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# The diabetes pandemic and associated infections: suggestions for clinical microbiology

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There are 425 million people with diabetes mellitus in the world. By 2045, this figure will grow to over 600 million. Diabetes mellitus is classified among noncommunicable diseases. Evidence points to a key role of microbes in diabetes mellitus, both as infectious agents associated with the diabetic status and as possible causative factors of diabetes mellitus. This review takes into account the different forms of diabetes mellitus, the genetic determinants that predispose to type 1 and type 2 diabetes mellitus (especially those with possible immunologic impact), the immune dysfunctions that have been documented in diabetes mellitus. Common infections occurring more frequently in diabetic vs. nondiabetic individuals are reviewed. Infectious agents that are suspected of playing an etiologic/triggering role in diabetes mellitus are presented, with emphasis on enteroviruses, the hygiene hypothesis, and the environment. Among biological agents possibly linked to diabetes mellitus, the gut microbiome, hepatitis C virus, and prion-like protein aggregates are discussed. Finally, preventive vaccines recommended in the management of diabetic patients are considered, including the bacillus calmette-Guerin vaccine that is being tested for type 1 diabetes mellitus. Evidence supports the notion that attenuation of immune defenses (both congenital and secondary to metabolic disturbances as well as to microangiopathy and neuropathy) makes diabetic people more prone to certain infections. Attentive microbiologic monitoring of diabetic patients is thus recommendable. As genetic predisposition cannot be changed, research needs to identify the biological agents that may have an etiologic role in diabetes mellitus, and to envisage curative and preventive ways to limit the diabetes pandemic.



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## Introduction

Due to increasing incidence worldwide, diabetes mellitus is a major medical problem. Diabetes mellitus is classified among noncommunicable diseases (NCDs) [1]. Strong evidence points to a key role of microbes in diabetes mellitus, both as infectious agents associated with the diabetic status and as possible causative factors of diabetes mellitus. Diabetes mellitus-related infections involve bacteria, viruses, fungi, parasites, and – possibly – prions.

## Classification of diabetes mellitus

Diabetes mellitus includes a group of metabolic conditions characterized by hyperglycemia resulting from

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defects in insulin action, insulin secretion or both. Chronic hyperglycemia is associated with long-term damage and dysfunction of eyes, kidneys, blood vessels, nerves, and heart.

Table 1 summarizes the current classification of diabetes mellitus with the estimated global prevalence of different forms [3]. Type 2 diabetes mellitus (T2DM; classic or with relative insulin deficiency) accounts for over 80% of cases followed by latent autoimmune diabetes of the adult (LADA), an autoimmune form of diabetes defined by adult-onset and presence of diabetes-associated autoantibodies (especially glutamic acid decarboxylase p65, or GADA). LADA shares genetic features with both type 1 diabetes mellitus (T1DM) and T2DM. LADA patients have higher glycated hemoglobin ($HbA_{1c}$) levels than T2DM patients, lower BMI, and more frequent, earlier need for insulin treatment than T2DM cases [4].

T1DM accounts for about 10% of cases. Secondary diabetes mellitus and the maturity-onset diabetes of the young account for less than 1% of cases. Gestational diabetes mellitus (GDM) is any degree of glucose intolerance with first recognition during pregnancy. GDM usually resolves after delivery but evolves to permanent diabetes mellitus in 5–10% of cases.

Impaired glucose tolerance (IGT) and impaired fasting glucose refer to individuals whose glucose levels are intermediate between normal values and values conventionally diagnostic of diabetes (Table 2). Collectively, these individuals are said to have 'prediabetes'. The metabolic syndrome (insulin resistance, upper-body obesity, hypertension, hypertriglyceridemia, low levels of HDL cholesterol) identifies persons at high risk for glucose intolerance and diabetes mellitus [5].

Diagnosis requires a blood sample taken after an overnight (12–14-h) fast and/or the ingestion of a standard (75 g) glucose load oral glucose tolerance test. Plasma C-peptide/insulin levels and detection of diabetes-related autoantibodies are essential for identifying specific forms

**Table 1. Major forms of diabetes mellitus.**

| Forms of diabetes | Prevalence (%) |
|---|---|
| Type 2 diabetes mellitus | 80 |
| T2DM classic: fasting C-peptide >0.6 nmol/l (>1.82 ng/ml) | 70 |
| T2DM with relative insulin deficiency: fasting C-peptide 0.2–0.6 nmol/l (0.61–1.82 ng/ml) | 10 |
| LADA | |
| LADA: autoimmune form of diabetes defined by age at onset >35 years, presence of diabetes-related autoantibodies, no insulin requirement for at least a period after diagnosis (www.actionlada.org) | 11 |
| Type 1 diabetes mellitus (immune-mediated or idiopathic) | 7.9 |
| T1DM with absolute insulin deficiency: age at onset <35 years, fasting C-peptide <0.2 nmol/l (<0.61 ng/ml) | 6 |
| T1DM above 35 years | 1.3 |
| T1DM with relative insulin deficiency: fasting C-peptide 0.2–0.6 nmol/l (0.61–1.82 ng/ml) | 0.5 |
| 'Fulminant diabetes' with absolute insulin deficiency: abrupt onset, no diabetes-related autoantibodies, mainly reported from Asia | 0.1 |
| Secondary diabetes mellitus | |
| DM secondary to pancreas diseases: pancreatitis, trauma, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, other | |
| DM secondary to endocrinopathies: acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma, other | |
| DM caused by drugs or chemicals: vacor, pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, β-adrenergic agonists, thiazides, dilantin, α-interferon, other | 0.8 |
| DM secondary to viral infections: congenital rubella, hepatitis C, Cytomegalovirus, other | |
| DM associated with genetic syndromes: Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Wolfram's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence–Moon-Biedl syndrome, Myotonic dystrophy, Porphyria, Prader–Willi syndrome, other | |
| DM due to genetic defects of insulin action and to uncommon causes: type-A insulin resistance, leprechaunism, Rabson–Mendenhall syndrome, lipoatrophic diabetes, 'stiffman' syndrome, antiinsulin receptor antibodies, other | |
| MODY: hereditary forms of diabetes associated with mutations in an autosomal dominant gene disrupting insulin production | 0.1 |
| MODY 1: chromosome 20, HNF-4alpha | |
| MODY 2: chromosome 7, glucokinase | |
| MODY 3: chromosome 12, HNF-1alpha | |
| MODY 4: chromosome 13, insulin promoter factor-1 | |
| MODY 5: chromosome 17, HNF-1beta | |
| MODY 6: chromosome 2, NeuroD1 | |
| GDM | |
| GDM: state of carbohydrate intolerance with onset or first recognition during pregnancy. Definition applies irrespective of whether the condition persists after pregnancy. Hyperglycemia usually resolves after delivery, but 5–10% of women may continue to have diabetes, often T2DM. | Prevalence not included |

DM, diabetes mellitus; GDM, gestational diabetes mellitus; LADA, latent autoimmune diabetes of the adult; MODY, maturity-onset diabetes of the young; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus. Adapted from [2].

