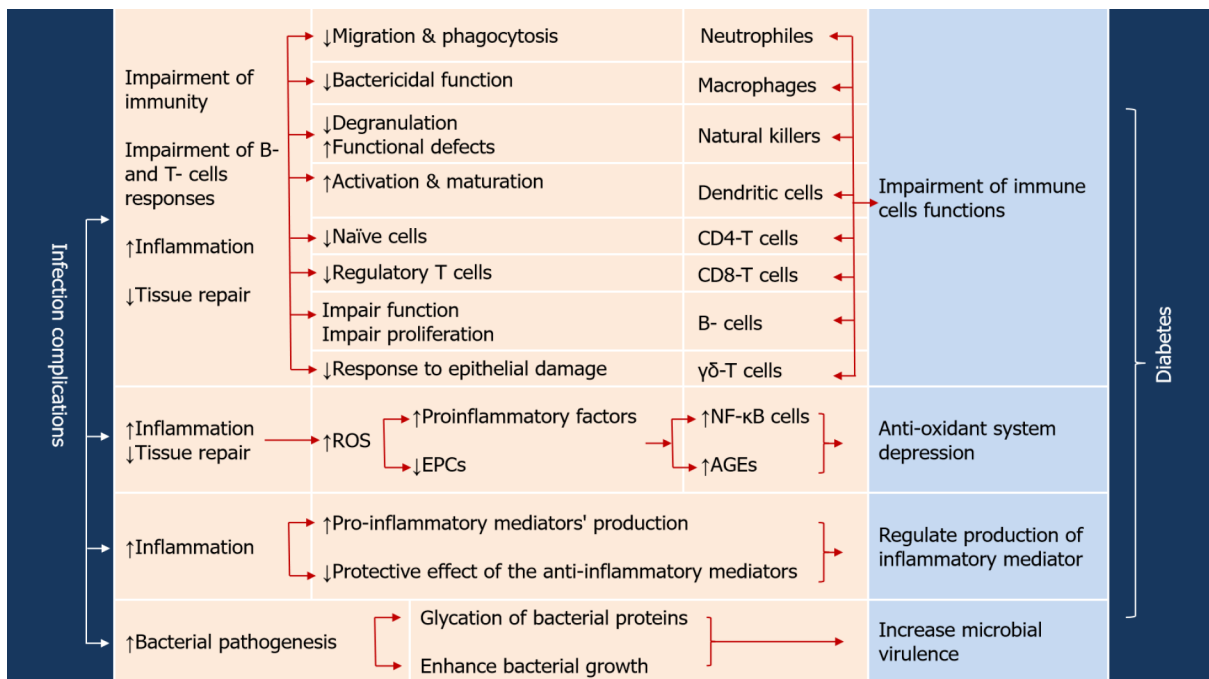
Figure 2 Some proposed mechanisms for the effect of diabetes on enhancement of microbial infections. NF-κB: Nuclear factor kappa B; AGEs: Advanced glycation end; EPCs: Endothelial progenitor cells; ROS: Reactive oxygen species.

diabetic mice promotes the *Staphylococcus aureus* growth in the airways increasing the possibility of infection[99]. Moreover, the influences of diabetes on patient's immunity are considered in defensing mechanisms against mycotic, parasitic and viral infections. For instance, *Candida* spp. constitute the most frequent isolates from urogenital tract of hyperglycemic patients[100,101] and the severity of infection is in correlation with glucose level[102]. The adhesion of *Candida* spp is enhanced in presence of high glucose which increases the expression of intercellular adhesion molecule-1[103]. Diabetes changes the morphology of *Leishmania major* lesions[104] and particularly causes severe cutaneous *Leishmania infantum* lesions[105]. Chickenpox complications such as postherpetic neuralgia are more severe and persistent in diabetics[106], and T1DM vascular complications confers an additional virulence to herpes zoster[107]. The severity of liver damage is more observed in HCV patients with uncontrolled glucose levels[108].

