



Review

Burden and disease pathogenesis of influenza and other respiratory viruses in diabetic patients



Swapna Thomas^{a,b}, Allal Ouhtit^b, Hebah A. Al Khatib^a, Ali H. Eid^c, Shilu Mathew^a,
Gheyath K. Nasrallah^{a,d}, Mohamed M. Emara^c, Muna A. Al Maslamani^e, Hadi M. Yassine^{a,d,*}

^a Biomedical Research Center, Qatar University, Doha 2713, Qatar

^b Department of Biological and Environmental Sciences, College of Arts and Sciences, Qatar University, Doha 2713, Qatar

^c Basic Medical Science Department, College of Medicine-QU Health, Qatar University, Doha 2713, Qatar

^d Department of Biomedical Sciences, College of Health Sciences-QU Health, Qatar University, Doha 2713, Qatar

^e Communicable Diseases Center, Hamad Medical Corporation, Doha, Qatar

ARTICLE INFO

Article history:

Received 13 September 2021

Received in revised form 24 February 2022

Accepted 7 March 2022

Keywords:

Influenza
Diabetes mellitus
Autoimmunity
Mechanisms
Vaccine

ABSTRACT

Over the past two decades, diabetes mellitus (DM) has been receiving increasing attention among autoimmune diseases. The prevalence of type 1 and type 2 diabetes has increased rapidly and has become one of the leading causes of death worldwide. Therefore, a better understanding of the genetic and environmental risk factors that trigger the onset of DM would help develop more efficient therapeutics and preventive measures. The role and mechanism of respiratory viruses in inducing autoimmunity have been frequently reported. On the other hand, the association of DM with respiratory infections might result in severe complications or even death. Since influenza is the most common respiratory infection, DM patients experience disease severity and increased hospitalization during influenza season. Vaccinating diabetic patients against influenza would significantly reduce hospitalization due to disease severity. However, recent studies also report the role of viral vaccines in inducing autoimmunity, specifically diabetes. This review reports causes of diabetes, including genetic and viral factors, with a special focus on respiratory viruses. We further brief the burden of influenza-associated complications and the effectiveness of the influenza vaccine in DM patients.

© 2022 The Author(s). Published by Elsevier Ltd on behalf of King Saud Bin Abdulaziz University for Health Sciences.
CC BY 4.0

Contents

Introduction	413
Causes of diabetes	413
Anti-islets autoantibodies and genetic factors in T1D	413
Genetics of type 2 diabetes	414
Viral infections and diabetes	416
Viruses and T1D	416
Respiratory viruses	416
Viruses and T2D	417
Mechanisms of virus-induced diabetes	417
Bystander activation	417
Epitope spreading	418
Molecular mimicry	418
Vaccines as a cause of diabetes	419

* Corresponding author at: Biomedical Research Center, Qatar University, Doha 2713, Qatar.

E-mail addresses: swapna.thomas@qu.edu.qa (S. Thomas), aouhtit@qu.edu.qa (A. Ouhtit), halkhatib@qu.edu.qa (H.A. Al Khatib), ali.eid@qu.edu.qa (A.H. Eid), shylu.ibt@gmail.com (S. Mathew), gheyath.nasrallah@qu.edu.qa (G.K. Nasrallah), memara@qu.edu.qa (M.M. Emara), Malmaslamani@hamad.qa (M.A. Al Maslamani), hyassine@qu.edu.qa (H.M. Yassine).

Complications of influenza in diabetic patients	419
COVID-19, disease severity in DM patients	420
Conclusion	420
Authors' Contributions	420
Acknowledgment	420
Competing interests	420
Ethical Approvals	420
Availability of data and material	420
Consent to participate	420
Consent for publication	421
References	421

Introduction

Diabetes mellitus (DM) is a global challenge affecting millions of people. In 2019 total death toll of 1.5 million due to diabetes was reported [1]. DM is a metabolic disorder characterized by elevated blood sugar levels, polyuria, loss of body weight, and fatigue. The disease mainly results from the inability of pancreatic β cells to produce insulin, a critical hormone for glucose uptake, glycogenesis, lipogenesis, and protein synthesis [2]. There are two main types of DM, Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM) [3].

T1DM usually appears at a young age (below 14 years) and is known as juvenile diabetes [4]. People with T1DM represent 5–10% of total diabetic patients. Development of T1DM occurs when a cellular-mediated autoimmune response damages pancreatic β cells. Apart from genetic inheritance, this autoimmune process is predominantly associated with agents causing autoimmunity, including viral and bacterial infections, chemical toxins within food, and/or other factors like pollutions that precipitate the disease during childhood, even years before diagnosis. [5]. On the other hand, T2DM represents 90–95% of diabetic patients and is primarily diagnosed in middle-aged and older people. The onset of T2DM is due to genetic factors and factors like overweight/obesity, lifestyle, diet, and lack of exercise [6]. The combinational effect of these factors results in insulin resistance (IR), which eventually leads to the development of T2DM. IR in T2DM mainly occurs in fat, muscle, and liver cells due to genetic defects or abnormalities in insulin receptors that render them unresponsive to insulin [7]. On the other hand, recent studies reports that environmental factors [8,9], obesity [10] or an unhealthy diet [11,12], can lead to hypersecretion of insulin that eventually causes gradual loss of pancreatic β cells and leads to a total decrease in insulin secretion [8,13]. In 2009, Wilkin et al. proposed that T1D and T2DM are the same disorder of insulin resistance against different genetic backgrounds [14]. However, generally, it is hypothesized that T1DM results from islet autoimmunity [15–17], whereas T2DM is the impaired insulin tolerance to different cells/organs [18].

The prevalence of diabetes has been steadily increasing over the past three decades. In a study conducted in 2010, the number of DM patients was projected to reach 438 million in 2025 [19]. However, in 2019, the total number reached 463 million for T2DM alone and another 1.1 million for T1DM. The International Diabetic Federation (IDF) estimates that the prevalence of diabetes by 2030 will be 578 million [20] (Fig. 1). Notably, 1.6 million deaths were directly associated with diabetes in 2016 [21].

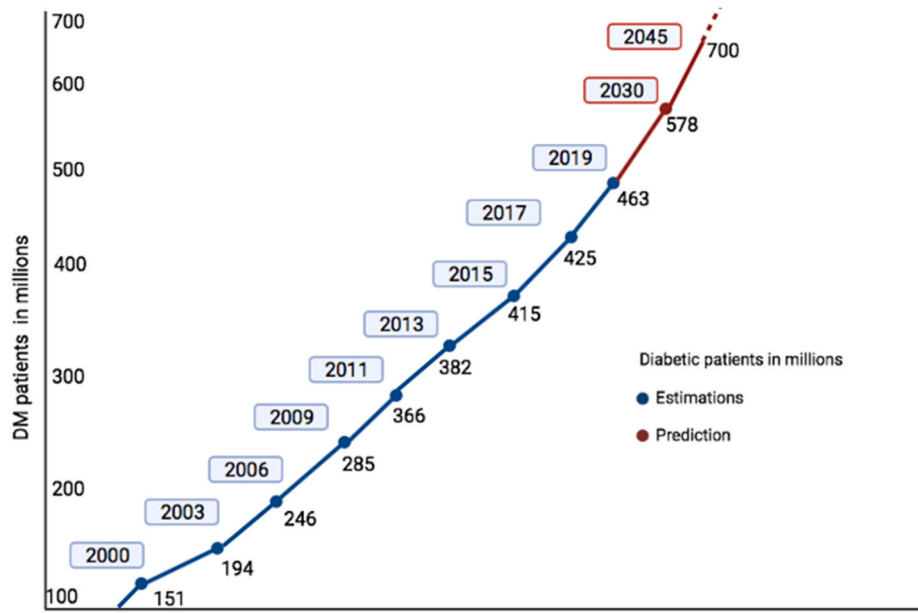
Causes of diabetes

Dysfunction of the immune system can be manifested at birth or develop later in adulthood [23]. Autoimmune diabetes(T1DM) results from such immune dysfunction that produces autoantibodies against insulin-secreting pancreatic β cells. The etiological factors that trigger autoimmune response include genetic, physiological,

microbial including viral, and environmental factors [24]. During the past decade, several T1DM- and T2DM-associated genetic markers have been identified. These included specific genetic mutations that affect gene expression and other cellular activities contributing to the disease pathogenesis and prognosis [25,26]. In T1DM, many of these mutations exist within the human leukocyte antigen (HLA) family genes [27]. On the other hand, more than 222 genes are associated with a higher risk of developing T2DM [6]. Most of these genes affect insulin secretion, adipogenesis and leads to insulin resistance [6,26]. Although the genetic background contributes to T1DM development, they are responsible only for 40% of cases. This means that non-genetic factors are the significant contributors to the development of T1DM [28]. Viral infection appear to be one of the most common risks associated with the onset, development, and progression of different autoimmune diseases, including T1DM. Indeed, the ability of several viruses to directly or indirectly destroy pancreatic β -cells has been reported by several studies [29,30]. Interestingly, viral infections contribute to the development of T1DM and augment insulin resistance and progression of T2DM [31,32].

Anti-islets autoantibodies and genetic factors in T1D

The hallmark of T1DM is the presence and function of autoantibodies against pancreatic islets through T-cell mediated inflammatory response [33]. Macrophages and dendritic cells identify the autoantigens released from pancreatic β cells during cellular turnover or damage. As a result, the interleukin - 12(IL-12) produced by macrophages and dendritic cells activates CD4 + T cells to produce interleukin-2 (IL-2) which further activates β cell antigen-specific CD8 + T cells. Activated CD4 + T cells and β cell antigen-specific CD8 + T cells are cytotoxic and act together to destroy pancreatic β cells [34]. These autoantibodies that are specific to insulin, glutamic acid decarboxylase (GAD) protein tyrosine phosphatase (IA2 and IA2 β), and zinc transporter protein (ZnT8A) could be directed to islet β cells [35]. Studies infer that such antibodies could be detected in a patient's sera months or even years before the onset of the disease [36,37]. The main genetic factor that is associated with the development of autoantibodies is the HLA class II region of the major histocompatibility complex (MHC). According to Miller (1995), the genes involved in the development of autoimmunity are the ones that encode the production of MHC, the protein involved in the antigen processing and T-cell receptor binding. Human MHCs are also called Human Leukocyte Antigen (HLA) and are classified into three subtypes (DP, DQ, and DR) and each one to four isotypes [38]. Indeed, the HLA complex complies with around 50 – 60% of the overall genetic risk factors linked to the development of autoimmunity [38,39]. Various studies have reported genetic interaction that has stimulated the risk of autoimmunity [40,41]. For example, the combination of HLA genetic marker serotypes- DR3-DQ2 or DR4-DQ8 haplotypes or both, is a much higher risk factor than a single gene is expressed [42,43]. Studies on Genetic Risk Score (GRS) from the T1DM associated single nucleotide polymorphisms