**Table 2. Diagnostic criteria for prediabetes and diabetes (plasma glucose concentration).**

| Diagnostic categories | Fasting plasma glucose | 2-h Plasma glucose | Random plasma glucose | Necessary criteria |
|---|---|---|---|---|
| Prediabetes | | | | |
| IFG | 6.1–6.9 mmol/l | <7.8 mmol/l | – | Both |
| | 110–125 mg/dl | <140 mg/dl | – | |
| IGT | <7.0 mmol/l | ≥7.8 and <11.1 mmol/l | – | Both |
| | <126 mg/dl | ≥140 and <200 mg/dl | – | |
| Diabetes | | | | |
| | ≥7.0 mmol/l | ≥11.1 mmol/l | >11.1 mmol/l | One or more |
| | ≥126 mg/dl | ≥200 mg/dl | >200 mg/dl | |

IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

of diabetes mellitus. $HbA_{1c}$ is used both at diagnosis and during therapy.

## The diabetes pandemic

Diabetes mellitus hits people at the most productive age, slows economic growth, reduces life-expectancy in elders, causes increasing healthcare expenditure. Diabetes mellitus is among the top 10 causes of death and (together with major NCDs – cardiovascular, cancer, respiratory disease) accounts for over 80% premature NCD deaths. Upon introduction of insulin, insulin-dependent people with diabetes started enjoying longer lives, but long-term complications emerged and T1DM became a chronic disease [5].

### Current prevalence and perspectives

In developed countries, 87–91% of people with diabetes have T2DM, 7–12% have T1DM, 1–3% other types of diabetes mellitus [2,5]. As shown in Table 3, in the age group 20–79 (year 2017) there were 425 million people with diabetes worldwide. The figure is expected to increase to 629 million by 2045 [6]. Almost half of people living with diabetes (49.7%) are undiagnosed and there were 352 million people with IGT, that is 7.3% of adults 20–79 years. By 2045, in the same age group the number of people with IGT is projected to 532 million (8.3% of adults). In 2017, 21.3 million live births were affected by some form of hyperglycemia in pregnancy. Worldwide, in the 20–99 years age range, approximately 5 million deaths/year are attributable to diabetes. In Europe (Table 4) the gross prevalence of diabetes mellitus ranges from 2.9% in Ireland to approximately 10% in Portugal and Bosnia-Herzegovina [2].

Diabetes mellitus is more prevalent in the urban vs. the rural environment (10.2 vs. 6.9%) [2] and urbanization is expanding, particularly in Asia and Africa. The Chinese area of Pearl River Delta witnessed the most rapid urban expansion in human history: an agricultural region transformed into the world's largest city of over 40 million inhabitants. In Italy there are over 3 million people with T2DM and 1 million people with undiagnosed hyperglycemia (ISTAT, 2013). In Finland, the incidence of T1DM is now five times higher than 60 years ago and children who get diabetes have lower genetic risk than earlier [7]. Together with Scandinavia and Sardinia, Australia is among the high-incidence countries for T1DM [8].

### Healthcare costs

Based on 2017 data, the global healthcare expenditure on people with diabetes mellitus was estimated at USD 850 billion [6]. The cost of diagnosed diabetes mellitus in the United States has been USD 327 billion (including USD 90 billion for reduced productivity) and care for diabetes mellitus accounts for 1 in 4 healthcare dollars [9]. Over the last 5 years, cost has grown by 26%. In Lombardy

**Table 3. World: adults with diabetes in 2017 and projected figures for 2045.**

| Population data | 2017 | 2045 |
|---|---|---|
| Total world population | 7.5 billion | 9.5 billion |
| Adult population (20–79 years) | 4.8 billion | 6.4 billion |
| Number of people with diabetes (20–79 years) | 425 million | 629 million |
| Number of deaths due to diabetes (20–79 years) | 4.0 million | – |
| Number of people with impaired glucose tolerance (20–79 years) | 352 million | 532 million |
| Population (<20 years) | 2.5 billion | – |
| Number of children and adolescents with type 1 diabetes (0–19 years) | 1.1 million | – |

Adapted from [2].

**Table 4. Adults with diabetes in ten European countries (2017).**

| European countries | Population (thousands) | Adults with diabetes (thousands) | Diabetes prevalence (%) |
|---|---|---|---|
| Germany | 82 600.00 | 7476.80 | 9.05 |
| Spain | 46 600.00 | 3584.53 | 7.69 |
| Italy | 60 600.00 | 3402.34 | 5.61 |
| France | 66 900.00 | 3276.42 | 4.9 |
| United Kingdom | 65 640.00 | 2747.71 | 4.19 |
| Poland | 37 950.00 | 2235.78 | 5.89 |
| Romania | 19 700.00 | 1785.33 | 9.06 |
| Portugal | 10 329.51 | 1065.03 | 10.31 |
| Netherlands | 17 035.94 | 969.83 | 5.69 |
| Serbia | 8790.57 | 858.9 | 9.77 |

Adapted from [2].

(Northern Italy) the average yearly expense per diabetic subject was 3300 Euro. Hospitalizations were the cost drivers contributing 54% of the total, followed by drugs (32%) and outpatient claims (14%) [10].

## Genetics of diabetes mellitus

T1DM and T2DM are polygenic disorders, that is multiple genes contribute to their development [11,12]. Rare forms of diabetes mellitus (about 1% of cases) are single-gene disorders leading to beta cell or other defects [13].

### Genetic predisposition to type 1 diabetes mellitus

The genetic basis of T1DM is well established, with more than 60 identified genes explaining ~80% of its heritability [14,15].

In the human leukocyte antigen (HLA) system, the primary disease risk determinant is the *DQB1* gene, which encodes the beta chain of the Class II DQ molecule responsible for antigen presentation. Its alleles in combination with the neighboring *DQA1* and *DRB1* gene variants form the DR-DQ haplotypes that can be categorized into risk, neutral ad protective groups (Table 5). The heterozygous combination of the two susceptibility haplotypes DRB1*03-DQA1*0501-DQB1*0201/DRB1*0401-DQA1*0301-DQB1*03 (DR3-DQ2/DR4-DQ8 in terms of serological specificity) represents the highest disease risk and is linked to approximately 50% of disease heritability in white people [14,16]. The DR15-DQ6 haplotype is protective. Different ethnic groups may have different HLA associations [11]. HLA Class II haplotypes are also linked to beta cell-specific autoantibody patterns: GADA are more frequent in patients with the HLA DR3-DQ2 haplotype, while insulin and IA-2 autoantibodies are associated with DR4-DQ8. Heritability is declining with increasing age at diagnosis [17].

Outside the HLA region, other predisposing gene variants have been identified by genome wide association (GWAS) studies (e.g., INS, PTPN22, IL27, IFIH1 – Table 6). These genes are frequently involved in immune function and – possibly – in pathogenic pathways, for example, insulin expression in thymus, regulation of T-cell activation, innate virus immunity [28]. Thus, the risk of T1DM can be better predicted by using a genetic score that combines measurements of HLA and non-HLA loci [16].