In context with prominent effects of diabetes on both innate and adaptive immunity, diabetic patients are more susceptible than nondiabetics to all types of infections such as nosocomial infections[95], sepsis[10] tuberculosis[109-111], *Legionella* infections [112], gum infections[113], fungal infections[114], dengue fever[115], influenza virus [116], herpes zoster[106,117,118], and other infections reviewed in[9]. Moreover, the risk of post-sepsis infections increases due to alterations in innate and adaptive immune responses resulting in chronic inflammation and persistence of causative microbe[10,96]. As a consequence of impaired immunity, diabetic patients are prone to more aggressive, recurrent and life uncommon life-threatening infections[9,10,95,119, 120]. Conclusively, diabetes augments the bacterial virulence either by impairing the patient's immune responses or even by enhancing the invasion and spreading of bacterial[9,10,120,121].

Diabetes complications favor the microbial pathogenesis due to decreased blood supply to the affected areas and reduced neural sensation[122]. Furthermore, the development of resistance to antimicrobial agents is more common in diabetic patients as compared to nondiabetics[123]. The prevalence methicillin-resistant *S. aureus*[124-126], vancomycin-resistant *Enterococci*, carbapenem-resistant *Enterobacteria*, extended-spectrum β-lactamases-producing *Enterobacteria*, and non-fermenting Gram-negative bacilli are elevated in diabetic patients[9,120,127,128]. This is owed to the impaired immunity of diabetic patients which principally leads to increasing their susceptibility to infectious agents and failure in complete eradication of persistent infections, this results in more exposure to antimicrobial agents and subsequently higher risk of antimicrobial resistance. Examples for the antimicrobial resistance development in treatment of surgical infections and diabetic foot are tremendous and very serious as reviewed[9,10,120,129]. Although *H. pylori* is well known for its susceptibility to usual

therapy regimen, it resists eradication in diabetics which require specific modified antimicrobial regimen[130].

ANTIMICROBIALS WITH ANTI-DIABETIC ACTIVITY

Antimicrobial agents can induce multiple pharmacological effects beyond their lethality to invading pathogens; these effects can be reflected as metabolic changes which sometimes affect glucose homeostasis. Recently, it was shown that the exposure to antibiotics in childhood has been linked to increased risk of metabolic disorders later in life and associated with changes in development of pancreas[63]. Additionally, some antibiotics may alter the antidiabetic plasma levels; diabetic patients with tuberculosis were advised to take rifampicin and metformin with sufficient time interval[131]. Clarithromycin is another antimicrobial agent associated with severe hypoglycemia in diabetic patients receiving hypoglycemic medications, the risk increases with renal impairment and in elderly patients[132]. The suggested mechanism for clarithromycin induced hypoglycemia is the inhibition of the cytochrome-P450 enzyme which is responsible for metabolic inactivation of sulfonylurea or meglitinide hypoglycemics, this leads to increased plasma concentration of these medications and subsequent hypoglycemia[133]. Similar hypoglycemic effects were reported for metronidazole which also inhibits CYP2C9 inhibitor which interferes with the metabolism of hypoglycemic agents[134]. It can be concluded from the above that clarithromycin and metronidazole don't have a direct hypoglycemic effect, rather they increase the systemic concentration of sulfonylurea or meglitinide drugs as a result of the delay in their metabolism[134]. More considerably, some antibiotics impose disrupting effects on gut microbiota with alterations in the expression of their key metabolic pathways which influences both their response to antibiotics and the glucose metabolism[135-137]. In addition to the above mentioned indirect hypoglycemic effects of some antimicrobial agents, others have showed direct hypoglycemic effects. In the next paragraphs we will give a glance at some of these drugs.

Sulfonamides are of the oldest known antimicrobial agents. During their long use, clinical observations revealed other clinical effects of sulfonamides including anti-carbonic anhydrase, anti-obesity, diuretic, hypoglycemic, antithyroid, antitumor, anti-neuropathic and anti-inflammatory activities[138]. The hypoglycemic activity of some sulfonamides received the most attention from the mid-20th century scientists, it was concluded that sulfonylureas have the best hypoglycemic activity through stimulating insulin secretion from pancreatic β-cells and decrease in hepatic clearance of insulin [139]. Further investigations into the hypoglycemic effects of sulfonylureas lead to the development of first and second generations of hypoglycemic sulfonylureas which constitute an important group of anti-diabetic agents that are still widely used today for the treatment of T2DM[140]. It was repeatedly advised to be cautious while combining sulfonamides with other hypoglycemic agents due to the synergistic effects that can lead to life threatening hypoglycemia, which is more common in case of elderly and renal dysfunction patients[141-143].