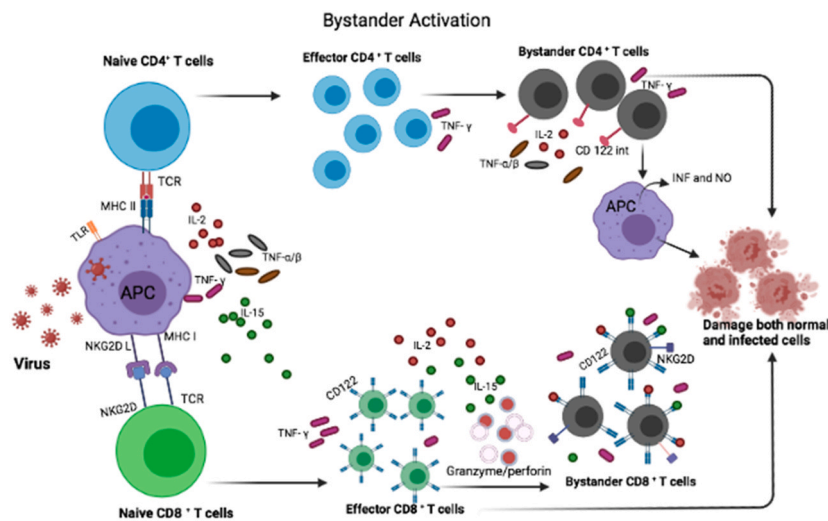
Created in BioRender.com bio

Fig. 1. : Global prevalence of DM from 2000 to 2019 as per the data from the International Diabetic Federation (IDF). According to IDF the number of DM patients is expected to exceed 700 million by 2045 [22].

independently predict the progression of T1DM and the stages of autoantibody progression [44]. This study investigated the ability of T1D GRS to predict islet autoimmunity progression. Out of 291 participants, who tested positive for at least one autoantibody at the beginning of this study, 157 tested positive for multiple autoantibodies later, and 55 turned diabetic. GRS model with a combination of clinical variables including DTP-1 risk score, age, and a number of autoantibodies showed better accuracy in predicting T1DM than to HLA DR3/DR4 [44]. Apart from genetic causes, viral infections are the most reported cause of T1DM. Recent studies find a significant relationship between viral infections and the onset of autoimmune diabetes [31].

Genetics of type 2 diabetes

In defining T2DM, there is no definite pathophysiologic mechanism, indicating that there are multiple mechanisms involved in the development and progression [45,46]. Reports say that T2DM develops due to the combination of hereditary components and factors, including obesity [47], aging [48], reduced physical activity [49], and viral infections [50–52]. More than 30 genes have been identified to be associated with T2DM. The risk gene that is mainly studied and identified to be associated with the development of T2DM is TCF7L2 (Transcription factor 7 like 2) [53]. It is previously reported that this gene encodes for the transcription factor associated with blood glucose homeostasis and is regulated by the



Created in BioRender.com bio

Fig. 2. : Bystander activation: Viruses trigger activation of auto-reactive CD4⁺ or CD8⁺ T cells. Bystander activation of T cells occurs as a result of interferon and cytokine secretion. The activated unspecific bystander T cells further destroy both normal and infected cells resulting in autoimmunity.

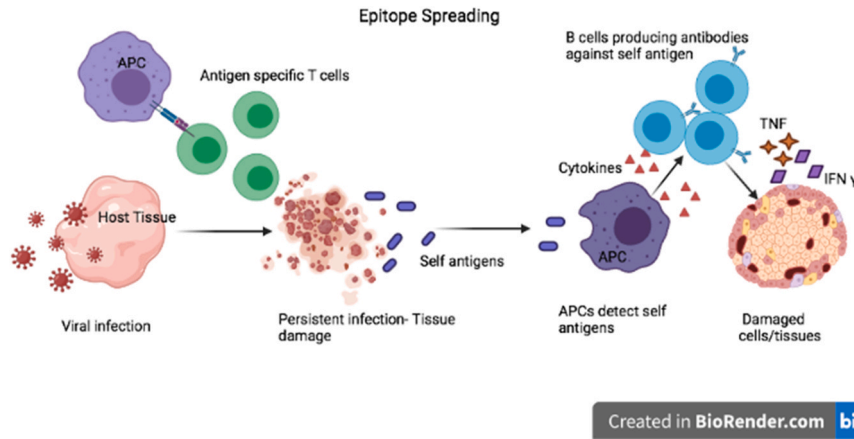


Fig. 3. Epitope Spreading: When viral infection persists, dying cells release self-antigens that are presented by APCs to activate B cells. Activated B cells produce antibodies against self-antigens that can damage the host cell/tissue.

expression of the proglucagon gene via Wnt signaling in the endocrine cells [54]. Lyssenko et al., 2007 reported that TCF7L2 locus that carries risk genotypes in combination with obesity impacts the progression of pancreatic islet autoimmunity [55]. Another gene reported to be associated with the onset of T2DM is the HLA gene. Shreds of evidence indicate the intensification of immune response and the destruction of insulin-secreting cells involves HLA genes [56]. Using genome-wide association studies (GWAS), more than 50 susceptibility loci were found to be expected in T1DM and around 100 susceptibility loci in T2DM [57–59]. However, more variants are being identified with the advantage of new sequencing technologies [60,61]. A genome-wide screening study for T2DM associated genes in 2010 revealed another gene associated with sustained elevations in plasma glucose levels. The gene encodes a ubiquitously expressed member of the calpain-like cysteine protease family (CAPN10), located in the NIDDM1 region but with largely unknown functions in glucose metabolism [62]. Meta-analysis showed a consistent association of the CAPN10 with T2DM. However, the large GWAS did not confirm the exact role of the CAPN10 gene in T2DM [63,64]. Several candidate genes were identified in monogenic forms and seemed to be involved as standard genetic forms in the onset and progression of T2DM [65,66]. However, the genetic reasons for T2DM also include epigenetic changes. The three known mechanisms of epigenetics are chromosomal DNA methylation, histone modifications (acetylation, methylation, phosphorylation, ubiquitination, and ADP (adenosine diphosphate) ribosylation), and non-coding RNA regulations [67–69]. Epigenetic studies conducted in T2DM patients in pancreatic islets and skeletal muscles initially analyzed only DNA

methylation of candidate genes. Studies report the alteration via gene methylation is associated with disease development in T2DM patients [70,71]. Many candidate genes are studied to have increased DNA methylation [71], decreased expression of genes such as INS (encodes insulin), PDX1-encodes insulin promoter factor-1, PPARC-CIA (encodes Peroxisome proliferator-activated receptor-gamma coactivator)(PGC1 α), and GLP1R, encodes (Glucagon-like-peptide (GLP-1) receptor), in pancreatic islet cells, in a comparative study between T2DM patients and non-diabetic controls [70,72]. Post-translational histone modifications are reported to alter chromatin structure and are associated with the development of T2DM [73]. Elevated histone modification, more specifically acetylation and methylation, are observed in T2D patients. A study reported acetylation of CoX-2 and tumor necrosis factor α (TNF α) in the peripheral blood mononuclear cells. Another study reported increased histone H3K9me2 near the promotor gene of IL-1A and PTEN coding regions [74,75]. A third study reported lysine three histones four monomethylation that is set7-dependent in 68 T2DM patients [76]. Further epigenetic changes during RNA slicing are reported in T2DM patients. Long non-coding RNA (lnc RNA), such as β linc1 (β cell long intergenic RNA), and ANRIL (antisense non-coding RNA) have been associated with loss of pancreatic β cells and their mass [77,78]. Another lncRNA, H19 (impaired maternally expressed transcript) was also associated with increased birth weight and T2DM in a study conducted by Dandolo et al. and team [79].

In addition to the genetic factors, environmental factors including unhealthy diet, pollution, lack of physical activity, and exposure to viral infections, trigger DM onset and progression [80,81].

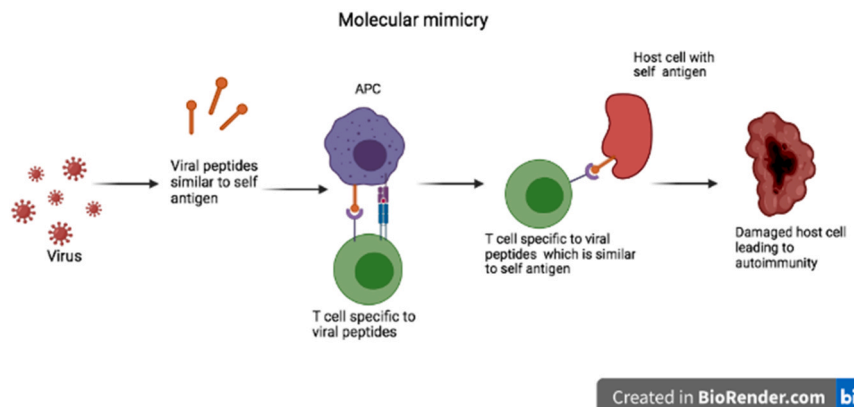


Fig. 4. Molecular mimicry: The viral peptides that are similar to self-antigens are recognized by APCs and activate T cells that are specific to viral peptides. Activated T cells destroy host cells that are similar to viral peptides resulting in autoimmunity.

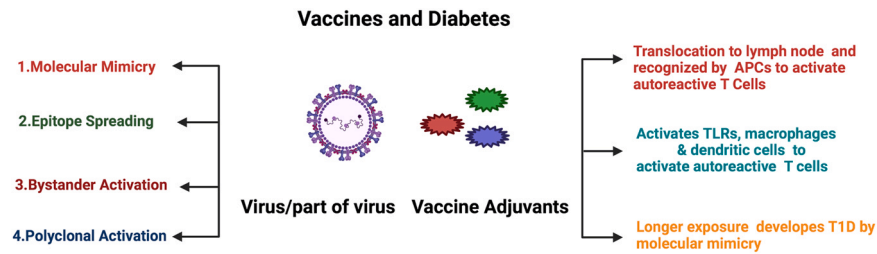


Fig. 5. Vaccine-induced autoimmunity The whole virus or parts of virus vaccines can induce autoimmunity via different mechanisms (Molecular mimicry, Epitope Spreading, Bystander activation, and Polyclonal activation). Adjuvants, which are viral vaccine enhancers, are proposed to induce autoimmunity in 3 different ways: Adjuvants can translocate to lymph nodes and be recognized by APCs to induce autoreactive T cells; Prolonged exposure to adjuvants can induce T1DM by molecular mimicry; and/or activate auto-reactive T lymphocytes by activating TLRs, macrophages, and dendritic cells and by inducing cytokine release.

Viral infections, including respiratory infections, are reported to be associated with the clinical onset of DM [28,82].

Viral infections and diabetes

There are more than 80 diseases reported as a result of autoimmune attacks that damage our tissues or organs [83–85]. Viral infections are among the most studied environmental factors that trigger many autoimmune diseases [86,87]. The role of viral infections in the induction, development, and progression of autoimmune diseases such as diabetes, multiple sclerosis, autoimmune chronic active hepatitis, systemic lupus erythematosus, and juvenile rheumatoid arthritis has been extensively studied. [88,89]. About 14 viruses have been identified to induce T1DM in human and animal models studies [28]. These include seasonal respiratory viruses, including influenza viruses [90,91]. However, there are only a few reports on the association between viral infections and T2DM [92,93].