### Genetic predisposition to type 2 diabetes mellitus

Having a parent with diabetes increases the risk of developing diabetes mellitus by 30–40% [12]. GWAS studies have implicated more than 200 genomic regions in the predisposition to T2DM (i.e., there are common alleles with small cumulative effects on risk) [29]. In T2DM, genetic and environmental factors regulate the interplay between insulin sensitivity, appetite regulation, adipose storage, and beta cell failure [30]. Genes work by regulating a variety of aspects. For instance, the insulin-mediated glucose uptake in skeletal muscle (e.g., *TBC1D4* gene), the ability to generate new adipocytes and the regulation of gene expression in these cells (e.g., *PPARG*, *KLF14*, *IRS1* genes), lipoprotein lipas (LPL)-mediated lipolysis [31], insulin secretion either through beta cell dysfunction or through impaired beta cell development (e.g., KCNJ11, ABCC8). Table 7 lists a few the implicated genes, some of which also play key roles in immunity. Thus, people carrying diabetes-predisposing gene variants are also likely to have flawed immune defenses. As in the case of T1DM, a genetic score combining measurements of multiple loci would be of help in assessing T2DM genetic risk.

## Immune dysfunction in diabetes

Hyperglycemia is linked with both chronic inflammatory processes and diabetes mellitus-related vulnerability to infection. People with diabetes are more susceptible than people without diabetes to periodontal disease [41], tuberculosis (TB) [42], lung infection by *Legionella*

**Table 5. Type 1 diabetes mellitus: association with common human leukocyte antigen class II haplotypes.**

| HLA class II haplotypes | | | Risk level | Notes |
|---|---|---|---|---|
| DRB1*04 | DQA1*03 | DQB1*0302 | Strong risk | DRB1 subtypes associated with variable risk |
| DRB1*0408 | DQA1*03 | DQB1*0304 | Strong risk | Rare haplotype |
| DRB1*03 | DQA1*05 | DQB1*02 | Risk | Stronger effect in Southern Europe |
| DRB1*0405 | DQA1*03 | DQB1*02 | Risk | Predominantly in the Mediterranean area |
| DRB1*09 | DQA1*03 | DQB1*0303 | Risk | |
| DRB1*0405 | DQA1*03 | DQB1*0401 | Risk | Predominantly in Orientals |
| DRB1*0802 | DQA1*03 | DQB1*0302 | Risk | |
| DRB1*07 | DQA1*03 | DQB1*02 | Risk | Predominantly in Blacks |
| DRB1*1501 | DQA1*0102 | DQB1*0301 | Protective | |

HLA genes play key roles in immunity. HLA, human leukocyte antigen. Adapted from [14].

**Table 6. Major nonhuman leukocyte antigen genes predisposing to type 1 diabetes mellitus.**

| Gene | Chromosome | Functions |
|---|---|---|
| *INS* | 11p15.5 | Insulin: binding of insulin to the insulin receptor stimulates glucose uptake. Different mutant alleles with phenotypic effects have been identified. Single nucleotide polymorphisms may constitute risk factors for T1DM [18] |
| *PTPN22* | 1p13.2 | Protein tyrosine phosphatase, nonreceptor type 22: lymphoid-specific intracellular phosphatase involved in the T-cell receptor signaling pathway. PTPN22 plays a role in regulating the function of immune cells, particularly T cells. Polymorphisms of PTPN22 have been associated with autoimmune diseases, including T1DM – immune function [19] |
| *IL27* | 16p11.2 | IL-27: modulation of T-cell subsets and regulation of inflammatory response. Single nucleotide polymorphisms have been studied in relation to T1DM pathogenesis – immune function [20] |
| *BAD* | 11q13.1 | BCL2-associated agonist of cell death: belongs to the BCL-2 family (regulators of apoptosis). Balance between pro-apoptotic proteins, such as BAD, and antiapoptotic proteins may play a role in hyperglycemia-induced β-cell apoptosis [21] |
| *CD69* | 12p13.31 | CD69 molecule: member of the calcium dependent lectin superfamily of type II transmembrane receptors. Expression induced upon activation of T lymphocytes; may play a role in cell proliferation. Early lymphocyte activation antigen; limits the inflammatory response. Participates in signaling of natural killer cells. CD69 is related to multiple autoimmune diseases in children – immune function [22] |
| *CLEC16A* | 16p13.13 | C-type lectin domain containing 16A: is expressed in NK, DC, B cells and beta cells. May be associated with increased susceptibility to T1DM, multiple sclerosis, adrenal dysfunction – immune function [23] |
| *ERBB3* | 12q13.2 | Erb-b2 receptor tyrosine kinase 3: member of the epidermal growth factor receptor family; modulates antigen presentation, autoimmunity, cytokine-induced beta-cell apoptosis. A single nucleotide polymorphism in intron 7 seems associated with predisposition to T1DM – immune function [24] |
| *CTSH* | 15q25.1 | Cathepsin H: lysosomal cysteine proteinase important in degradation of lysosomal proteins, apoptosis, TLR3 functions, antigen presentation, insulin synthesis in beta cells. CTSH may regulate β-cell function during T1DM progression – immune function [25] |
| *IFIH1* | 2q24.2 | Interferon induced with helicase C domain 1: senses and initiates antiviral activity and is involved in inflammatory response in islets. IFIH1 polymorphisms seem associated with initial events of T1DM – immune function [26] |
| *TYK2* | 19p13.2 | Tyrosine kinase 2: component of both type I and type III interferon signaling pathways. Plays a role in antiviral immunity. Loss-of-function variants reduce the response to interferons. Genetic variants seem associated to autoimmune diseases, including T1DM – immune function [27] |

Some genes may play a role in immunity. DC, dendritic cell; NK, natural killer; T1DM, type 1 diabetes mellitus. Adapted from [14,15].