Fluoroquinolones represent a group of broad-spectrum antimicrobial agents that are widely used for treatment of respiratory tract and urinary tract infections. Despite the fact that this group has outstanding antimicrobial efficiency against a wide range of infections, they suffer from serious risk factors like the significant risk of aortic aneurysm, neuropathy, tendinopathy, and interference with glucose homeostasis[127, 144,145]. Fluoroquinolones can induce life threatening hypoglycemia in diabetic patients, and dysglycemia in nondiabetic individuals. The suggested mechanism of hypoglycemia is *via* blocking the ATP-sensitive K^+ channels in the pancreatic β-cell in the pancreas which boosts insulin secretion, however the mechanism behind the hyperglycemic effect is unclear[146]. The FDA repeatedly reported the high risk of dysglycemia associated with different members of fluoroquinolones. The multiple reports of severe hypo- and hyperglycemic clinical observations were the reasons behind the withdrawal of oral and systemic gatifloxacin preparations from the markets in 2006[147].

Hydroxychloroquine is an antimalarial drug that shows additional anti-inflammatory, immunomodulatory, anti-rheumatic and hypolipidemic activities. Hydroxy-chloroquine is also known to exert a significant hypoglycemic effect[148]. The exact mechanism of the hypoglycemic effect is not known; however, it is suspected to increase insulin receptors sensitivity, decrease hepatic clearance of insulin and reduce systemic inflammation[148-150]. Benzimidazoles are group of medications mostly

used as anti-helminthic. It was reported that they have hypoglycemic activity mediated by augmenting insulin secretion and activity[151,152].

Telaprevir is a protease inhibitor effective against HCV genotype 1. Some studies reported the development of hypoglycemia in diabetic patients receiving the antiviral telaprevir treatment course. One case study reported a female diabetic patient with obesity and HCV-related cirrhosis. She was given triple antiviral treatment by interferon-α, ribavirin and telaprevir. During the course of treatment multiple episodes of severe hypoglycaemia were recorded, however this effect disappeared after course completion which drove the general conclusion that telaprevir could impose a hypoglycemic effect[153]. Similar conclusions were obtained from another case study of a male diabetic patients receiving anti-HCV triple treatment with interferon, ribavirin and boceprevir. The study reported reversal of diabetes and termination of the anti-diabetic treatment after the successful viral treatment. The study suggests a relation between HCV and diabetes and possible reversibility of glucose abnormalities with successful eradication of HCV[154]. Two years later, similar outcomes were reproducible with another diabetic male also receiving triple HCV treatment in addition to anti-diabetic regimen including insulin and metformin. After the successful antiviral treatment, the patient was able to gradually withdraw insulin from his anti-diabetic treatment regimen and continued only the oral hypoglycemic linagliptin. This study weighs on the possibility of reduced glucose imbalance and even reversal of diabetes as an unexpected outcome after the antiviral treatment, the study attributes the improved glucose homeostasis due to retained normal functions of the liver after the termination of the viral infection[155]. Similar conclusions were reached in another retrospective study that included 65 diabetic patients subjected to the anti HCV triple-treatment including sofosbuvir, the results indicated improved blood glucose levels in all enrolled cases after the antiviral treatment as a result of retained normal liver activity[156].

ANTI-DIABETICS WITH ANTIMICROBIAL ACTIVITIES

Just as there are antimicrobials that can induce dysglycemia, some anti-diabetic can alter the antibacterial metabolism[157]. Searching into new fields for application of currently approved medicinal drugs, scientists have been more interested in drug repurposing as an elegant strategy for applying maximum use of already approved medicinal agents[158,159]. The benefits may be augmented by repurposing routinely used anti-diabetics as antimicrobial agents, this decreases the dose and number of administrated drugs that results in saving time and cost, decreasing the drug-drug interactions and enhancing the patients' compliance with the applied treatment regimens.