Viruses and T1D

Several studies have linked autoimmunity to viral infections and its relation to T1D development, but the mechanisms are still not very well described [94,95]. The viral agents that are reported to be associated with T1DM include enteroviruses such as Coxsackieviruses B (CVB) [96], cytomegalovirus [97], mumps virus [98], and rotavirus [99,100]. Many studies proposed the association between the onset of T1DM and enteroviruses. The first report on enterovirus (coxsackievirus) infection to induce T1DM was in 1969 by Gamble et al. The study conducted in patients with recent onset of T1DM found a high titer of neutralizing antibodies against coxsackievirus [101]. Antibodies against enteroviruses were found in pregnant women and their children, who developed T1DM later [102,103]. Another study reported the presence of CVB RNA in the blood from patients at the onset of T1DM, and CVB4 was the most commonly detected enteroviral strain [104,105]. Further, enterovirus infections were more frequent in siblings who developed T1DM compared to siblings who did not develop the disease [106]. These pieces of evidence powerfully illustrate the role of enterovirus infection in triggering the onset of T1DM. Other than enteroviruses that are the most common virus to induce T1DM, recent studies report few respiratory viruses as potential causal agents for T1DM in humans.

Respiratory viruses

Respiratory viruses are known to induce diabetes, especially T1DM, in children. [31,107–109]. A study conducted in Germany during September 2013 and October 2014 among 40 children aged between one and 16 years showed that the newly diagnosed T1DM was reported in the fall-winter season, which is the season of respiratory virus infections. All children who developed T1DM were infected with either respiratory virus (H3N2, IVB, and PIV4) or enterovirus (ECHO7 and CAV7) [110]. Another study conducted among

148 children who had a first-degree relative with T1DM was observed for three years. The results revealed that children who suffered from respiratory infections during their first six months of life showed more than twice the odds of developing autoantibodies against islet β cells than non-infected controls [111], suggesting that along with genetic background, viral infections are an important risk factor to develop T1DM. The most common respiratory viruses reported to be associated with the onset of T1DM are Respiratory Syncytial Virus (RSV) and Influenza A (IA) virus.

Respiratory syncytial virus. Respiratory syncytial virus (RSV) is primarily a significant cause of respiratory illness in children younger than two years [112–114]; still, adults are also frequently infected [115]. A study in Turkey (2013–2014) reported a significance in the increased incidence of T1DM in children after the seasonal viral infections during fall/winter [110]. Their findings include the association of RSV with the development of T1DM [110]. In another study conducted in Norway in 2011, among 885 children having HLA high-risk genotype DR4-DQ8/DR3-DQ2 for four years, 42 children developed autoimmunity, of whom 15 developed T1D. Out of these 42 children, 17 children had pneumonia, bronchitis, or RSV infection [32]. This suggests a strong link between lower respiratory tract infections and increased risk of developing autoantibodies against islet β cells. Another study found that the single nucleotide polymorphisms (SNP) associated with Toll-like Receptor (TLR) and Vitamin D receptors (VDR), which are called loss-of-function variants, and the patients with these variants are more susceptible to RSV infection [116]. These SNPs are located on interferon induced with helicase C domain 1 (IFIH1), and several studies reported that IFIH1 is associated with T1DM development [27,117].

Influenza virus. Around 5–15% of the total population is infected with influenza worldwide every year [118]. The annual influenza epidemics are up to 1 billion every year, with 3–5 million severe cases and up to 200,000 deaths worldwide [119]. Clinical evidences show an association between influenza infection and the onset of T1DM. A study in 1970 reported the large number of new T1DM onsets followed by the influenza epidemic [120]. They reported very high incidents of ketoacidosis followed by the epidemic. In 2011 Nenna et al. also reported that the H1N1 pandemic of 2009 is a significant cause in the pathogenesis of T1DM [121]. In their study conducted among children living in Rome, they observed an increase in the new diagnosis of T1DM after H1N1 pandemic infection (October 2009– January 2010) compared to previous years (2004–2005). Also, there are other clinical evidences to link the influenza infection to diabetes; followed by H1N1 infection. A woman in China developed diabetic ketoacidosis after H1N1 infection, which was reported in 2012 [122]. A study conducted in Norway in pandemic influenza-infected cases reports a 20% higher risk of developing T1DM [123]. The first study conducted to analyze the long-term risk of T1DM among individuals diagnosed positive

Table 1

The list of studies reporting a link between respiratory viral infections and DM.

Year	Country	Model	Virus	Type of DM	Reference
Respiratory viruses induced T1DM					
2013–2014	Turkey	Human Clinical Study	H3N2, IVB, PIV4,RSV, ECHO7 and CAV7	T1DM	[110]
2013	Germany	Clinical Study in children	Rhinovirus	T1DM	[111]
2011	Norway	Clinical Study in children	RSV	T1DM	[32]
2000	USA	Monocytes/Macrophages	RSV	T1DM	[116]
Influenza induced T1DM					
2011	Rome	Clinical Study in children	H1N1	T1DM	[121]
2008–2014	Norway	Children and young adults	Influenza	T1DM	[124]
2010	Israel	Human Case Study	H1N1	T1DM	[125]
1990	USA	Mice	Influenza A	T1DM	[107]
2013	Italy	Turkey	H1N1and H3N2	T1DM	[127]
2013	Italy	Human Pancreatic cells	H1N1 and H3N2	T1DM	[127]
Virus induced T2DM					
2019	Korea	Human-adults	CMV	T2DM	[130]
2013	California	Human- Case study	RSV	T2DM	[92]
2012	Netherlands	Human-adults	CMV	T2DM	[131]

for influenza during June 2009, were observed until December 2014 by Ruiz et al. and team. From his register-based study in Norway, in a cohort of patients below 30 years, he reported that the risk factor of developing T1DM after the influenza pandemic (H1N1) is approximately 20% higher [124]. A case study in a 37-year-old man in 2010 reported the occurrence of acute pancreatitis immediately after severe infection with H1N1 [125]. When this epidemiological evidence reports the association between influenza and autoimmune T1DM, the experimental evidence, including animal models, sheds insight into this association. The primary replication site of the Influenza virus is the respiratory tract, but there are in vitro study reports on the viral replication in internal organs, including pancreatic islets [126]. Roman et al. reported, in transgenic mice, the virus induces insulinitis and diabetes with the expression of hemagglutinin in pancreatic beta cells [107]. The transgenic mice expressing haemagglutinin (RIP-HA) of influenza virus (A/Japan/305/57) on their pancreatic β cells developed hyperglycemia. This study reports an association between hyperglycemia, which was associated to islet cell lymphatic infiltration and humoral response against β cell antigens [107]. Also, in turkeys, the virus is reported to cause tissue damage in the pancreas to result in diabetes [127,128]. The in vitro experiments using human (H1N1 and H3N2) and avian (H7N1 and H7N3) strains show that all these strains can replicate in human pancreatic cells. In vitro studies using the common seasonal human influenza strains H1N1 and H3N2 reports influenza virus growth in human pancreatic cell lines [125,129]. Viral replication in hCM and HPDE6 cell lines was continuously increased up to 72 h post-infection with H1N1 and H3N2 viruses [129]. This study observed the infectivity of both human(H1N1 and H3N2) and avian (H7N1 and H7N3) in human pancreatic cell lines. The results of hybridization assays detected virus nucleoprotein in β cells [129]. Table 1.

Viruses and T2D

Infection with certain viruses has a proposed risk of insulin resistance which is the hallmark of T2DM. This includes cytomegalovirus [132], and RSV [92]. A population-based study in Korea in 576 patients infected with CMV and not diagnosed with T2DM was subjected to this investigation. After a follow-up of 5 years, the authors reported the development of T2DM. The case group showed a significantly higher frequency of T2DM onset when compared to the control group (5.6% vs. 2.2%) [130]. Mike et al. at Stanford University reported a sudden development of T2DM after a severe cold caused by RSV infection. Unlike the usual T2DM, which is a slow resistance to insulin, Mike showed a sudden development of T2DM after RSV

infection [92]. The study discusses that some people may have genes involved in developing T2DM from a viral infection. In another study conducted in Netherlands, among adults ages 85 and above and infected with cytomegalovirus, results show that infected people were twice likely to develop diabetes when compared to uninfected. However, this study reports only an association, not the cause-effect link between viral infection and T2DM [131]. Limited reports are available on virus-triggered T2DM, however many studies suggests a link between viral infections and trigger of T1DM.

The complex mechanism by which the genetic factors and virus interaction leads to the onset of autoimmune T1DM is not entirely elucidated. The studies to date report that the modulated autoimmunity during viral infections depends not only on the virus's inherent properties but also on the innate host factors. An in-depth investigation on this area is essential to reveal the complete mechanism of viral infections and T1DM.

Mechanisms of virus-induced diabetes

Autoimmune destruction of pancreatic cells is the major characteristic of autoimmune diabetes. The cross-reactivity of lymphocytes that may damage host cells leading to autoimmunity is extensively studied. Different mechanisms are proposed to account for autoimmune diabetes developed after viral infections. When auto-reactive B and T cells are activated in an antigen-independent manner, autoimmunity against self-antigens is developed. The three mechanisms accounting for autoimmunity are bystander activation, epitope spreading, and molecular mimicry.

Bystander activation

The bystander activation is the mechanism in which viral infections trigger the unspecific activation of CD4+ and CD8+ T cells or B cells, independent of T and B cell receptor specificity. The stimulation of T lymphocytes is the characteristic of bystander activation [133]. The virus-infected cell activates neighboring uninfected cells by releasing cytokines and nitric oxide or by intracellular communications with the help of co-receptors and through gap junctions resulting in activation of auto-reactive T cells [134]. These auto-reactive T-cells stimulate the expression of T-cell receptors (TCR) to identify the viral as well as self-antigens, both T-cells (antiviral and autoreactive) can become activated as a consequence of viral antigens presented by the antigen-presenting cells (APCs). The activated auto-reactive T cells destroy the neighboring cells in the infected organ or the cells bearing these syngeneic MHC antigens, contributing to autoimmunity [135,136]. The ability of activated

allospecific cytotoxic T cells to recognize self-antigens (self-MHC) in the absence of viral antigens is reported by Duke et al. in a set of experiments in mice [136]. The heterologous immune response in bystander activation mainly occurs in two ways: the activation of cross-reactive memory T cells and cytokine release [137,138]. The mechanism of bystander activation was first reported by Sprent et al. [137]. They reported the involvement of interferon type 1 (IFNs) in the proliferation of non-specific T cells upon viral infection. Based on their observation, CD8 + T cells are directly activated by IFNs to drive the expression of T cells during lymphocytic choriomeningitis virus infection (LCV) [137,139]. IFNs driving the bystander activation of T cells were also reported in case of persistent HIV infection [140]. It is also reported in coxsackievirus B(CVB) infection of human pancreatic islets that the persistent infection induces the synthesis of IFN- α , a result of bystander activation leading to the destruction of β cells [141]. However, the complete mechanism of CD8 + T cell activation by IFNs is not known. On the other hand, in vitro experiments did not show significant activation of T cells when treated with IFNs alone, but the functional activation was observed after a secondary signal by other cytokines, including IL-18 [142]. In murine models, the interaction between IL-18 and other proinflammatory cytokines, including IL-2, IL-12, IL-15, and IL-21 resulting in IFN- γ production that is antigen non-specific. Hence it is clear that IL-18, along with other cytokines, plays a significant role in bystander activation of T cells [143,144]. Another factor that is reported to have a significant role in the production of non-specific IFN- γ is Toll-like receptors (TLRs) expressed on the innate immune cells and functions as part of the adaptive immune system [145]. Recent studies report that ligands for TLR2 and TLR7 can directly stimulate memory CD8 + T cells in murine to release IFN- γ and also the combination of TCR triggering and TLR2 and TLR7 stimulation drive cells to produce IFN- γ , TNF - α and IL-2 [146]. TLR mediated bystander activation is observed in different pathogen infections while studying the reaction of TLR-2/3/7 with different ligands derived from pathogens [147,148]. Another study described the role of Natural Killer (NK) cells in the persistence of CVB 4 infection in pancreatic β cells [149]. They found that the persistent infection of pancreatic β cells by CVB4 virus can result in impaired cytolytic activity of NK cells activated by IL-2 in T1D patients. The defective viral clearance by NK cells may have a role in the viral pathogenesis of T1D [149]. It was earlier reported that NK cells can reduce inflammatory process by releasing IL-10 in response to viral infections [150]. Dotta et al. in 2013 demonstrated non-destructive insulinitis and loss of β cell function in CVB4- infected islets was observed when the presence of NK cells was abundant [151]. This indicates the role of NK cells in autoimmune destruction of pancreatic islets.