**Table 7. Major protein-coding genes and intron/intergenic variants associated with type 2 diabetes.**

| Gene | Chromosome | Functions |
|---|---|---|
| *TCF7L2* | 10q25.2 | Transcription factor 7 like 2: transcriptional effector of the Wnt/β-catenin signaling pathway that regulates adipogenesis and dendritic cell activation. Variants associated with increased risk of T2DM [32] – immune function [33] |
| *JAZF1* | 7p15.1 | JAZF zinc finger 1: role in glucose homeostasis by improving glucose metabolism and insulin sensitivity; may also have antiapoptotic functions. Possible role for JAZF1 variants in T2D susceptibility in African-American individuals [34] |
| *CDKN2A/2B* | 9p21.3 | Cyclin dependent kinase inhibitor 2A/2B: causes cycle arrest in G1 and G2. Known as tumor suppressor, downregulates proliferation of normal cells interacting with CDK4/CDK6. Regulator of innate immunity. Correlation between CDKN2A/2B polymorphisms and predisposition to gestational diabetes – Immune function [35] |
| *ADRA2A* | 10q25.2 | Adrenoceptor alpha 2A: mediates catecholamine-induced inhibition of adenylate cyclase through G proteins. Involved in glucose homeostasis, antigen uptake, maturation of dendritic cells. Single nucleotide polymorphisms in or near *ADRA2A*, *ADCY5*, *CDKAL1*, *CDKN2A/B*, *GRB10*, *TCF7L2* have effects on plasma glucose in childhood – immune function [36] |
| *PPARG* | 3p25.2 | Peroxisome proliferator activated receptor gamma: promotes alveolar macrophage development. In dendritic cells and T cells drives pathogenic type-2 responses in lung inflammation and allergy. The C/C genotype may predispose to diabetic nephropathy, while the G allele would be protective in T2DM patients – immune function [37] |
| *SLC30A8* | 8q24.11 | Solute carrier family 30 member 8: zinc efflux transporter and zinc accumulation in intracellular vesicles. High-level expression only in pancreas, particularly islets. Variants confer susceptibility to T2DM [38] |
| *PRKCQ* | 10p15.1 | Protein kinase C theta: important for T-cell activation; interaction of APC with T cells. Diacylglycerol activation of PRKCQ has a role in lipid-induced muscle insulin resistance in obese and T2DM – immune function [39] |
| *ARG2* | 14q24.1 | Arginase 2: hydrolyzes arginine to ornithine and urea. Type II isoform located in mitochondria of extra-hepatic tissues (kidney); role in nitric oxide and polyamine metabolism. Inhibition of arginase-2 might be effective for limiting diabetic renal injury. Modulates infection by *H. pylori* [40] |

Some variants may play a role in immunity. T2DM, type 2 diabetes mellitus. Adapted from [29].

*pneumoniae* [43], 'mucormycosis'caused by the *Mucoraceae* family of fungi [44]. Defects of the innate response come with dysfunction of granulocytes, monocyte/macrophages, dendritic cells, natural killer (NK) cells, B cells, T cells, and cytokine signaling.

Examples of immune defects associated to DM are summarized in Table 8. Hyperglycemia affects innate immunity by impeding production of type I interferon and IL22 [51,52]. Type I interferon has multiple effects, including antiviral activity [66], while IL22 reduces chronic inflammation and elicits antimicrobial immunity, preserves gut mucosal barrier, and improves insulin sensitivity [53]. Hyperglycemia also downregulates the expression of cathelicidins in macrophages (thereby implying diminished antimicrobial effects [54], reduces chemotaxis, impairs bactericidal activity, and neutrophil degranulation in response to bacterial lipopolysaccaride (LPS) [57]. High glucose causes nonenzymatic glycation of multiple proteins, including those of the complement system involved in the opsonization of pathogens [49]. Glycation inhibits complement activation via the mannan-binding lectin pathway as well as functions of the CD59 inhibitor of the membrane attack complex [50]. Poor glycemic control also affects the production of reduced glutathione. Lack of reduced glutathione reduces the production of IL2 and IFN-γ by mononuclear cells with lessened killing of intracellular bacteria [55]. Protein glycation may favor bacterial growth by promoting the availability of micronutrients such as iron [56]. Long-term alterations of glucose homeostasis associate also with the formation of advanced glycation end-products (AGEs) that bind proteins, including albumin. AGE-albumin acts on neutrophils and macrophages by hindering trans-endothelial migration [47] and altering gene expression [48].

Neutrophils of people with diabetes show an elevated expression of peptidylarginine deiminase 4, a citrullinating enzyme involved in the release of the cell genome as neutrophil extracellular traps. Unbalanced NETosis promotes inflammation and has a negative impact on immune defenses and wound healing [45]. Reduced innate cell activation is seen in diabetes mellitus: peripheral blood mononuclear cells show an impaired production of IL1β a key mediator in inflammation [46,67]. In T1DM, elevated serum levels of IL15 and its soluble receptor (sIL15Rα) have been detected. As in other autoimmune conditions, the disordered expression of IL15 signaling may play a pathogenic role [60]. IL15 is a membrane-associated molecule that promotes the activation of NK and CD8 T-effector memory cells. Expression of IL15/IL15Ra occurs in viral infection (e.g., enterovirus-infected islets). In T1DM [63] and GDM [64] there may be reduced numbers of circulating NK cells and altered cytokine signaling. In visceral adipose tissue, conventional dendritic cells (cDCs) acquire a tolerogenic phenotype through upregulation of pathways involved in adipocyte differentiation. Although activation of the Wnt/β-catenin pathway in cDC1 DCs induces IL10 production (an anti-inflammatory mediator), upregulation of the PPARγ pathway in cDC2 DCs directly suppresses their activation. Combined, these effects promote an anti-inflammatory milieu that limits chronic inflammation and insulin resistance. However, with long-term over-nutrition, changes in adipocyte biology curtail β-catenin and PPARγ activation, contributing to persistent inflammation (Tables 8 and 9) [59].

Alterations of costimulatory molecules are also reported. Binding of CD40L on the surface of T cells to CD40 on the surface of antigen-presenting cells (dendritic cells, macrophages, B cells, other) activates immune responses. Plasma levels of sCD40L are elevated in hyperglycemic T2DM patients [70]. Binding of sCD40L to CD40 induces the production of proinflammatory cytokines, thus perpetuating the inflammatory status, perturbing insulin production, and downregulating antigen-specific responses [71].

In T1DM, beta cell damage is mediated by the combined actions of CD4+ and CD8+ T cells specific for islet autoantigens. T cell dysfunctions [especially FOXP3+ T regulatory cells (Tregs)] have been reported in the disease [61]. In addition, T cells responsive to beta cell autoantigens have an increased granulocyte-macrophage colony-stimulating factor (GM-CSF)-producing component (GM-CSF+, IFNγ−, IL17A−, IL21−, IL22− CD4 T cells) [62]. T2DM cases associated with lung TB are characterized by CD8 T cells exhibiting diminished expression of cytotoxic markers (perforin, granzyme B, CD107a) and, possibly, lessened antimicrobial activity [65]. B cells are also important: in T2DM patients as they promote inflammation through regulation of T-cell function and an inflammatory cytokine profile [72]. In T1DM, anti-CD20 therapy delays – but fails to prevent – the onset of the disease and B cells present autoantigens to T cells [73]. The numbers of B cells that infiltrate the pancreas correlate with β-cell loss [74]. The reported immune defects may be secondary to the functions of diabetes-predisposing alleles as shown for T1DM [75], and/or to metabolic alterations in lymphoid cells [76].