Likewise, most of the commonly used anti-diabetic agents offer additional anti-inflammatory activity as a favorable side effect during the treatment; the anti-inflammatory properties of glitazones, metformin, sulfonylureas and Dipeptidyl peptidase (DPP)-4 inhibitors were authenticated and appraised. The hypoglycemic effect of these agents is usually associated with decreased oxidative stress, decreased pro-inflammatory and increased anti-inflammatory mediators[160].In this context, it is highly valuable to clearly identify anti-diabetic agents that have additional antimicrobial activity, which is considered an interesting and promising area of active research[18,19]. During this search, we are interested in projecting the antimicrobial activities of some anti-diabetics (Table 1).

INSULIN

Insulin is a peptide hormone produced by β-cells of the pancreatic islets. It regulates glucose metabolism in all body cells[161]. Yano *et al*[162], showed the antibacterial activity of insulin on surgical site *S. aureus* infection *via* restoring neutrophil phagocytosis and bactericidal activity[162]. In 1946, Bollenback and Fox[163] showed the antibacterial activity of protamine zinc insulin against *Lactobacillus arabinousus, S. aureus* and *E. coli*. they owed the antibacterial activity to the additive protamine sulphate not to insulin itself[163]. Similar conclusion was derived from another study performed on commercial U.S.P. insulin, the bactericidal activity against *Staphylococcus epidermidis*, *S. aureus* and *E. coli* was secondary to the preservatives placed in the insulin and not to the insulin itself[164]. In general, most studies suggest that insulin doesn't have a direct antimicrobial effect, rather an indirect antimicrobial effect can be

Table 1 Examples of antimicrobial activities of some antidiabetic drugs

Antidiabetic drug	Antimicrobial activity	Proposed mechanism	Ref.
Metformin	Antibacterial	Activation of the AMPK-mediated phagocytosis and production of mROS	[170]
		Disruption of the outer membrane permeability	[170]
		Down regulation of the Q.S encoding genes and mitigate the bacterial virulence	[19,186]
	Anti-TB	Increasing the production of β-defensin-2, -3 and -4 which diminish bacterial growth and multiplication	[178]
		Inhibition of mitochondrial complex-I which is analogous to mycobacterial NDH-I complex	[176]
		Activation of T regulatory and CD8 memory T cells responses activity	[177]
Sitagliptin	Antibacterial	Downregulation of the Q.S encoding genes, occupy the Q.S receptors and diminish bacterial virulence	[18,19,186]
	Anti-COVID-19	Reduction of the inflammation intensity	[190,191]
		Targeting viral proteins	[192]
		Binding to viral spikes	[193]
	Antibiofilm	Targeting enzyme XPDAP, analogous to mammalian enzyme DPP IV	[187]
Vildagliptin	Antibiofilm	Targeting enzyme XPDAP, analogous to DPP IV	[187]
	Anti-amoebic	-	[188]
Saxagliptin	Antibiofilm	Targeting enzyme XPDAP, analogous to DPP IV	[187]
Pioglitazone	Antibacterial	Increasing phagocytosis and production of reactive oxygen species in phagocytes	[197,198]
Tolbutamide	Antibacterial and antifungal	-	[205]
2nd generation sulfonylureas	Antifungal	Inhibition of the NLRP3 inflammasome	[206]
	Antibacterial	Prevention of inflammasome effector IL-1β	[207]
Glimepiride	Anti-amoebic	-	[188]
Repaglinide	Anti-amoebic	-	[188]
Glucagon-like Peptide-1	In HIV treatment	Reduction of HIV-associated metabolic adverse effects	[212]
α-glucosidase inhibitors	Antibacterial	Targeting bacterial glucosidase	[220]
	Antiviral and anti-COVID	Alter glycosylation in viral life cycle	[221]

mROS: Mitochondrial reactive oxygen species; IL: Interleukin; AMPK: Adenosine monophosphate-activated protein kinase; XPDAP: X-prolyl dipeptidyl peptidase; Q.S: Quorum sensing; COVID-19: Coronavirus disease 2019; HIV: Human immunodeficiency virus.