In influenza virus infection, little is known about the bystander activation of memory CD8 + T cells specifically to induce T1DM. Study reports show that the bystander memory CD8 + T cells down to lung airways during influenza A virus (IAV) infection are not specific to IAV but processes solid cytolytic activity. However, it is not clearly understood whether these bystander T cells have any role during the primary infection or in the inflammatory response at a later stage [152,153]. They reported that the protection during secondary infection by CD8 + T cells is due to antigen-independent cytolytic protein activity. Nevertheless, the ability of these cells to destroy the target cells is antigen-dependent [153]. Results from a single B cell transcriptomics and longitudinal clone tracking study from influenza vaccinated 18-year-old male suggests that bystander activation of memory B cells that are non-specific to the vaccine should be shared in influenza vaccinated individuals [154]. However, their findings indicate that this bystander activation is confined to a small number of clones. Further investigation is needed to understand the mechanism of bystander activation to damage pancreatic β cells.

Epitope spreading

In the second mechanism, the epitope spreading model, viruses could alter the immune system to attack host cells, including pancreatic β cells, due to diversions in the epitope specificity [155]. In a persistent viral infection, self-antigens released by dying cells are presented by APCs to CD4 + and CD8 + T cells. These T cells further activate Th1 and B cells to produce antibodies against self-antigens leading to autoimmunity and further damage to tissue/organs [156]. This immune system modulation can occur by different means: (a) by autoantibodies against self-antigen produced by B cells that are activated by the presentation of self-antigens by APCs, (b) recruitment of immunocytes to host tissues by tumor necrosis factor (TNF) and interferon-gamma (INF- γ), (c) breakdown of immune tolerance by activated immune cells, and (d) by disrupting Th1/Th2 immune balance [157–160]. Experiments in transgenic mice expressing glycoprotein or nucleoprotein of lymphocytic choriomeningitis virus (LCMV) showed the development of T1DM. They observed that IFN- γ deficient transgenic mice did not develop T1DM as the β cell injury was limited. Increased cytokine secretion, specifically IFN- γ along with perforin, could enhance MHC expression and presentation of self-antigens destroying host cell/tissues where these self-antigens are present [156]. Several human clinical studies observed epitope spreading as the mechanism of humoral responses that are specific to β cells. These responses are recorded in children of diabetic patients from birth till disease onset [161–163]. Viral markers resulting from persistent infection with coxsackievirus were seen in the islet β cells of patients with T1DM several years after disease diagnosis [164,165]. Evidence of epitope spreading was also reported in another study where enteroviral infection resulted in overexpression of MHC class 1 protein in islet cells of diabetic patients both in infected and non-infected cells. However, the viral replication was low [166], suggests the epitope spreading mechanism in developing an autoimmune response. This overexpression is resulted from the type 1 interferon release locally and activated tyrosine kinase 2 (TYK2) [167]. Such long-time expression leads to the presentation of β cell epitopes by APCs to immune cells leading to their destruction.

Molecular mimicry

A third mechanism is called molecular mimicry, in which viral antigens that are similar to self-antigens are presented by APCs to activate autoreactive T-cells, which binds to both self and non-self-antigens leading to the development of autoimmunity [28]. The MHC class II molecules on APC present these peptides of autoantigens to CD4 + T cells. [168]. The viral mimicry peptides efficiently stimulate T and B cells. These antiviral T and B cells, after the viral clearance, further attack and damage β cells depending on viral antigen expression [169]. Molecular mimicry between host cell protein, including pancreatic β cells and viral peptides, is explained as a cause of T1DM by many viruses, including coxsackievirus [170], measles virus, herpesvirus [171], and cytomegalovirus [172]. Studies report a significant cross-reactivity between human antigen GAD65 and coxsackie B virus protein P2-C [173]. Most of the monoclonal antibodies produced against the measles virus and herpes viruses reacted with cellular proteins (self-proteins) from uninfected cells also, while only a few were viral-specific [171]. Christeen et al. in 2004., in mice experiments, reported evidence for autoimmunity. Mice that are expressing viral protein as self-antigens in the β cells developed autoimmunity when infected with viruses [174]. However, T1DM was observed only after enhancing T cell receptor (TCR) signal transduction [175]. This indicates that there may be some tolerance to autoantigens mimicked as viral antigens until some stimulation occurs, precipitating autoimmune T1DM. Another study reports the evidence for molecular mimicry in the development of

autoimmune T1DM, the RIP-LCMV mice that express a protein of LCMV virus in their pancreatic β cells developed T1DM when they were infected with the virus. These mice also developed an enhanced autoimmune process after being infected with the Pichinde virus (PV) with structurally similar epitopes to LCMV [174,176]. Clinical onset of T1DM has been reported to be diagnosed, followed by CMV infection [177]. The study reports a significant correlation between the CMV genome and autoantibodies islet β cells confirming molecular mimicry as the mechanism of autoimmune T1DM in patients who had a persistent infection.

The experimental evidence suggests that different viruses exhibit different mechanisms to induce autoimmune diabetes, but the complete understanding of the mechanism by which viruses mediate immune responses against pancreatic islet cells is lacking. Further studies may shed more light on the pathway by which lymphocytes develop cross-reactivity towards self-antigens.

Vaccines as a cause of diabetes

Vaccines, like other drugs, result in the generation of specific adverse effects. The link between vaccines and autoimmunity has been explained as bidirectional: 1. immunization protects from infectious diseases and, in turn, prevents the development of autoimmune diseases; 2. from the light of clinical reports and in vitro studies, vaccine-induced autoimmunity has been reported in humans. Many studies investigated the association between autoimmunity and vaccines in humans, but there are only a few reporting a positive connection between them. Singh et al. reported in 2000 that certain vaccines trigger the development of autoimmunity by the exact mechanism which prevents infection [178]. Few vaccines which are reported to trigger the induce of autoimmunity are Measles, Mumps, and Rubella (MMR) [179], Yellow fever [180], Rotavirus, and influenza vaccines [181]. Also, specific vaccine adjuvants are reported to trigger autoimmunity; the most studied are aluminum hydroxide and phosphate, which are the widely used adjuvants [182], and are termed as autoimmune syndrome induced by adjuvants (ASIA) [183]. In the case of diabetes, there are very few reports suggesting vaccination as a cause of diabetes. Classen JB et al. reported the link between Type 1 diabetes and vaccination, including smallpox, Haemophilus influenza type b (Hib), and tuberculosis vaccines [184,185]. He proposed an increased risk of developing T1DM when the vaccine is provided after two months of birth, but when the vaccinated within two months after birth, that does not induce T1DM [186,187]. Later from the light of his experiments in non-obese diabetic prone (NOD) mice immunized with Haemophilus influenza B vaccine, he reported that the relative risk of developing T1DM is 1.26. Also, immunized mice with pediatric vaccines demonstrated an increased incidence of T1DM development [186]. Palmieri et al. reported that individuals who are more susceptible to developing autoimmunity due to family history and other reasons are more prone to vaccine-induced autoimmunity [188]. Genetically prone individuals to T1DM, such as people with HLA DRB1 upon exposure to vaccine adjuvants that are homologous to human peptides, may develop autoimmunity by molecular mimicry model [189]. Influenza vaccination may cause autoimmunity via molecular mimicry mechanism [190], but a clear association and the complete mechanism is still unproved. While these studies point towards the risk of vaccines to cause diabetes, on the other hand, diabetic patients are more susceptible to respiratory infections and may develop severe infections, which leads to hospitalization and even death.

Complications of influenza in diabetic patients

Respiratory infections and diabetes are two significant causes of illness worldwide, and hence make a dangerous combination and

has got attention for more than a decade. Many clinical studies reported that respiratory infections are the most common cause of hospitalization in diabetic patients [191–193]. The typical respiratory infections seen in diabetic patients are caused by streptococcus pneumonia and influenza virus [194,195]. It is argued that during the influenza epidemic, hospitalization is six times higher for diabetic patients when compared to non-diabetic patients [193]. A systematic analysis of 93,000 H1N1 cases in diabetic patients from the 2009 outbreak reports a prevalence of 14.6% severe outcome [196].

It has been previously reported that patients with DM have weakened immune response, impaired chemotaxis, phagocytosis, and antigen presentation in response to the infection. This results in a defective T cell function and proliferation and leads to disease progression [197,198]. The defects in innate immunity in DM patients are associated with complements, cytokines, and hyperglycemia. A study conducted on 86 patients found that 26% of them had a low complement factor (C4) content resulting in neutrophil dysfunction and inadequate response to cytokines [199]. Lowered secretion of interleukin-1 (IL-1) and interleukin-6 (IL-6) by mononuclear cells and monocyte has also been seen in diabetic patients as a result of stimulation by lipopolysaccharide (LPS), which gets activated by phagocytosis [200]. In hyperglycemic conditions, reduced neutrophil degranulation, impaired complement activation, and impaired phagocytosis are reported [201–203], resulting in the severity of respiratory infections, including Influenza infection. Study reports from Canada showed that DM patients have triple the risk of disease severity and hospitalization during 2009 H1N1 infection. The rate of patients admitted to ICU was fourfold higher in the case of DM patients when compared to non-diabetic [93]. A similar report of increased burden and mortality of influenza infection in DM patients was reported from a study conducted in Germany by Wilking et al. in 2010. He reported that DM patients doubled the risk of fatality after infection with the 2009 influenza strain. Shreds of evidence show that influenza infection can also worsen blood glucose levels and increase complications of diabetes [204]. A study using metabolome analysis in mice infected with influenza virus infection revealed a significant reduction in most metabolites associated with the TCA (Tricarboxylic acid) cycle affecting insulin signaling [204].