## Common infections and resistance to antimicrobial drugs

Due to impaired defenses and disease complications, people with diabetes are prone to new infections and recurrences [urinary tract infection (UTI), periodontitis, pneumonia, skin, and soft tissue (including the diabetic foot), osteomyelitis, peritonitis]. Uncommon life-threatening infections are more frequent in people with diabetes than in people without diabetes (necrotizing soft tissue infection, emphysematous pyelonephritis,

**Table 8. Immune defects in diabetes (examples).**

| Associated condition | Target | Possible mechanism | Effect(s) |
|---|---|---|---|
| DM | Neutrophils | excessive activation of peptidylarginine deiminase 4 and formation of NETs | NETosis promotes inflammation and iterferes with immune defences and wound healing [45] |
| | Peripheral blood mononuclear cells | reduced production of IL1beta | Diminished production of a key mediator of the inflammatory response [46] |
| Hyperglycemia | Albumin | Formation of AGE that bind proteins | AGE-albumin binds to neutrophils and macrophages obstructing trans-endothelial migration [47] and gene expression [48] |
| | | | Defective opsonization of pathogens, decreased phagocytosis [49] |
| | Complement system | Nonenzymatic glycation of proteins | Reduced activation of complement via mannan-binding lectins and interference with the CD59 inhibitor of complement-dependent cytolysis [50] |
| | | | Downregulation of IFN-I [51,52] |
| | Innate immunity | Unknown | Downregulation of IL22 [51–53] |
| | Macrophages | Unknown | Diminished production of cathelicidines, antimicrobial peptides [54] |
| | Metabolism | Lack of reduced glutathione | Diminished production of IFN-gamma and IL2 with reduced killing of intracellular pathogens [55] |
| | Micronutrient-binding proteins | Nonenzymatic glycation of proteins | Increased availability of micronutrients for microbial growth [56] |
| | Peripheral blood neutrophils | Unknown | Diminished degranulation in response to LPS [57] |
| | Peripheral blood phagocytes (?) | Unknown | Diminished chemotaxis and engulfement of microbes [58] |
| Long-term overnutrition | Conventional dendritic cells in visceral adipose tissue | Defective activation of beta-catenin and PPARgamma | Loss of tolerogenic phenotype in dendritic cells contributes to persistent inflammation [59] |
| T1DM | Pancreatic islet cells (?) | Disordered expression of IL15 and its receptor molecule IL15Ralpha | Expression of IL15 and IL15Ralpha on target allows NK and T effector cells to kill [60] |
| | Peripheral blood T cells | Unknown | Diminished numbers of regulatory T cells [61] |
| | | Unknown | Increased numbers of CD4 cells producing GM-CSF [62] |
| T1DM and GDM | Peripheral blood NK cells | Unknown | Diminished numbers of NK cells [63,64] |
| T2DM and hyperglycemia | Antigen-presenting cells and T cells | Enhanced expression of costimulatory molecules CD40 and CD40L | Promoted inflammation, downregulation of immune responses, perturbed insulin production |
| T2DM and tuberculosis | Cytotoxic T cells | Reduced expression of cytotoxic mediators (perforin, granzyme B, CD107a) | Diminished antimicrobial activity [65] |

AGE, advanced glycation end-product; DM, diabetes mellitus; GDM, gestational diabetes; GM-CSF, granulocyte-macrophage colony-stimulating factor; LPS, lipopolysaccaride; NET, neutrophil extracellular trap; NK, natural killer cells; T1DM, type-1 diabetes; T2DM, type 2 diabetes.

emphysematous cholecystitis, malignant otitis, perioperative infection). Two recent chapters [68,77] and a review [78] cover the heightened susceptibility of people with diabetes to infections including tubercular mycobacteria [79,80]. Notably, the antimicrobial properties of metformin could reinforce antiinfectious treatments in people with diabetes and metformin itself influences the composition of gut microbiome [81].

Common infections in people with diabetes are summarized in Table 9. Diabetes mellitus and $HbA_{1c}$ more than 6.5% are associated with the risk of community-acquired and hospital-acquired bloodstream infection and sepsis [82,83]. After recovery from sepsis, alterations in innate and adaptive immune responses endure, resulting in immune dysfunction, chronic inflammation, and microbial persistence that carries an increasing risk of postsepsis infections [84]. In a vicious cycle, infection can worsen glycemic control and vice versa. Glycation of FimH (an *Escherichia coli* adhesin in urinary tract epithelial cells) does enhance susceptibility to infection [85]. Similarly, expression of intercellular adhesion molecule-1 (ICAM-1) in vaginal cells is upregulated by high glucose, thus promoting adhesion of *Candida* spp. [86]. In people with diabetes with urinary tract infection (UTIs), elevated $HbA_{1c}$ levels represent a

**Table 9. Common infectious events in people with diabetes.**

| Body site | Infection | Etiologic agent(s) |
|---|---|---|
| Head and neck | Periodontal disease | Oral commensals, *Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola,* other species |
| | Mucormycosis (zygomycosis) | *Rhizopus* spp., *Mucor* spp. |
| | Endophthalmitis | *E. coli, K. pneumoniae* |
| | Malignant otitis externa | *P. aeruginosa, Aspergillus* spp. and other fungi |
| Respiratory tract | Pneumonia and bronchopneumonia | *S. pneumoniae, S. aureus, K. pneumoniae* and other Gram-negative bacilli |
| | | *Legionella* spp. |
| | | *Influenza virus* |
| | Tuberculosis | *M. tuberculosis complex* |
| Urinary tract | Urinary tract infection: cystitis, urethritis, pyelonephritis, complications | *E. coli, Klebsiella* spp. and other enterobacteria |
| | | *Acinetobacter* spp. |
| | | *P. aeruginosa* |
| | | *S. agalactiae* |
| | | *Candida albicans*, other yeasts |
| Intra-abdominal compartment | Hepatic and intra-abdominal abscesses | *K. pneumoniae* |
| | Cholecystitis | Enterobacteriaceae: *Escherichia coli*, other species |
| | | Obligate anaerobic bacteria: *Bacteroides fragilis, Clostridium perfringens* |
| Skin and subcutaneous tissues | Intertrigo | *Candida* spp. |
| | Skin lesions | *Varicella-Zoster virus* |
| | Cellulitis | *S. aureus* |
| | | *S. pyogenes* |
| | Superficial mycoses and onychomycosis | Dermatophytes |
| Soft tissue, bones, joints | Necrotizing fasciitis | *S. pyogenes; S. aureus, Enterobacteriaceae* |
| | | Obligate anaerobic bacteria: *Bacteroides* spp., *Clostridium perfringens* |
| | | *Vibrio* spp. |
| | | *Aeromonas* spp. |
| | | *Salmonella* spp. |
| | | *Enterococcus* spp. |
| | Diabetic foot | *S. pyogenes, S. aureus,* Gram-negative bacilli, anaerobic bacteria, fungi |
| | Osteomyelitis, septic arthritis | *S. aureus*, *M. tuberculosis* complex |
| Bacteremia and sepsis | Community-acquired and hospital-acquired | *Escherichia coli, Staphylococcus aureus*, *Streptococcus pneumoniae,* enterobacteriaceae, enterococci, *Pseudomonas aeruginosa*, *Candida albicans,* other agents |

Adapted from [68].

risk factor for bacteremia and sepsis [87]. In the course of dengue epidemics, people with diabetes are at risk for hemorrhagic fever [88].