expected due to the adjustment of hyperglycemia and relief in inflammation and oxidative stress. It is noteworthy to highlight the intrinsic anti-inflammatory nature of insulin as opposed to the inflammatory downfalls of hyperglycemia, additionally insulin promotes protein and lipid biosynthesis thus improving wound healing. Moreover, insulin induces the expression of the anti-inflammatory cytokines IL-4/IL-13, IL-10 and down regulates the pro-inflammatory cytokines IL-6 and IL-10[17,165]. However, research groups are invited to further investigate the insulin effects on microbial growth and virulence.

BIGUANIDE (METFORMIN)

Metformin is a hypoglycemic drug used as first line treatment in T2DM. The hypoglycemic activity is owed to the suppression of hepatic glucose production, the reduced intestinal absorption of glucose and the increase in peripheral glucose uptake, however, the exact molecular mechanism of metformin is still the focus of active

research[166]. Metformin also showed multiple beneficial effects that extend beyond diabetes control, with increasing studies referring to anti-inflammatory, cardio- and nephro-protective, anti-proliferative, antifibrotic and antioxidant effects. Moreover, metformin was suggested as an anti-aging compound with promises of increased lifespan and delayed onset of aging-associated diseases[167-169]. The repurposing of metformin extended to explore its antimicrobial activity, which also presented promising antimicrobial effects. A late study has shown the ability of metformin to restore tetracycline susceptibility in multidrug resistant strains of *S. aureus*, *Enterococcus faecalis*, *E. coli*, and *Salmonella enteritidis* both *in vivo* and *in vitro*. The study proposed the disruption of outer membrane permeability in resistant bacteria as a mechanism for reversing the bacterial intrinsic resistance to tetracyclines. Furthermore, the study reported that metformin imposed anti-inflammatory and improved innate immunity responses due to activation of the adenosine monophosphate-activated protein kinase (AMPK)-mediated phagocytosis and production of mitochondrial ROS (mROS)[170]. Metformin is associated with reduced serum levels of C reactive protein (CRP) and monocyte release of TNF-α, IL-1β, IL-6, MCP-1, and IL-8 in pre-diabetic patients[171]. Another study reported elevated bactericidal and anti-inflammatory outcomes upon combining metformin with photodynamic therapy for the treatment of chronic resistant periodontitis[172].

The antibacterial activity of metformin also attracted the attention of scientists as an adjuvant in tuberculosis (TB) treatment regimens[173]. Meta-analysis studies revealed reduced mortality rates and improved treatment outcomes in diabetic patients subjected to anti-TB regimen combined with metformin as anti-diabetic drug, also metformin administration was linked to reduced risk of TB disease among diabetics [174,175]. One suggested explanation was based on the fact that metformin is an inhibitor of mitochondrial complex-I which is analogous to mycobacterial NDH-I complex, hence giving the way for another mechanism of bactericidal activity of metformin[176]. Another study suggested that metformin had an immunomodulating effect by activating T regulatory and CD8 memory T cells responses activity leading to decreased pro-inflammatory responses which is reflected as reduction in lungs' lesions [177]. In another study, metformin was observed to reduce TB bacilli load in lung epithelial cells in relation to increased production of β-defensin-2, -3 and -4 which restrain bacterial growth and multiplication[178]. Contrary to expected, metformin has an enrichment rather than inhibition effect on gut microbiota, shifting the balance towards more short chain fatty acids-producing bacteria which are reported to confer protection against inflammation, maintain intestinal barrier integrity and augment insulin production from b-cells due to stimulation of glucagon-like peptide 1 (GLP-1) secretion[179,180].