In addition to being a cause of DM induction, DM patients are more susceptible to influenza infection and disease severity. Hence, routine influenza vaccination is highly recommended for DM patients. Influenza vaccination in diabetic patients, especially during pandemics, has been found effective, considering the hospitalization rates as well as the mortality risk. A study conducted in England over seven years between 2003 and 2010 included 124,503 diabetic patients, influenza vaccine recipients and non-recipients [205]. The results show that vaccination was associated with lower hospitalization and death in vaccine recipients when compared to non-vaccine recipients. Their findings observed significant reduction in cardiovascular events including acute myocardial infarction (19%), stroke (30%), heart failure (22%). They also found 15% reduction for pneumonia in vaccinated individuals. [205]. Another study among vaccine recipients vs. non-vaccine recipients of elderly diabetic patients reported a lower incidence of respiratory failure and pneumonia in vaccine recipients. The vaccine recipients showed a significantly low rate in hospitalization that is 11% less than non-vaccine recipients [206]. An older study (1986) among ten T1DM, 21 T2DM, and ten normal subjects found that anti-influenza vaccination provides proper protection against influenza infection in DM patients. In the study, none of the participants who received the anti-influenza vaccine developed influenza during the following year, and the activated T cells with IL-2 receptor were significantly reduced,

especially in T2DM patients compared to age-matched control subjects [207]. However, these reports are not of high values as the study sample size is small, and the correlation between influenza antibody titer and the clinical protection was not proved. From the light of all the study reports on the effectiveness of influenza vaccination, Seasonal influenza vaccination is suggested to diabetic patients by WHO and IDA as the most appropriate method to reduce hospitalization and death due to Flu- diabetic complications, followed by declaring a global pandemic of Influenza A(H1N1) [208,209].

COVID-19, disease severity in DM patients

The recent COVID-19 pandemic is caused by the beta-coronavirus SARS-CoV-2 and may result in severe acute respiratory illness in up to 15% of the infected population [210]. People with comorbidities, including DM are more likely to develop serious complications [51,211]. Results from a prospective cohort study in COVID-19 infected patients who were previously diagnosed with either T1DM or T2DM show that COVID-19 has significant adverse effects in diabetic patients when compared to non-diabetic [211]. In the study that observed 40 T1DM and 273 T2DM COVID-19 patients, the odds ratio for disease severity was 3.35 and hospitalization was 3.90 for T1DM patients and 3.42 and 3.36 T2DM, respectively [211]. Another recent study reported that out of 52 ICU COVID-19 patients, 32 non-survivors were reported with diabetes(T2DM) [212]. Another study reported that out of 140 patients hospitalized with a severe COVID-19 infection, 12% were DM patients [213]. A study from Saudi reports that the death rate of T2DM-COVID-19 patients was much higher (20.5%) when compared to control (12.3%). The study was conducted on 439 COVID-19 patients, out of which, 68.3% were DM patients [214]. Another study reported presence of significantly increased levels of autoimmune antibodies in ICU patients [215]. Seven out of 126 ICU patients showed positive antinuclear antibodies (ANA) where all tested non-ICU patients (273) were negative [215]. A study conducted in severe COVID-19 DM patients found that reduced levels of triacylglycerols were associated with disease severity in DM patients. These triacylglycerols includes unsaturated, monosaturated and polysaturated long chain fatty acids [216]. The risk factors associated with COVID-19 disease severity or even morbidity in DM patients are cardiovascular disease, dyspnea, lung disease and decreased platelet and neutrophil count [217]. A meta-analysis based on 30 studies having 6452 patients found that DM is associated with composite poor outcome with a risk ratio(RR)=2.38[1.88, 3.03] [218]. The study further reports the association of DM with mortality (RR = 2.12[1.44,3.11]), disease severity (RR=2.45[1.44,3.11]) and acute respiratory distress syndrome (RR = 4.64[1.86,11.58]). There are several other studies suggesting an association between COVID-19 disease severity and DM condition [219–221] however, the mechanism of diseases pathogenesis is not well understood.

Regardless of age, DM patients were given with priority in the COVID-19 vaccination campaign worldwide, and few studies reported on the the efficacy of COVID-19 vaccine in DM patients in terms of disease severity and progression [222–224]. One study indicated a lower levels of neutralizing antibody response in DM patients when compared to healthy individuals, however the levels are only slightly lower, 87.1 ± 11.6 in healthy individuals and 79.7 ± 19.5 in DM patients [222]. Dagan, N., et al. also found slightly lower antibodies in people with chronic conditions including DM [224]. This study reported that the vaccine effectiveness is 91% in people with no conditions, however it was reduced to 86% in people with comorbidities including DM [224]. Overall, COVID-19 vaccines have been proven effective in DM patients that were able to elicit high neutralizing antibodies, very similar to healthy individuals.

Conclusion

The increasing prevalence of diabetes mellitus crossing the predictions makes it one of the most severe health complications of the century. The combination of diabetes with other diseases makes it riskier and sometimes deadly. Hence, it is essential to study the risk factors that induce diabetes to develop better treatment and control measures. The combination of genetic and non-genetic factors (environmental), which are growing as part of urbanization, becomes challenging. Though genetic predisposition is considered the primary cause of diabetes, recent studies strongly suggest that non-genetic factors, including viruses, play an essential role in developing this autoimmune disease. Knowing viruses as a common environmental factor to induce diabetes, primarily type 1 diabetes in children, vaccination against viral infections becomes a necessity. Influenza is one of the frequently seen viral infections; anti-influenza vaccination would effectively reduce the burden and hospitalization among DM patients. Reports from different countries on the significant reduction in hospitalization and death incidents give some light to controlling influenza complications in diabetic patients. T2D is considered a main risk factor for developing severe COVID-19, probably due to too much inflammation, often called a cytokine storm [211]. Controlling the disease severity of respiratory infections in DM patients is a multi-factorial process, with vaccines being an ideal preventative measure. With the advanced technologies in vaccine development, vaccinated DM patients develop optimal B- cell response to many seasonal vaccines including influenza and COVID-19 [225]. While some studies support the viral vaccine as a triggering factor of diabetes, most do not provide sufficient evidence that proves the suggested pathways. More shreds of evidence are needed to understand in depth the post-vaccination autoimmunity development. Hence, for diabetic patients looking at the available reports on the vaccine's effectiveness in reducing health complications and fatality, the influenza vaccine is recommended to DM patients.

Authors' Contributions

HMY conceived and designed the study. ST wrote the first draft of the manuscript. All authors revised the manuscript and approved it before submission for publication.

Acknowledgment

This study was supported by funds from QNRF – National Priority Research Program NPRP11S-1212-170092. Open Access funding provided by the Qatar National Library (QNL).

Competing interests

All authors declare no conflict of interest.

Ethical Approvals

Not applicable.