## Drug-resistant organisms and diabetes

Since people with diabetes are more exposed to antimicrobials than people without diabetes, drug-resistance is particularly prevalent in this group. Table 10 shows the prevalence of common drug-resistance phenotypes in bacterial isolates from patients diagnosed with infection worldwide (data of a 2015 1-day survey made in 53 countries) [69] compared with figures observed for people with diabetes mellitus at our own hospital in 2017 (Varese, Italy). Prevalence of resistance to common antibacterials is enhanced compared with nondiabetic patients. The prevalence of methicillin-resistant *Staphylococcus aureus* was high and comparable in both groups, confirming the extremely elevated prevalence of methicillin-resistant *S. aureus* strains in Italy [89]. In contrast, the prevalence of common resistance phenotypes (vancomycin-resistant enterococci, extended-spectrum β-lactamases-producing enterobacteria, carbapenem-resistant enterobacteria and nonfermenting Gram-negative bacilli) was more pronounced in people with diabetes vs. nondiabetic patients. Thus, early diagnosis and prompt treatment of infections are critical for people with diabetes, including surgical debridement when needed. Compared with people without diabetes, diabetes mellitus implies a higher risk of failure of *Helicobacter pylori* therapy, suggesting the need of specific regimens for its eradication [90].

## Mycotic genital infections

People with diabetes are at an increased risk of being diagnosed with infections of the urogenital tract, especially individuals of younger age, with a history of prior genital infections, and with poorly controlled glycemia [91]. *Candida* spp. constitute the most frequent isolate [92]. The most recent addition to the therapeutic options for the treatment of T2DM are the sodium-glucose cotransporter 2 (SGLT2) inhibitors (three members of the class – canagliflozin, dapagliflozin, and empagliflozin currently marketed in Western countries).

**Table 10. Prevalence of drug-resistant isolates in adult inpatients diagnosed with bacterial infection worldwide and in Europe (1-day survey, year 2015) compared with adult nondiabetic and diabetic inpatients at a single hospital (Varese, Italy, year 2017).**

| | Prevalence of drug-resistant bacterial isolates (%) | | | | |
|---|---|---|---|---|---|
| | MRSA[a] | VRE | ESBL-enterobacteria | CarbaR enterobacteria | CarbaR GNNF bacilli |
| World, $n=6750$ | 5.3 | 1.1 | 8.1 | 1.2 | 2.6 |
| Europe, $n=3981$ | 5.3 | 1.6 | 14.8 | 0.9 | 6.7 |
| Nondiabetic inpatients, Varese, $n=6540$ | 34.1 | 2.9 | 13.2 | 1.8 | 32.4 |
| Diabetic inpatients, Varese, $n=518$ | 33.8 | 3.5 | 16.7 | 2.9 | 45.6 |

Adapted from [69].
[a]Common resistance phenotypes: CarbaR, carbapenem-resistant; ESBL, production of extended-spectrum β-lactamases; GNNF, Gram-negative nonfermenting rods; MRSA, methicillin-resistant *S. aureus*; VRE, vancomycin-resistant enterococci.

SGLT2 inhibitors reduce hyperglycemia by increasing urinary glucose excretion. These agents have shown significant clinical benefit with regard to weight loss, low risk of hypoglycemia, reduction in blood pressure, reduction in cardiovascular and renal events in high-risk patients, leading to their increasing popularity for T2DM. However, common to all SGLT2 inhibitors is that chronic use is associated with a definite increase in genital infections (up to 8–10% of treated patients), with the following characteristics: mild-to-moderate severity, incidence dependent on drug dosage, hence roughly proportional to the amount of urinary glucose loss, more frequent in women (vulvovaginitis) than men (balanitis), more frequent in association with obesity, antecedent history of genital infection, poor hygiene, often recurrent but seldom leading to treatment discontinuation [93]. Urinary tract infections show the same pattern, although with a lower incidence (+15% vs. placebo or non-SGLT2 medications) than genital infections (+180%).

### Parasites and diabetes

Case reports suggest that diabetes mellitus can affect the phenotype of cutaneous disease, with unusually vegetative *Leishmania major* lesions occurring in patients with diabetes [94] and particularly severe cutaneous *Leishmania infantum* lesions in French and Italian people with diabetes compared with nondiabetic patients [95]. In a study from Indonesia, the prevalence of infection with soil-transmitted helminths (ascaris, trichuris, hookworm, strongyloides) was inversely related with insulin resistance [96]. Epidemiology shows an inverse relationship between the decreasing prevalence of helminth infections and the increasing prevalence of metabolic diseases (hygiene hypothesis) [97]. One way by which helminth infections can modulate insulin resistance and the associated inflammation is by inducing a chronic low-grade immune suppression due to both Th2 and regulatory T cells which can quench inflammation and promote insulin sensitivity [98]. Schistosomiasis appears to protect against diabetes mellitus [78].

### Herpes zoster and diabetes

Large studies indicate that T1DM and T2DM patients are at risk for herpes zoster [99–101]. Postherpetic neuralgia is more severe and persistent in people with diabetes [102] and vascular complications confer an additional risk [101]. Significantly, statins increase the risk of Herpes Zoster (HZ) [103].

### Complications of diabetes favor infection

Complications of diabetes mellitus confer an additional risk for infection: vascular pathology and reduced perfusion, sensory neuropathy and autonomic neuropathy that implies reduced sensitivity to painful stimuli and repeated trauma, reduction of sweating, urinary retention, alterations of gastrointestinal mobility and absorption. Other diabetes mellitus-related conditions include increased body mass, dehydrosis and superficial skin infections (especially at body folds), infection of foot ulcers [104]. Insulin injections, even if sporadically, may aid subcutaneous infection. In addition, people with diabetes are exposed to risks of infection associated with semi-invasive or invasive procedures (e.g., general hospital assistance, dialysis, surgery).

## Diabetes mellitus and environmental factors

### Type 1 diabetes mellitus and environment

Potential triggers of islet autoimmunity include diet, toxins, infections that affect children (*in utero*, perinatally, during childhood). Comparisons between the genetically-related populations of Finland and the neighboring Karelian Republic of Russia indicate that T1DM is six times more common in Finland and that other immune mediated diseases (celiac disease, autoimmune thyroiditis, allergy) follow a similar trend [105]. Supporting the impact of environment or lifestyle on risk, migrants tend to acquire the same risk of T1DM as the population in their new area of residence [106,107]. In African migrants to France, T1DM is developing earlier compared with those staying in their country of birth [108]. Thus, environmental factors have a key role in T1DM.

### Type 1 diabetes mellitus and infection

Viruses have long been suggested as environmental triggers. A meta-analysis showed a significant association between enterovirus detection in blood and T1DM at the

time of clinical onset [109]. The finding has been confirmed in multiple studies both at onset and in later phases [110–115]. The MIDIA study suggested that in genetically predisposed children enterovirus infection may precede islet autoimmunity [116]. Viral serology has shown that infection by coxsackievirus B1 is associated with islet autoimmunity and progression to clinical diabetes [117,118]. Enterovirus infection during pregnancy may have a pathogenic role [119,120]. In support of these association studies, the enterovirus capsid protein VP1 was found in islets of patients with T1DM both close to the time of onset and several years after onset, indicating that enteroviruses establish a persistent infection in beta cells [121–123]. Virus does not produce a lytic effect in islet cells, rather T1DM occurs in the presence of a persistent low-grade infection triggering an inflammatory response, beta cell damage and autoantigen release [124]. The observation that children with T1DM show an incomplete antibody response to enteroviruses [125] supports the hypothesis of defective antiviral resistance leading to a chronic infection, then to endocrine autoimmunity. Molecular and immunologic methods for detecting minute amounts of mutated enterovirus types will assist in defining diabetes-associated viruses [126,127]. As indirect evidence for enterovirus infection, viral signatures such as interferon and major histocompatibility complex class-I (MHC-I) hyperexpression have been found in T1DM [128].