In recent studies, the anti-virulence effects of metformin have been extensively studied. Significantly, metformin mitigated the virulence of *Pseudomonas aeruginosa invitro*[19,181]. It reduced the production extracellular virulence enzymes such as protease, elastase and hemolysin and inhibited bacterial motility and biofilm formation. The anti-virulence activity of metformin was owed to its ability to downregulate the quorum sensing (Q.S) encoding genes[19]. Q.S is a process uses chemical language by which bacterial populations can communicate. This intercellular communication is performed through signaling molecules produced by bacterial cell called autoinducers that are detected by receptors on another cell. The Q.S signaling system controls various virulence factors and physiological functions in both Gram-positive and Gram-negative bacteria. Q.S targeting has been proposed as an effective strategy to cripple the bacterial virulence[18,182,183]. Despite the *in vitro* metformin success in mitigation of Q.S, it failed to confer the protection to mice from *P. aeruginosa*. The *in vivo* failure of metformin was owed to its chemical nature which changed by the change of pH during bacterial growth, these changes hinder the complete blocking of Q.S receptors by metformin molecule[19]. Taking in consideration that metformin was not tested in combination with other antibiotics and was used in sub-MIC concentrations (10 mg/mL) which can be increased to enhance its efficacy, we encourage research group for further investigation of anti-virulence effects of metformin.

DPP-IV INHIBITORS (GLIPTINS)

Gliptins are oral hypoglycemic medications used for management of T2DM, they act by selective inhibition of DPP-IV leading to increased plasma GLP-1 and gastrointestinal insulinotropic peptide (GIP) levels, hence increased β-cell activity and suppression of glucagon secretion[184]. The alteration effects of gliptins on the

composition of gut microbiota developed functional shifts in the microbiome, that improves the glucose homeostasis[185]. Interestingly, DPP-4 inhibitors are associated with reduced inflammatory effects in adipose tissue and pancreatic islets through reduced expression of inflammatory cytokines and adjusted macrophage activity[171]. Among the thirteen members of gliptins, sitagliptin has an attractive chemical structure that may antagonize the Q.S receptors, plus it is the most prescribed gliptin. Hegazy *et al*[186], investigated the sitagliptin effects on the virulence behavior of *Serratia marcescens*. Interestingly, sitagliptin showed a significant capability of quenching the bacterial virulence both *in vitro* and *in vivo via* significant downregulation of the virulence encoding genes[18,186]. These findings encouraged us to further investigate another gliptin member: Vildagliptin in comparison to sitagliptin on virulent *Pseudomonas aeruginosa*[18,181]. Despite the marked downregulation effect of both vildagliptin and sitagliptins on Q.S encoding genes, vildagliptin failed to attain significant inhibition of bacterial virulence *in vitro* and *in vivo* as compared to the effects of sitagliptin. Docking studies provided us with the satisfying explanation that sitagliptin structure offers better fitting onto Q.S receptors as compared to the weak association of vildagliptin on the same receptors. We hypothesized that the anti-virulence or anti-Q.S activity of sitagliptin is not only due to its down regulation of responsible genes, but also due to its ability to block the Q.S receptors[19].

The potent competitive inhibition of bacterial virulence determinants of other bacterial species by sitagliptin and other gliptins were demonstrated (unpublished data). In a separate work, saxagliptin, vildagliptin and sitgliptin decreased *ex vivo* the biofilm formation by dental caries causing odontopathogen *Streptococcus mutans*. As bacterial enzyme X-prolyl dipeptidyl peptidase (XPDAP) is analogous to mammalian enzyme DPP-IV, it was hypothesized that anti-protease activity of gliptins may affect XPDAP and bacterial growth[187]. In a separate prospect, vildagliptin reduced the numbers of viable *Acanthamoeba castellanii* that causes fatal granulomatous amoebic encephalitis. The amoebicidal activity of vildagliptin was significantly enhanced when formulated as vildagliptin-conjugated silver nanoparticles[188]. Surprisingly, some studies linked between reduction in COVID-19 mortality rates and treatment with sitagliptin[189]. Gliptins, especially sitagliptin, reduced the inflammation intensity and may control cytokine storms mostly *via* nuclear factor kappa B signaling pathway[190, 191]. Nevertheless, cheminformatics suggested sitagliptin as anti-severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[192] as a result of the expected potential molecular binding between sitagliptin and viral spikes[193]. Nar *et al*[194], showed the ineffectiveness of gliptins against SARS-CoV-2 protease[194]. An enzymatic assay was performed to measure the sitagliptin, linagliptin, alogliptin and saxagliptin inhibitory effects on catalytic activity of SARS-CoV-2 main protease M^{pro}, significantly tested gliptins were inactive. They owed this inactivity due to lack of apparent structural similarity between M^{pro} and DPP-IV[194]. Regardless of the controversy about the efficacy of gliptins as anti-COVID-19, more investigations are required to explore whether gliptins harbor anti-viral activity or not. That being said, we consider gliptins in general and sitagliptin in particular to be promising targets for drug repurposing as bacterial anti-virulence agents.