Availability of data and material

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

References

- [1] WHO, 2021. Diabetes. World Health Organisation. April 13. https://www.who.int/health-topics/diabetes#tab=tab_1.
- [2] Diabetes Overview, 2016. NIGDDK. <https://www.niddk.nih.gov/health-information/diabetes/overview>.
- [3] Lin X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. *Sci Rep* 2020;10(1):14790.
- [4] Patterson CC, et al. Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005–20: a multicentre prospective registration study. *Lancet* 2009;373(9680):2027–33.
- [5] Katsarou A, et al. Type 1 diabetes mellitus. *Nat Rev Dis Prim* 2017;3:17016.
- [6] Ali O. Genetics of type 2 diabetes. *World J Diabetes* 2013;4(4):114–23.
- [7] Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest* 2006;116(7):1793–801.
- [8] Group HS, et al. A school-based intervention for diabetes risk reduction. *N Engl J Med* 2010;363(5):443–53.
- [9] Lee DH, et al. Association between serum concentrations of persistent organic pollutants and insulin resistance among nondiabetic adults: results from the national health and nutrition examination survey 1999–2002. *Diabetes Care* 2007;30(3):622–8.
- [10] Ota T. Obesity-induced inflammation and insulin resistance. *Front Endocrinol* 2014;5.
- [11] Panagiotakos DB, et al. The relationship between dietary habits, blood glucose and insulin levels among people without cardiovascular disease and type 2 diabetes; the ATTICA study. *Rev Diabet Stud* 2005;2(4):208–15.
- [12] Nseir W, Nassar F, Assy N. Soft drinks consumption and nonalcoholic fatty liver disease. *World J Gastroenterol* 2010;16(21):2579–88.
- [13] White MP, et al. Recreational physical activity in natural environments and implications for health: a population based cross-sectional study in England. *Prev Med* 2016;91:383–8.
- [14] Wilkin TJ. The accelerator hypothesis: a review of the evidence for insulin resistance as the basis for type I as well as type II diabetes. *Int J Obes* 2009;33(7):716–26.
- [15] Lamb MM, et al. Height growth velocity, islet autoimmunity and type 1 diabetes development: the diabetes autoimmunity study in the young. *Diabetologia* 2009;52(10):2064–71.
- [16] Vehik K, et al. Childhood growth and age at diagnosis with Type 1 diabetes in Colorado young people. *Diabet Med* 2009;26(10):961–7.
- [17] Johnston C, et al. Islet-cell antibodies as predictors of the later development of type 1 (insulin-dependent) diabetes. A study in identical twins. *Diabetologia* 1989;32(6):382–6.
- [18] Ferrannini E, et al. Progression to diabetes in relatives of type 1 diabetic patients: mechanisms and mode of onset. *Diabetes* 2010;59(3):679–85.
- [19] Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010;87(1):4–14.
- [20] Thomas R, et al. IDF diabetes atlas: a review of studies utilising retinal photography on the global prevalence of diabetes related retinopathy between 2015 and 2018. *Diabetes Res Clin Pract* 2019(157):107840. <https://doi.org/10.1016/j.diabres.2019.107840>. link <https://pubmed.ncbi.nlm.nih.gov/31733978/>.
- [21] Aynalem SB, Zeleke AJ. Prevalence of diabetes mellitus and its risk factors among individuals aged 15 years and above in Mizan-Aman Town, Southwest Ethiopia, 2016: a cross sectional study. *Int J Endocrinol* 2018;9317987. <https://doi.org/10.1155/2018/9317987>. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5944196/pdf/IJE2018-9317987.pdf>.
- [22] IDF DIABETES ATLAS. 6th edition. <https://www.idf.org/component/attachments/attachments.html?id=813&task=download>.
- [23] Guffroy A, et al. Primary immunodeficiency and autoimmunity. *Rev Med Interne* 2017;38(6):383–92.
- [24] Karagianni P, Tzioufas AG. Epigenetic perspectives on systemic autoimmune disease. *J Autoimmun* 2019;104:102315.
- [25] Consortium T, et al. The SIGMA type 2 diabetes consortium. Sequence variants in SLC16A11 are a common risk factor for type 2 diabetes in Mexico. *Nature* 2013;506. <https://doi.org/10.1038/nature12828>
- [26] Saxena R, et al. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science* 2007;316(5829):1331–6.
- [27] Barrett JC, et al. Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. *Nat Genet* 2009;41(6):703–7.
- [28] Jun H-S, Yoon J-W. A new look at viruses in type 1 diabetes. *ILAR J* 2004;45(3):349–74.
- [29] Petzold A, Solimena M, Knoch KP. Mechanisms of beta cell dysfunction associated with viral infection. *Curr Diabetes Rep* 2015;15(10):73.
- [30] Jaïdane H, Hober D. Role of coxsackievirus B4 in the pathogenesis of type 1 diabetes. *Diabetes Metab* 2008;34(6 Pt 1):537–48.
- [31] van der Werf N, et al. Viral infections as potential triggers of type 1 diabetes. *Diabetes/Metab Res Rev* 2007;23(3):169–83.
- [32] Rasmussen T, et al. Self-reported lower respiratory tract infections and development of islet autoimmunity in children with the type 1 diabetes high-risk HLA genotype: the MIDIA study. *Diabetes/Metab Res Rev* 2011;27(8):834–7.
- [33] Devendra D, Liu E, Eisenbarth GS. Type 1 diabetes: recent developments. *Bmj* 2004;328(7442):750–4.
- [34] Yoon JW, Jun HS. Autoimmune destruction of pancreatic beta cells. *Am J Ther* 2005;12(6):580–91.
- [35] Vermeulen I, et al. Contribution of antibodies against IA-2 β and zinc transporter 8 to classification of diabetes diagnosed under 40 years of age. *Diabetes Care* 2011;34(8):1760–5.
- [36] Couper J, Donaghue KC. Phases of diabetes in children and adolescents. *Pedia Diabetes* 2009;10(Suppl 12):13–6.
- [37] Falorni A. Anti-Pancreatic islet cell antibodies in type I diabetes mellitus and in latent autoimmune diabetes in adults (LADA). *Rivista Italiana della Medicina di Laboratorio* 2009;5:191–205.
- [38] Heath WR, et al. Autoimmunity caused by ignorant CD8+ T cells is transient and depends on avidity. *J Immunol* 1995;155(5):2339–49.
- [39] Noble JA, Erlich HA. Genetics of type 1 diabetes. *Cold Spring Harb Perspect Med* 2012;2(1):a007732.
- [40] Mine K, et al. Genetic susceptibility of the host in virus-induced diabetes. *Microorganisms* 2020;8:8.
- [41] Redondo MJ, et al. A type 1 diabetes genetic risk score predicts progression of islet autoimmunity and development of type 1 diabetes in individuals at risk. *Diabetes Care* 2018;41(9):1887–94.
- [42] Alexander EL, et al. Congenic autoimmune murine models of central nervous system disease in connective tissue disorders. *Ann Neurol* 1983;14(2):242–8.
- [43] Pociot F, Lernmark A. Genetic risk factors for type 1 diabetes. *Lancet* 2016;387(10035):2331–9.
- [44] Redondo MJ, et al. A type 1 diabetes genetic risk score predicts progression of islet autoimmunity and development of type 1 diabetes in individuals at risk. *Diabetes Care* 2018;dc180087.
- [45] Galicia-García U, et al. Pathophysiology of type 2 diabetes mellitus. *Int J Mol Sci* 2020;21(17):6275.
- [46] Muoio DM, Newgard CB. Molecular and metabolic mechanisms of insulin resistance and β -cell failure in type 2 diabetes. *Nat Rev Mol Cell Biol* 2008;9(3):193–205.
- [47] Eckel RH, et al. Obesity and type 2 diabetes: what can be unified and what needs to be individualized? *J Clin Endocrinol Metab* 2011;96(6):1654–63.
- [48] Kalyani RR, Golden SH, Cefalu WT. Diabetes and aging: unique considerations and goals of care. *Diabetes Care* 2017;40(4):440.
- [49] Sigal RJ, et al. Physical activity/exercise and type 2 diabetes. *Diabetes Care* 2006;29(6):1433.
- [50] Karim S, et al. An association of virus infection with type 2 diabetes and Alzheimer's disease. *CNS Neurol Disord Drug Targets* 2014;13(3):429–39.
- [51] Turk Wensveen T, et al. Type 2 diabetes and viral infection: cause and effect of disease. *Diabetes Res Clin Pract* 2021;172:108637.
- [52] Toniolo A, et al. The diabetes pandemic and associated infections: suggestions for clinical microbiology. *Rev Med Microbiol* 2019;30:1.
- [53] Grant SF, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. *Nat Genet* 2006;38(3):320–3.
- [54] Yi F, Brubaker PL, Jin T. TCF-4 mediates cell type-specific regulation of proglucagon gene expression by β -catenin and glycogen synthase kinase-3 β . *J Biol Chem* 2005;280(2):1457–64.
- [55] Lysenko V, et al. Mechanisms by which common variants in the TCF7L2 gene increase risk of type 2 diabetes. *J Clin Invest* 2007;117(8):2155–63.
- [56] Hawa MI, et al. Impact of genetic and non-genetic factors in type 1 diabetes. *Am J Med Genet* 2002;115(1):8–17.
- [57] Basile KJ, et al. Overlap of genetic susceptibility to type 1 diabetes, type 2 diabetes, and latent autoimmune diabetes in adults. *Curr Diabetes Rep* 2014;14(11):550.
- [58] Pociot F, et al. Genetics of type 1 diabetes: what's next? *Diabetes* 2010;59(7):1561–71.
- [59] Fortune MD, et al. Statistical colocalization of genetic risk variants for related autoimmune diseases in the context of common controls. *Nat Genet* 2015;47(7):839–46.
- [60] Flannick J, et al. Assessing the phenotypic effects in the general population of rare variants in genes for a dominant Mendelian form of diabetes. *Nat Genet* 2013;45(11):1380–5.
- [61] Yang Y, Chan L. Monogenic diabetes: what it teaches us on the common forms of type 1 and type 2 diabetes. *Endocr Rev* 2016;37(3):190–222.
- [62] Horikawa Y, et al. Genetic variation in the gene encoding calpain-10 is associated with type 2 diabetes mellitus. *Nat Genet* 2000;26(2):163–75.
- [63] Demirci H, et al. Calpain 10 SNP-44 gene polymorphism affects susceptibility to type 2 diabetes mellitus and diabetic-related conditions. *Genet Test* 2008;12:305–9.
- [64] Song Y, et al. Are variants in the CAPN10 gene related to risk of type 2 diabetes? A quantitative assessment of population and family-based association studies. *Am J Hum Genet* 2004;74(2):208–22.
- [65] Florez JC, et al. Haplotype structure and genotype-phenotype correlations of the sulfonylurea receptor and the islet ATP-sensitive potassium channel gene region. *Diabetes* 2004;53(5):1360–8.
- [66] Nielsen EM, et al. The E23K variant of Kir6.2 associates with impaired post-OGT serum insulin response and increased risk of type 2 diabetes. *Diabetes* 2003;52(2):573–7.
- [67] Cubas P, Vincent C, Coen E. An epigenetic mutation responsible for natural variation in floral symmetry. *Nature* 1999;401(6749):157–61.
- [68] Gardner RJ, et al. An imprinted locus associated with transient neonatal diabetes mellitus. *Hum Mol Genet* 2000;9(4):589–96.
- [69] Longnecker DS. Abnormal methyl metabolism in pancreatic toxicity and diabetes. *J Nutr* 2002;132(8 Suppl):2373s–6s.