Respiratory infections in children are temporally associated with initiation of islet autoimmunity in the TEDDY study [129]. Similarly, detection of enteroviruses in stools precedes islet autoimmunity [130]. Other reports document the frequent exposure to infectious agents at time points close to the clinical onset of T1DM [131]. Later, progressive beta cell loss may be secondary to activation of autoreactive mechanisms [124]. Among mechanisms leading to virus-induced autoimmunity and beta cell death, molecular mimicry reflects the possible cross reactivity between viral components and islet proteins [124]. Additional mechanisms include epitope spreading, bystander activation, bystander damage.

Rare variants of IFIH1, a gene implicated in antiviral responses, have been shown to protect from or predispose to T1DM [132], thus confirming the possible role of viruses in initiating the diabetogenic process [133,134]. Should enteroviruses be pathogenic contributors to T1DM, efforts at developing effective antivirals and an enterovirus vaccine will be of utmost importance [135–137].

Additional factors possibly involved in the origin of T1DM include breastfeeding [138], exposure to cow milk [139], exposure to *Mycobacterium avium-paratubercolosis* in bovine milk [140], timing of introduction of cereals [141] or egg [142], toxic chemicals such as nitrates and derivatives [143], vitamin D intake during pregnancy and thereafter [115,144]. Recently, tenuous evidence has been published for a possible causative role of influenza viruses [145].

## Fulminant diabetes

Fulminant T1DM (FDM) was first reported by Imagawa [146]. FDM is defined as remarkably abrupt onset; very short duration of hyperglycemic symptoms (less than 1 week); ketoacidosis at diagnosis; negativity of islet-related autoantibodies; almost nil C-peptide; elevated levels of pancreatic enzymes; high ratios of glycated albumin to glycated hemoglobin (indicating that hyperglycemia was of short duration) [147]. These characteristics are found in about 20% new cases in Japan. Influenza-like symptoms are frequent before the onset [148]. FDM may be associated with pregnancy [149], leads to early microvascular damage, is associated with HLA DRB1*04 : 05DQB1*04 : 01 [147] and autoantibodies to C300 (a protein family expressed in dendritic cells [150]. FDM has been reported from Korea, China, other areas of Asia, and – sporadically – in whites [151]. Notably, titers of enterovirus IgA antibodies were elevated in patients with recent-onset FDM compared with those with recent-onset autoimmune T1DM [151]. Enterovirus antigens are detected in islets and exocrine tissue together with upregulation of MDA5, RIG-I, TLR3, and TLR4 [148]. Features of FDM point to a short pathogenic process of infectious origin leading to rapid beta cell destruction.

## Enteroviruses in waters

Health risks associated with sewage-contaminated waters are a public health concern. Water monitoring systems rely predominantly on the enumeration of bacterial indicators. However, human enteric viruses – due to their resilience and persistence in the environment – may represent more significant indicators. In Hawaiian waters, 11/20 sites tested positive for enteroviruses, indicating fecal contamination. In addition, shellfish from six of nine sites tested positive for enteroviruses of different species [152]. In the context of poliovirus surveillance, waters examined for polio and nonpolio enteroviruses in Helsinki (Finland) and Islamabad (Pakistan) contained multiple nonpolio enteroviruses, predominantly of the B species (coxsackieviruses and select echoviruses) [153]. Comparable results have been obtained in Varese, Italy: diverse nonpolio enterovirus types have been detected in sewage and wastewater, belonging mostly to the B species and the Echovirus group (unpublished observations). Importantly, enteroviruses were not found in drinking waters. In contrast, in Egypt nonpolio enteroviruses were found in 100% sewage and wastewater and also in one third of drinkable water samples [154]. It has also been proposed that enteroviruses may persist in free-living amoebae within environmental waters [155]. Thus, waters may represent a common vehicle of transmission for these agents and could contribute to the spreading of diabetes mellitus.

### The hygiene hypothesis in type 1 diabetes mellitus

Over the last century, improved hygienic conditions have led to reduced circulation and exposure to biological agents (pathogens, commensals, parasites). This may have resulted in lessened antimicrobial immunity with consequences possibly relevant to the young and older ages [97,156]. In addition, vaccines could reduce communicable diseases. These events correlate with the heightened frequency of autoimmune conditions and the increasing incidence of common infections at older ages [156,157]. Lack of intestinal parasites seems particularly linked to autoimmune conditions [78,158] and helminth-induced immunomodulation may well prevent diabetes mellitus and ameliorate insulin sensitivity [159,160].

### Type 2 diabetes mellitus and environment

Epidemiologically, high levels of walkability and green space are associated with lower T2DM risk, while increased levels of air pollution and noise are associated with greater risk [161]. Thus, an important risk factor is urbanization itself, which is linked to consumption of unhealthy foods, sedentary lifestyle, scarce exposure to sunlight. Randomized controlled trials in Finland, USA, China, and India established that lifestyle modification with physical activity [162] and healthy diets [163] can delay or prevent T2DM. A variety of environmental factors may play a role in T2M. These include: delivery mode, weight at birth, placental function, maternal nutrition, postnatal growth, antibiotic usage, diet with processed foods, calorie intake, macro, and micronutrients, vitamins, basal metabolism, exercise, sleep debt, endocrine disruptors, chronic inflammation [164]. To prevent T2DM, WHO recommends limiting saturated fatty acid consumption to less than 10% of total energy intake and achieving adequate intake of dietary fiber (minimum 20 g daily). Reducing the intake of free sugars to less than 10% of total and physical activity 3–5 days a week for at least 30–45 min are also recommended [2].

### Gut microbiome

Though medicine is mostly concerned with pathogenic bacteria, a symbiotic interaction of intestinal bacteria with the human body forges the immune system. Gut microbes participate in polysaccharide breakdown, nutrient absorption, gut permeability, bile acid modification, inflammatory responses, and may produce vitamins and nutrients. In the distal gut microbiota, more than 90% of phylogenetic types belong to two divisions: the Firmicutes (mostly Gram-positive) and the Bacteroidetes (Gram-negative, nonsporeforming, rod-shaped bacteria). The remaining types are distributed among eight divisions. Alterations in Gammaproteobacteria (Gram-negative) and Verrucomicrobia (Gram-negative) and the ratios of Firmicutes to Bacteroidetes (Gram-positive) are associated with weight gain and insulin resistance, while alterations in butyrate-producing bacteria (e.g., Roseburia spp., Clostridium spp., Eubacterium rectale, Faecalibacterium prausnitzii – all Gram-positive) could contribute to diabetes mellitus [165]. Butyrate is thought to cause beneficial effects through enhancement of mitochondrial activity, activation of intestinal gluconeogenesis, prevention of metabolic endotoxemia [166].