GLITAZONES

Thiazolidinediones (TZDs), also known as glitazones, are a group of oral hypoglycemic agents used in T2DM. Glitazones work by restoring insulin sensitivity through the selective activation of the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) which controls the transcription of genes regulating glucose and lipids metabolism[195]. Glitazones also exert anti-inflammatory effects through suppression of IL-6 and reduction in circulating CRP levels [196]. One study reported direct impact of TZDs *via* increasing phagocytosis by liver recruited macrophages, increased production of ROS in phagocytes and decreased serum pro-inflammatory cytokines (TNF-α, IL-12, IFN-γ)[197]. It was shown that pioglitazone has antibacterial activity against *Streptococcus pneumoniae*, *E. coli* and *Klebsiella pneumoniae*. Moreover, pretreatment of bacteria with a suboptimal concentration of pioglitazone enhanced the antibacterial activity of some antibiotics[198]. In another study, pioglitazone was used as an adjuvant to amphotericin B to ameliorate cryptococcosis in a murine model, that may indicate its promising application as an adjuvant for controlling fungal infection[199]. Interestingly, thiazolidinedione nucleus is present in several antimicrobial compounds, *e.g.*, antibacterial, anti-mycobacterium, anti-malarial and antiviral, which was reviewed[200]. However, the mechanism of the

antimicrobial activity is not fully understood since prokaryotes lack the PPAR-γ receptor which is the target site for glitazones, the antibacterial activity of glitazones may be owed to thiazolidinedione nucleus[197,200]. Although there are no deep studies on the antimicrobial or anti-virulence activities of glitazones, we predict that their antimicrobial activities are owed to thiazolidinedione nucleus.

SULFONYLUREAS AND MEGLITINIDES

Sulfonylureas antidiabetic drugs stimulate insulin secretion from the pancreatic β-cells, they bind to ATP-sensitive K-channels in the β-cell membrane, depolarizes the cells and open voltage-gated Ca^{2+} channels that results in insulin release. Sulfonylureas anti-diabetics, especially the second generation, are widely used in the management of T2DM[201]. Multiple antidiabetic sulfonylurea derivatives showed significant bactericidal[202,203] and fungicidal activities[203,204]. The first generation of sulfonylurea antidiabetic tolbutamide analogues were screened for their antibacterial and antifungal activities, they showed activity against *S. aureus*, *E. coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis* and *C. albicans*[205]. Interestingly, Lowes *et al*[206], and others suggested repurposing the secondgeneration sulfonylurea anti-diabetics (glyburide, glisoxepide, gliquidone, and glimepiride) to treat fungal and bacterial infections[206-208]. They demonstrated the sulfonylurea anti-diabetics capability to inhibit activation of the NLRP3 inflammasome in various disease models such as vaginal candidiasis[206] and *Burkholderia pseudomallei* infection (melioidosis)[207]. Sulfonylureas were reported to decrease M1 macrophage activity and reduce IL-1β synthesis, pioglitazone is a direct PPAR-γ inhibitor that reduces adipose tissue inflammation[171]. It was supposed that sulfonylurea anti-diabetics prevent the release of major inflammasome effector IL-1β. Considerably, sulfonylurea anti-diabetics lack antimicrobial activity against *C. albicans* or *Burkholderia pseudomallei* and their anti-inflammatory activity was not specific to microbial infections, that means the possibility of repurposing these drugs against infectious and other immunopathological diseases[206,207]. Moreover, glimepiride was repurposed as amoebicidal agent, it decreased the numbers and encysts of *Acanthamoeba castellanii*[188].