- [70] Ling C, et al. Epigenetic regulation of PPAR α in human type 2 diabetic islets and effect on insulin secretion. *Diabetologia* 2008;51(4):615–22.
- [71] Mootha VK, et al. PGC-1 α -responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. *Nat Genet* 2003;34(3):267–73.
- [72] Hall E, et al. DNA methylation of the glucagon-like peptide 1 receptor (GLP1R) in human pancreatic islets. *BMC Med Genet* 2013;14:76.
- [73] Muka T, et al. The role of global and regional DNA methylation and histone modifications in glycemic traits and type 2 diabetes: a systematic review. *Nutr Metab Cardiovasc Dis* 2016;26(7):553–66.
- [74] Lennartsson A, Ekwall K. Histone modification patterns and epigenetic codes. *Biochim Biophys Acta (BBA)-Gen Subj* 2009;1790(9):863–8.
- [75] Hoffman PF. United plates of America, the birth of a craton: early Proterozoic assembly and growth of Laurentia. *Annu Rev Earth Planet Sci* 1988;16(1):543–603.
- [76] Allis CD, et al. New nomenclature for chromatin-modifying enzymes. *Cell* 2007;131(4):633–6.
- [77] Kotake Y, et al. Long non-coding RNA ANRIL is required for the PRC2 recruitment to and silencing of p15(INK4B) tumor suppressor gene. *Oncogene* 2011;30(16):1956–62.
- [78] Arnes L, et al. *plinc1* encodes a long noncoding RNA that regulates islet β -cell formation and function. *Genes Dev* 2016;30(5):502–7.
- [79] Gabory A, Jammes H, Dandolo L. The H19 locus: role of an imprinted non-coding RNA in growth and development. *Bioessays* 2010;32(6):473–80.
- [80] Sami W, et al. Effect of diet on type 2 diabetes mellitus: a review. *Int J Health Sci* 2017;11(2):65–71.
- [81] Rajagopalan S, Brook RD. Air pollution and type 2 diabetes. *Diabetes* 2012;61(12):3037.
- [82] Watanabe N. Conversion to type 1 diabetes after H1N1 influenza infection: a case report. *J Diabetes* 2011;3(2):103.
- [83] Wang L, Wang FS, Gershwin ME. Human autoimmune diseases: a comprehensive update. *J Intern Med* 2015;278(4):369–95.
- [84] Smith DA, Germolec DR. Introduction to immunology and autoimmunity. *Environ Health Perspect* 1999;107(Suppl 5):661–5. Suppl 5.
- [85] Davidson A, Diamond B. Autoimmune diseases. *N Engl J Med* 2001;345(5):340–50.
- [86] Arleevskaya MI, et al. Editorial: microbial and environmental factors in autoimmune and inflammatory diseases. *Front Immunol* 2017;8:243.
- [87] Lerner A, et al. Microbes and viruses are bugging the gut in celiac disease. Are they friends or foes? *Front Microbiol* 2017;8:1392.
- [88] Schattner A, Rager-Zisman B. Virus-induced autoimmunity. *Rev Infect Dis* 1990;12(2):204–22.
- [89] Talal N, Flescher E, Dang H. Are endogenous retroviruses involved in human autoimmune disease? *J Autoimmun* 1992;5:61–6.
- [90] Valdes C, et al. Is there a link between influenza and type I diabetes? Increased incidence of T1D during the pandemic H1N1 influenza of 2009 in Chile. *Pediatr. Endocrinol. Rev.* 2013;11(2):161–6.
- [91] Kalliora MI, et al. Seasonal variation of type 1 diabetes mellitus diagnosis in Greek children. *Hormones* 2011;10(1):67–71.
- [92] Virus-Induced Type 2 Diabetes. Dr. Barry Starr Aug 12, 2013. <https://www.kqed.org/science/6821/virus-induced-type-2-diabetes>.
- [93] Allard R, et al. Diabetes and the severity of pandemic influenza A (H1N1) infection. *Diabetes Care* 2010;33(7):1491–3.
- [94] Richardson SJ, Horwitz MS. Is type 1 diabetes "going viral"? *Diabetes* 2014;63(7):2203–5.
- [95] Alexander GJ. An association between hepatitis C virus infection and type 2 diabetes mellitus: what is the connection? *Ann Intern Med* 2000;133(8):650–2.
- [96] Hyöty H, Taylor K. The role of viruses in human diabetes. *Diabetologia* 2002;45(10):1353–61.
- [97] Pak C, et al. Association of cytomegalovirus infection with autoimmune type 1 diabetes. *Lancet* 1988;332(8601):1–4.
- [98] Hyöty H, et al. Mumps infections in the etiology of type 1 (insulin-dependent) diabetes. *Diabetes Res* 1988;9(3):111–6.
- [99] Honeyman MC, Stone NL, Harrison LC. T-cell epitopes in type 1 diabetes autoantigen tyrosine phosphatase IA-2: potential for mimicry with rotavirus and other environmental agents. *Mol Med* 1998;4(4):231–9.
- [100] Honeyman MC, et al. Association between rotavirus infection and pancreatic islet autoimmunity in children at risk of developing type 1 diabetes. *Diabetes* 2000;49(8):1319–24.
- [101] Gamble DR, et al. Viral antibodies in diabetes mellitus. *Br Med J* 1969;3(5671):627–30.
- [102] Hyöty H, et al. A prospective study of the role of coxsackie B and other enterovirus infections in the pathogenesis of IDDM. *Diabetes* 1995;44(6):652.
- [103] Hyöty H, et al. A prospective study of the role of coxsackie B and other enterovirus infections in the pathogenesis of IDDM. *Diabetes* 1995;44(6):652–7.
- [104] Clements GB, Galbraith DN, Taylor KW. Coxsackie B virus infection and onset of childhood diabetes. *Lancet* 1995;346(8969):221–3.
- [105] Andréoletti L, et al. Detection of coxsackie B virus RNA sequences in whole blood samples from adult patients at the onset of type I diabetes mellitus. *J Med Virol* 1997;52(2):121–7.
- [106] Hyöty H, Hiltunen M, Knip M, Laakkonen M, Vähäsalo P, Karjalainen J, Koskela P, Roivainen M, Leinikki P, Hovi T, et al. A prospective study of the role of coxsackie B and other enterovirus infections in the pathogenesis of IDDM. Childhood Diabetes in Finland (DiMe) Study Group. *Diabetes* 1995;44(6):652–7. <https://doi.org/10.2337/diab.44.6.652>. PMID: 7789630.
- [107] Roman LM, et al. The expression of influenza virus hemagglutinin in the pancreatic beta cells of transgenic mice results in autoimmune diabetes. *Cell* 1990;61(3):383–96.
- [108] Tan H, Wang C, Yu Y. H1N1 influenza: the trigger of diabetic ketoacidosis in a young woman with ketosis-prone diabetes. *Am J Med Sci* 2012;343(2):180–3.
- [109] Watanabe N. Conversion to type 1 diabetes after H1N1 influenza infection: a case report. *J Diabetes* 2011;3(2):103–103.
- [110] Karaoglan M, Eksi F. The coincidence of newly diagnosed Type 1 diabetes mellitus with igm antibody positivity to enteroviruses and respiratory tract viruses. *J Diabetes Res* 2018;2018:8475341.
- [111] Beyerlein A, et al. Respiratory infections in early life and the development of islet autoimmunity in children at increased type 1 diabetes risk: evidence from the BABYDIET study. *JAMA Pediatr* 2013;167(9):800–7.
- [112] Chanock R, Roizman B, Myers R. Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent (CCA). I. Isolation, properties and characterization. *Am J Hyg* 1957;66(3):281–90.
- [113] Mufson MA, et al. Epidemiology of respiratory syncytial virus infection among infants and children in Chicago. *Am J Epidemiol* 1973;98(2):88–95.
- [114] Brandt CD, et al. Epidemiology of respiratory syncytial virus infection in Washington, D.C. 3. Composite analysis of eleven consecutive yearly epidemics. *Am J Epidemiol* 1973;98(5):355–64.
- [115] Walsh EE, Peterson DR, Falsey AR. Risk factors for severe respiratory syncytial virus infection in elderly persons. *J Infect Dis* 2004;189(2):233–8.
- [116] Kurt-Jones EA, et al. Pattern recognition receptors TLR4 and CD14 mediate response to respiratory syncytial virus. *Nat Immunol* 2000;1(5):398–401.
- [117] Wu B, et al. Structural basis for dsRNA recognition, filament formation, and antiviral signal activation by MDAs. *Cell* 2013;152(1–2):276–89.
- [118] Shirey KA, et al. The TLR4 antagonist Eritoran protects mice from lethal influenza infection. *Nature* 2013;497(7450):498–502.
- [119] Global Influenza Strategy 2019–2030. <https://www.paho.org/en/documents/global-influenza-strategy-2019-2030#:~:text=The%20Global%20Influenza%20Strategy%20for,control%20and%20preparedness%20for%20future>.
- [120] Watkins P, et al. Diabetic ketoacidosis during the influenza epidemic. *Br Med J* 1970;4(5727):89–91.
- [121] Nenna R, et al. Detection of respiratory viruses in the 2009 winter season in Rome: 2009 influenza A (H1N1) complications in children and concomitant type 1 diabetes onset. *Int J Immunopathol Pharmacol* 2011;24(3):651–9.
- [122] Tan H, Wang C, Yu Y. H1N1 influenza: the trigger of diabetic ketoacidosis in a young woman with ketosis-prone diabetes. *Am J Med Sci* 2012;343(2):180–3.
- [123] Trostad L, et al. Narcolepsy and hypersomnia in Norwegian children and young adults following the influenza A(H1N1) 2009 pandemic. *Vaccine* 2017;35(15):1879–85.
- [124] Ruiz PLD, et al. Pandemic influenza and subsequent risk of type 1 diabetes: a nationwide cohort study. *Diabetologia* 2018;61(9):1996–2004.
- [125] Blum A, et al. Acute pancreatitis may be caused by H1N1 influenza A virus infection. *Isr Med Assoc J* 2010;12(10):640–1.
- [126] Capua I, et al. Study of 2009 H1N1 pandemic influenza virus as a possible causative agent of diabetes. *J Clin Endocrinol Metab* 2018;103(12):4343–56.
- [127] Capua I, et al. Influenza A viruses grow in human pancreatic cells and cause pancreatitis and diabetes in an animal model. *J Virol* 2013;87(1):597–610.
- [128] Piccini B, et al. Type 1 diabetes onset and pandemic influenza A (H1N1). *Int J Immunopathol Pharm* 2012;25(2):547–9.
- [129] Capua I, et al. Influenza A viruses grow in human pancreatic cells and cause pancreatitis and diabetes in an animal model. *J Virol* 2013;87(1):597–610.
- [130] Yoo SG, et al. Impact of cytomegalovirus disease on new-onset type 2 diabetes mellitus: population-based matched case-control cohort study. *Diabetes Metab J* 2019;43(6):815–29.
- [131] Type 2 Diabetes Linked to Common Virus. Rachael Rettner. Aug 2012. infection.org.
- [132] Lee KH, et al. Association between cytomegalovirus end-organ diseases and moderate-to-severe dementia: a population-based cohort study. *BMC Neurol* 2020;20(1):216.
- [133] Kim T-S, Shin E-C. The activation of bystander CD8+ T cells and their roles in viral infection. *Exp Mol Med* 2019;51(12):1–9.
- [134] Pacheco Y, et al. Bystander activation and autoimmunity. *J Autoimmun* 2019;103:102301.
- [135] Horwitz MS, et al. Coxsackieviral-mediated diabetes: induction requires antigen-presenting cells and is accompanied by phagocytosis of beta cells. *Clin Immunol* 2004;110(2):134–44.
- [136] Duke RC. Self recognition by T cells. I. Bystander killing of target cells bearing syngeneic MHC antigens. *J Exp Med* 1989;170(1):59–71.
- [137] Tough DF, Borrow P, Sprent J. Induction of bystander T cell proliferation by viruses and type I interferon in vivo. *Science* 1996;272(5270):1947–50.
- [138] Welsh RM, Selin LK. No one is naive: the significance of heterologous T-cell immunity. *Nat Rev Immunol* 2002;2(6):417–26.
- [139] Tough DF, Borrow P, Sprent J. Induction of bystander T cell proliferation by viruses and type I interferon in vivo. *Science* 1996;272(5270):1947–50.
- [140] Hardy GA, et al. Interferon- α is the primary plasma type-I IFN in HIV-1 infection and correlates with immune activation and disease markers. *PLOS One* 2013;8(2):e56527.
- [141] Chehadeh W, et al. Persistent infection of human pancreatic islets by coxsackievirus B is associated with alpha interferon synthesis in beta cells. *J Virol* 2000;74(21):10153–64.
- [142] Freeman BE, et al. Regulation of innate CD8+ T-cell activation mediated by cytokines. *Proc Natl Acad Sci USA* 2012;109(25):9971–6.