In patients with T1DM or other autoimmune conditions a reduced diversity of microbiota has been reported [167]. Dysbiosis is also associated with T2DM [168]. Some bacterial groups seem related to plasma glucose concentrations, including the ratio of Bacteroidetes to Firmicutes and the ratio of Bacteroides-Prevotella to Clostridium coccoides and Eubacterium rectale. It is supposed that a microbiome enriched in the Gram-negative component (e.g., Proteobacteria) may release more LPS, thereby stimulating Toll-like receptors that induce a proinflammatory status [169]. Most of these studies have been performed with stool samples and are not representative of the small intestine that is preferentially linked to pancreas. Taken together, the results indicate that there is no well delineated bacterial taxon serving as a general marker for diabetes mellitus or one that can even be suspected of a causal influence in diabetogenesis. Bacteriome alterations could indeed be an effect of increased glycemia, its excursions, dietary changes following diagnosis, diabetes medications.

## Other infections possibly linked with diabetes

### Hepatitis C virus

In the United States, an estimated 9.4% of the population has diabetes mellitus and 1.4% carries hepatitis C virus (HCV) [170]. T2DM is nearly four times more likely to develop in HCV-positive than in HCV-negative individuals [171]. Thus, anti-HCV treatments have the potential to impact a remarkable proportion of the population not only regarding liver disease but also diabetes mellitus [172]. In fact, glycemic control may improve in people with diabetes who are treated with antivirals due to the HCV carrier status. Not only $HbA_{1c}$ levels improve, but insulin requirement is also reduced. Future studies will determine the duration of metabolic improvement in diabetes mellitus patients treated with antivirals and the effect of this treatment on complications [173]. In vitro, HCV may infect pancreatic islet cells. Infected islets have altered cytokine expression that may well contribute to insulin deficiency [174].

### Prion-like protein aggregates in diabetes

Prions are infectious agents devoid of nucleic acids that cause progressive neurodegenerative diseases with long incubation times (usually years). Prion disease can be initiated by a spontaneous event, transmitted through genetic inheritance, through body fluids and/or excreta, contact with the contaminated environment or food, medical intervention [175]. Prion diseases are

characterized by the accumulation of amyloid in tissues and are classified as protein misfolding disorders (PMDs).

Cats are one of the few species that develop a form of diabetes mellitus analogous to T2DM. The characteristic finding in cats with T2DM is deposition within islets of amyloid derived from the beta cell hormone amylin (islet amyloid polypeptide, IAPP). Increased IAPP concentration has been documented in islet cells and plasma of diabetic cats, supporting a pathogenic role for the polypeptide [176].

As in cats, the accumulation in islets of IAPP aggregates is a frequent finding in people with diabetes. IAPP aggregates promote the misfolding of endogenous IAPP in cultured islets, and inoculation of IAPP aggregates into transgenic mice expressing human IAPP accelerates amyloid deposition in islets. The phenomenon is accompanied by hyperglycemia and reduction of beta cell mass. Thus – if indeed a PMD – T2DM could be transmissible through mechanisms proper to the spread of prions in neurologic disease [177].

Beta cell dysfunction and abnormal blood glucose concentrations have been reported in rodents infected with scrapie prions [178]. The cellular prion protein (PrPC) is expressed in beta cells and appears to contribute to glucose homeostasis. Pancreatic iron stores are influenced by PrPC expression. Silencing of PrPC resulted in significant depletion of intracellular iron and upregulation of the glucose transporter GLUT2 and insulin. Iron overload, on the other hand, resulted in downregulation of GLUT2 and insulin in a PrPC-dependent manner. Glucose intolerance develops in iron-overloaded PrP+/+ but not in PrP−/− mice, indicating that PrPC-mediated modulation of intracellular iron does influence both insulin secretion and insulin sensitivity of target organs. Thus, the PrPC protein (and possibly its abnormal variants) appear to play a role in glucose homeostasis [179]. Current research is exploring the mechanism underlying the prion-like transmission of IAPP aggregates and its possible role in T2DM [180].

### Vaccines for people with diabetes

As reported above, diabetes mellitus confers enhanced risk of morbidity and mortality from a variety of infectious conditions [181]. Pneumococcal disease (including community-acquired pneumonia and invasive pneumococcal disease) poses a burden all year round. Thus, pneumococcal vaccination of people with diabetes should be started at any time of the year [182,183]. Current evidence indicates that vaccination of adult/elder people with diabetes against seasonal influenza is effective and safe [184]. People with diabetes have higher rates of hepatitis B than the rest of the population. Blood glucose monitoring exposes to additional risk. Individuals with chronic disease, including diabetes mellitus, have an enhanced likelihood of nonresponse to Hepatitis B virus (HBV) vaccine [185]. Diabetic nonresponders should be treated with increased vaccination dose, intradermal administration, alternative routes of administration, coadministration with other vaccines [185]. Currently, the CDC recommends the following vaccinations for people with diabetes (www.immunize.org/catg.d/p4043.pdf): seasonal flu vaccine: every year; pneumococcal vaccines (13-valent and 23-valent); hepatitis B vaccine series, Tdap vaccine (tetanus, diphtheria, and pertussis); Zoster vaccine after 50 years of age. Other vaccines may be administered if needed: hepatitis A, measles, mumps, rubella, varicella, papillomaviruses, hemophilus influenzae type b, meningococci of the ACWY and B types. It should not be underestimated that infectious conditions may hinder glucose homeostasis and require accurate metabolic control.

Recently, interest in the old TB vaccine bacillus calmette-Guerin (BCG) has been revived for possible use in T1DM. Clinical trials are testing the value of BCG in prevention and treatment of adult patients. BCG induces a host response – driven in part by tumour necrosis factor – that aims at eliciting selective death of autoreactive T cells with the concurrent expansion of beneficial Tregs. Preliminary results are promising [186,187]. BCG should also be considered for TB prevention in countries at high incidence of both diabetes mellitus and TB such as India and China [188–190].

## Conclusion

Evidence points to a bidirectional link of diabetes mellitus with infectious agents (viral, bacterial, fungal, parasitic, prion-like). On one hand, genetics and metabolic changes predispose people with diabetes to infectious events of varying severity. Notably, over a life time, the enhanced susceptibility of people with diabetes to infections tends to expose them to a substantial consumption of antimicrobials, facilitating the selection of drug-resistant strains. On the other hand, poorly identified biologic agents may participate in the pathogenic processes that lead to diabetes mellitus. As genetic predisposition cannot be changed, it will be crucial to identify the environmental factors that play an etiologic/triggering role in diabetes mellitus. Thus, clinical microbiology laboratories are encouraged to implement research and monitoring programs for diabetic people.

Should investigations continue to support the assumption that infections play a causative role in diabetes mellitus, then interventions should target the latter factors. However, even if some diabetes mellitus forms will be accepted as transmissible, NCDs will remain with us for a long time shaping the future of global health.

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### Conflicts of interest

There are no conflicts of interest.

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