Meglitinides mechanism of action closely resembles that of the sulfonylureas, they stimulate the insulin release from the pancreatic β-cells. Meglitinides are used orally and comprise nateglinide and repaglinide[209]. Unfortunately, there is a shortage in reports discussing the meglitinides' effects on both immune system and microbes. One study, the anti-amoebic activity of repaglinide was assessed against *Acanthamoeba castellanii*. It showed significant amoebicidal activity comparable to vildagliptin and glimepiride[188].

GLP-1 AGONISTS

Gut enteroendocrine cells release GLP-1 to control the meal related hyperglycemia through inhibition of glucagon and enhancement of insulin secretions. GLP-1 receptor agonists or incretin mimetics such as exenatide, liraglutide and albiglutide are used for the treatment of T2DM[210]. Liraglutide can lead to wight loss by changing the overall composition of gut microbiota as well as the relative abundance of weight-relevant phylotypes[211]. Generally, the hypoglycemic effects of GLP-1 agonists improve the immune status in diabetic patients to counteract the microbial infections. The associated metabolic activities of these drugs may be helpful in the treatment of human immunodeficiency virus (HIV)-associated metabolic adverse effects[212], and PEGylated exendin-4 has the potential to treat sepsis[213].

SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, represented by canagliflozin, empagliflozin and dapagliflozin, are hypoglycemic agents that work by increasing renal clearance of glucose through decreasing the renal tubular glucose reabsorption, hence reducing blood glucose level[214]. The interaction between SGLT-2 inhibitors and antibiotics is bidirectional, while the pharmacokinetic profile of SGLT-2 inhibitors may be influenced by co-administration of some antibiotics as rifampicin[215], they confer protection from gentamicin induced nephrotoxicity[216]. There are no reports

documenting direct anti-microbial activities of SGLT-2 inhibitors. On the other hand, SGLT-2 inhibitors associated glucosuria increases the risk of urogenital infections especially in postmenopausal women with T2DM[217].

α-GLUCOSIDASE INHIBITORS AND AMYLIN ANALOGS

α-glucosidase inhibitors (AGI) reversibly bind to oligosaccharide binding sites of glucosidase enzymes, resulting in delaying the polysaccharide degradation to glucose, slowing down the food digestion and decrease blood glucose levels after meals[218]. Amylin analogs such as pramlintide affect glucose levels *via* several mechanisms, including slowed gastric emptying, regulation of postprandial glucagon, and reduction of food intake[219]. It has been hypothesized that the interaction capabilities of AGI to glucosidase enzymes may be beneficial in targeting bacterial glucosidase [220] and altering glycosylation in viral life cycle, showing anti-viral activity against HIV, HBV and COVID-19[221]. However, we shortage in reporting antibacterial or antiviral activities of used antidiabetic AGI like acarbose, several studies indicated the antibacterial, anti-biofilm[222] and antifungal[223] activities of other similar AGI.

CONCLUSION

The relationship between diabetes, immunity and infection is complicated and bidirectional in most cases. This fact is clearly presented in the tangled interactions between diabetes and immunity disorders where each can potentially contribute to the other in a kind of "the egg or the chicken" dilemma. On a parallel basis, antimicrobial and anti-diabetic agents showed a grey area of overlapping activities that should be subjected to further investigations. It would be of great value to submit such information into practical applications by refining the currently used anti-diabetic regimens to include the anti-diabetic agents which offer antimicrobial protection as an accessory benefit. The systematic application of this approach would minimize the wide margins of morbidity and mortality usually associated with diabetes, in addition to reduced treatment costs and overall better treatment outcomes. In this review, we tried to aggregate the available information which would support this approach in addition to highlighting the proved antimicrobial activities of multiple anti-diabetic agents. By putting this information in the hands of clinicians and researchers, more attention can be paid during selection of the treatment options in order to offer diabetic patients the best outcomes and help in better containment of the emerging statistics of the diabetes pandemic.

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