- [143] Lertmemongkolchai G, et al. Bystander activation of CD8+ T cells contributes to the rapid production of IFN-gamma in response to bacterial pathogens. *J Immunol* 2001;166(2):1097–105.
- [144] Berg RE, et al. Memory CD8+ T cells provide innate immune protection against *Listeria monocytogenes* in the absence of cognate antigen. *J Exp Med* 2003;198(10):1583–93.
- [145] Reynolds JM, Dong C. Toll-like receptor regulation of effector T lymphocyte function. *Trends Immunol* 2013;34(10):511–9.
- [146] Salerno F, et al. Costimulation through TLR2 drives polyfunctional CD8(+) T cell responses. *J Immunol* 2019;202(3):714–23.
- [147] Kawai T, Akira S. Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. *Immunity* 2011;34(5):637–50.
- [148] Whiteside SK, et al. Bystander T cells: a balancing act of friends and foes. *Trends Immunol* 2018;39(12):1021–35.
- [149] Nekoua MP, et al. Pancreatic beta cells persistently infected with coxsackievirus B4 are targets of NK cell-mediated cytolytic activity. *Cell Mol Life Sci* 2020;77(1):179–94.
- [150] Perona-Wright G, et al. Systemic but not local infections elicit immunosuppressive IL-10 production by natural killer cells. *Cell Host Microbe* 2009;6(6):503–12.
- [151] Richardson SJ, et al. Expression of the enteroviral capsid protein VP1 in the islet cells of patients with type 1 diabetes is associated with induction of protein kinase R and downregulation of Mcl-1. *Diabetologia* 2013;56(1):185–93.
- [152] Sckisel GD, et al. Influenza infection results in local expansion of memory CD8(+) T cells with antigen non-specific phenotype and function. *Clin Exp Immunol* 2014;175(1):79–91.
- [153] Kohlmeier JE, et al. Type I interferons regulate cytolytic activity of memory CD8+ T cells in the lung airways during respiratory virus challenge. *Immunity* 2019;51(3):96–105.
- [154] Horns F, Dekker CL, Quake SR. Memory B cell activation, broad anti-influenza antibodies, and bystander activation revealed by single-cell transcriptomics. *Cell Rep* 2020;30(3):905–13. e6.
- [155] Wucherpfennig KW. Mechanisms for the induction of autoimmunity by infectious agents. *J Clin Invest* 2001;108(8):1097–104.
- [156] von Herrath MG, Oldstone MB. Interferon-gamma is essential for destruction of beta cells and development of insulin-dependent diabetes mellitus. *J Exp Med* 1997;185(3):531–9.
- [157] Ohashi PS, et al. Induction of diabetes is influenced by the infectious virus and local expression of MHC class I and tumor necrosis factor-alpha. *J Immunol* 1993;150(11):5185–94.
- [158] Campbell IL, et al. Essential role for interferon-gamma and interleukin-6 in autoimmune insulin-dependent diabetes in NOD/Wehi mice. *J Clin Invest* 1991;87(2):739–42.
- [159] Campbell IL, Harrison LC. Molecular pathology of type 1 diabetes. *Mol Biol Med* 1990;7(4):299–309.
- [160] Sarvetnick N, et al. Loss of pancreatic islet tolerance induced by beta-cell expression of interferon-gamma. *Nature* 1990;346(6287):844–7.
- [161] Braghi S, et al. Modulation of humoral islet autoimmunity by pancreas allotransplantation influences allograft outcome in patients with type 1 diabetes. *Diabetes* 2000;49(2):218–24.
- [162] Söhnlein P, et al. Epitope spreading and a varying but not disease-specific GAD65 antibody response in Type I diabetes. The childhood diabetes in Finland study group. *Diabetologia* 2000;43(2):210–7.
- [163] Bonifacio E, et al. Maturation of the humoral autoimmune response to epitopes of GAD in preclinical childhood type 1 diabetes. *Diabetes* 2000;49(2):202–8.
- [164] Dotta F, et al. Coxsackie B4 virus infection of beta cells and natural killer cell insulinitis in recent-onset type 1 diabetic patients. *Proc Natl Acad Sci USA* 2007;104(12):5115–20.
- [165] Krogvold L, et al. Detection of a low-grade enteroviral infection in the islets of langerhans of living patients newly diagnosed with type 1 diabetes. *Diabetes* 2015;64(5):1682–7.
- [166] Richardson SJ, et al. Expression of the enteroviral capsid protein VP1 in the islet cells of patients with type 1 diabetes is associated with induction of protein kinase R and downregulation of Mcl-1. *Diabetologia* 2013;56(1):185–93.
- [167] Marroqui L, et al. TYK2, a candidate gene for type 1 diabetes, modulates apoptosis and the innate immune response in human pancreatic beta-cells. *Diabetes* 2015;64(11):3808–17.
- [168] Fujinami RS, et al. Molecular mimicry, bystander activation, or viral persistence: infections and autoimmune disease. *Clin Microbiol Rev* 2006;19(1):80–94.
- [169] von Herrath MG, Dockter J, Oldstone MBA. How virus induces a rapid or slow onset insulin-dependent diabetes mellitus in a transgenic model. *Immunity* 1994;1(3):231–42.
- [170] Oikarinen S, et al. Virus antibody survey in different European populations indicates risk association between coxsackievirus B1 and type 1 diabetes. *Diabetes* 2014;63(2):655–62.
- [171] Fujinami RS, Oldstone MB. Amino acid homology between the encephalitogenic site of myelin basic protein and virus: mechanism for autoimmunity. *Science* 1985;230(4729):1043–5.
- [172] Roep BO, et al. Molecular mimicry in type 1 diabetes: immune cross-reactivity between islet autoantigen and human cytomegalovirus but not Coxsackie virus. *Ann N Y Acad Sci* 2002;958:163–5.
- [173] Atkinson MA, et al. Cellular immunity to a determinant common to glutamate decarboxylase and coxsackie virus in insulin-dependent diabetes. *J Clin Invest* 1994;94(5):2125–9.
- [174] Christen U, et al. A viral epitope that mimics a self antigen can accelerate but not initiate autoimmune diabetes. *J Clin Invest* 2004;114(9):1290–8.
- [175] Gronski MA, et al. TCR affinity and negative regulation limit autoimmunity. *Nat Med* 2004;10(11):1234–9.
- [176] Brehm MA, et al. T cell immunodominance and maintenance of memory regulated by unexpectedly cross-reactive pathogens. *Nat Immunol* 2002;3(7):627–34.
- [177] Pak CY, et al. Association of cytomegalovirus infection with autoimmune type 1 diabetes. *Lancet* 1988;2(8601):1–4.
- [178] Singh B. Stimulation of the developing immune system can prevent autoimmunity. *J Autoimmun* 2000;14(1):15–22.
- [179] Ramondetti F, et al. Type 1 diabetes and measles, mumps and rubella childhood infections within the Italian Insulin-dependent diabetes registry. *Diabet Med* 2012;29(6):761–6.
- [180] Duderstadt SK, et al. Vaccination and risk of type 1 diabetes mellitus in active component U.S. Military, 2002–2008. *Vaccine* 2012;30(4):813–9.
- [181] Guimarães LE, et al. Vaccines, adjuvants and autoimmunity. *Pharmacol Res* 2015;100:190–209.
- [182] Perricone C, et al. Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) 2013: Unveiling the pathogenic, clinical and diagnostic aspects. *J Autoimmun* 2013;47:1–16.
- [183] Shoenfeld Y, Agmon-Levin N. 'ASIA'—autoimmune/inflammatory syndrome induced by adjuvants. *J Autoimmun* 2011;36(1):4–8.
- [184] Jefferson TO, Rabinovich R, Tuomilehto J. Vaccines and their real or perceived adverse effects. Authors' conclusions are at odds with investigators. *BMJ* 1999;318(7196):1487–8.
- [185] Association between type 1 diabetes and Hib vaccine. *BMJ* 1999;319:1133. <https://www.bmj.com/content/319/7217/1133.1#%3Atext=The%20cumulative%20difference%20in%20cases,is%201.26%20at%207%20years>.
- [186] Classen JB, Classen DC. Clustering of cases of insulin dependent diabetes (IDDM) occurring three years after hemophilus influenza B (HiB) immunization support causal relationship between immunization and IDDM. *Autoimmunity* 2002;35(4):247–53.
- [187] Classen JB. The timing of immunization affects the development of diabetes in rodents. *Autoimmunity* 1996;24(3):137–45.
- [188] Vadalà M, et al. Vaccination and autoimmune diseases: is prevention of adverse health effects on the horizon? *EPMA J* 2017;8(3):295–311.
- [189] Segal Y, Shoenfeld Y. Vaccine-induced autoimmunity: the role of molecular mimicry and immune crossreaction. *Cell Mol Immunol* 2018;15(6):586–94.
- [190] Agmon-Levin N, Kivity S, Shoenfeld Y. Influenza vaccine and autoimmunity. *Isr Med Assoc J* 2009;11(3):183–5.
- [191] Casqueiro J, Alves C. Infections in patients with diabetes mellitus: a review of pathogenesis. *Indian J Endocrinol Metab* 2012;16 Suppl 1(Suppl1):S27–36.
- [192] Kornum JB, et al. Type 2 diabetes and pneumonia outcomes: a population-based cohort study. *Diabetes Care* 2007;30(9):2251–7.
- [193] Peleg AY, et al. Common infections in diabetes: pathogenesis, management and relationship to glycaemic control. *Diabetes Metab Res Rev* 2007;23(1):3–13.
- [194] Joshi N, et al. Infections in patients with diabetes mellitus. *N Engl J Med* 1999;341(25):1906–12.
- [195] Barros MM, Cartagena SC, Bavestrello FL. Prevention of community-acquired pneumonia in adults. *Rev Chil Infectol* 2005;22(Suppl 1):s67–74.
- [196] Badawi A, Ryouo SG. Prevalence of diabetes in the 2009 influenza A (H1N1) and the middle east respiratory syndrome coronavirus: a systematic review and meta-analysis. *J Public Health Res* 2016;5(3):733.
- [197] Restrepo BI, et al. Cross-sectional assessment reveals high diabetes prevalence among newly-diagnosed tuberculosis cases. *Bull World Health Organ* 2011;89(5):352–9.
- [198] Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. *Lancet Infect Dis* 2009;9(12):737–46.
- [199] Vergani D, et al. Low serum C4 concentrations: an inherited predisposition to insulin dependent diabetes? *Br Med J* 1983;286(6369):926–8.
- [200] Price CL, et al. Methylglyoxal modulates immune responses: relevance to diabetes. *J Cell Mol Med* 2010;14(6b):1806–15.
- [201] Stegenga ME, et al. Hyperglycemia enhances coagulation and reduces neutrophil degranulation, whereas hyperinsulinemia inhibits fibrinolysis during human endotoxemia. *Blood* 2008;112(1):82–9.
- [202] Ilyas R, et al. High glucose disrupts oligosaccharide recognition function via competitive inhibition: a potential mechanism for immune dysregulation in diabetes mellitus. *Immunobiology* 2011;216(1–2):126–31.
- [203] Alexiewicz JM, et al. Polymorphonuclear leukocytes in non-insulin-dependent diabetes mellitus: abnormalities in metabolism and function. *Ann Intern Med* 1995;123(12):919–24.
- [204] Ohno M, et al. Influenza virus infection affects insulin signaling, fatty acid-metabolizing enzyme expressions, and the tricarboxylic acid cycle in mice. *Sci Rep* 2020;10(1):10879.
- [205] Vamos EP, et al. Effectiveness of the influenza vaccine in preventing admission to hospital and death in people with type 2 diabetes. *CMAJ* 2016;188(14):E342–51.
- [206] Wang IK, et al. Effectiveness of influenza vaccination in elderly diabetic patients: a retrospective cohort study. *Vaccine* 2013;31(4):718–24.
- [207] Pozzilli P, et al. The immune response to influenza vaccination in diabetic patients. *Diabetologia* 1986;29(12):850–4.
- [208] Wang I-K, et al. Effectiveness of influenza vaccination in elderly diabetic patients: a retrospective cohort study. *Vaccine* 2013;31(4):718–24.
- [209] Association AD. Standards of medical care in diabetes—2014. *Diabetes Care* 2014;37:S14.

- [210] Tang X, et al. On the origin and continuing evolution of SARS-CoV-2. *Natl Sci Rev* 2020;7(6):1012–23.
- [211] Gregory JM, et al. COVID-19 severity is tripled in the diabetes community: a prospective analysis of the pandemic's impact in type 1 and type 2 diabetes. *Diabetes Care* 2020;44(2):526–32.
- [212] Yang X, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;8(5):475–81.
- [213] Zhang JJ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020;75(7):1730–41.
- [214] Alguwaihes AM, et al. Diabetes and Covid-19 among hospitalized patients in Saudi Arabia: a single-centre retrospective study. *Cardiovasc Diabetol* 2020;19(1):205.
- [215] Detection of autoimmune antibodies in severe but not in moderate or asymptomatic COVID-19 patients. Aisha D. Fakhroo, Gheyath K. Nasarallah, Taushif Khan, Farhan S. Cyprian, Fatima Al Ali, Manar M.A. Ata, Sara Taleb, Ali A. Hssain, Ali H. Eid, Laith J. Abu-Raddad, Abdullatif Al-Khal, Asmaa A. Al Thani, Nico Marr, Hadi M. Yassine. <https://doi.org/10.1101/2021.03.02.21252438>. <https://www.medrxiv.org/content/10.1101/2021.03.02.21252438v1>.
- [216] Elrayess MA, et al. Metabolic signatures of type 2 diabetes mellitus and hypertension in COVID-19 patients with different disease severity. *Front Med* 2022;8. 788687–788687.
- [217] Xiao Y-F, et al. Major characteristics of severity and mortality in diabetic patients with COVID-19 and establishment of severity risk score. *Front Med* 2021;8. 655604–655604.
- [218] Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia – a systematic review, meta-analysis, and meta-regression. *Diabetes Metab Syndr* 2020;14(4):395–403.
- [219] Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. *BMJ* 2020;368. (m1198).
- [220] Petrilli CM, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ* 2020;369. (m1966).
- [221] Zhou F, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395(10229):1054–62.
- [222] Ali H, et al. Robust antibody levels in both diabetic and non-diabetic individuals after BNT162b2 mRNA COVID-19 vaccination. *Front Immunol* 2021;12.
- [223] Stefan N. Metabolic disorders, COVID-19 and vaccine-breakthrough infections. *Nat Rev Endocrinol* 2022;18(2):75–6.
- [224] Dagan N, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med* 2021;384(15):1412–23.
- [225] Pal R, Bhadada SK, Misra A. COVID-19 vaccination in patients with diabetes mellitus: current concepts, uncertainties and challenges. *Diabetes Metab Syndr* 2021;15(2):505–8.