Connection between diabetes, viral and bacterial infections

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Abstract

Background: Diabetes mellitus is a clinical syndrome characterised by hyperglycemia. It is result of defects in insulin secretion, insulin action or both. In 2019 global prevalence of diabetes was 9.3 % . There is a lot of research , which shows key roles of infections including bacteria, viruses, fungi and parasites in the development of diabetes. This article aims to critically review current knowledge of how diabetes and infectious disease are connected to each other .
Methods: The Pubmed, Springer and sciencedirect databases were searched for articles published between 2000 and 2020 years . Articles published in languages other than English, articles without abstract, and those articles whose titles were not relevant to the purpose of this review were excluded .
Conclusion: More research is needed for clarification of the immunopathogenic mechanisms linking infections and diabetes .

Keywords: Diabetes, infections, hyperglycemia, induce , accelerate, prevent.

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Introduction

Diabetes mellitus is a clinical syndrome characterised by hyperglycemia. It is result of defects in insulin secretion, insulin action or both(1, 2) . Long-term chronic hyperglycemia damages blood vessels, heart, nerves, kidney and eyes (1). In 2019 global prevalence of diabetes was 9.3 % (3). The number of diabetes cases is still increasing . That's why it is major medical problem (1-3). There is a lot of researches , which shows key roles of infections including bacteria, viruses, fungi and parasites in the development of diabetes (1) . On the other hand some scientists suggests that viral and bacterial infections prevent diabetes.

This article aims to critically review current knowledge how diabetes and infectious disease are connected to each other .

Material and methods

The Pubmed, Springer and sciencedirect databases was searched for articles published between 2000 and 2020 years, using the following keywords in various combinations: "diabetes," "infections," "hyperglycemia", "induce " , "accelerate" , "prevent" . Bibliographic search included consensus papers, , original articles and review articles written in English. The articles were initially selected on the basis of their titles and abstracts. Articles published in languages other than English, articles without abstract, and those articles whose titles were not relevant to the purpose of this review were excluded .

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Do viral or bacterial infections cause Type 1 or Type 2 Diabetes?

Viral infections and diabetes

Certain bacterial and viral infections have been reported to cause diabetes (4-12). Infections have the potential to initiate inflammation, by pro inflammatory cytokines and chemokines , which may then stimulate expression of MHC I class molecules on the pancreatic islets(10, 13). This process made Beta cells recognizable by CD8+ and caused destruction of islets. Inflammation not only activated T cells and DCs(dendritic cells), but also caused direct destruction of Beta cells, which leaded development of diabetes.(13) On the other hand, it has been found, that TLRs (Toll like receptors) played important role for immune response and induced inflammation. Different TLRs have different functions and recognise spe-

cific molecules. TLRs ligand binding, including TLR2, TLR3, TLR9 on viral or bacterial molecules could trigger inflammatory cytokines, chemokines, upregulated expression of MHC I and MHC II molecules on the DCs and macrophage's cell surface, which initiated presentation of Beta cells to T cells and developed autoimmunity (10, 13). Also TLR2 signaling pathway could weaken function of T regulatory cells (Tregs), including $CD4^+CD25^+$ Tregs. Lose function of Tregs, leaded loss of self-tolerance, enhanced autoimmunity and caused Beta cell destruction, which resulted development of type 1 diabetes (T1D) (13).

HIV induced diabetes

Patient's life expectancy has been increased, because of new ART (antiretroviral treatment). As long as people with HIV live longer a lot of research has been conducted, to find a connection between HIV infection and Type 2 diabetes. There is a lot of debate, if the prevalence of diabetes is higher in the HIV infected people, compared to the general population. It is known, that the HIV infection can cause chronic inflammation (14, 15). During this process concentration of pro-inflammatory cytokines , tumor necrosis factor (TNF)-α , IL-6 , IL-8 and IL-18 is increased . Epithelial cells are producing precursors of IL-18 . Macrophages and dendritic cells are the main source of IL-18. It has been found, that elevated IL-18 level is associated with insulin resistance and metabolic syndrome , which might lead diabetes in future (16).

Systemic inflammation and tryptophan catabolism during AIDS alerts gut microbiota. Concentrations of *Bifidobacterium, Bacteroides , Clostridium, Anaerovibri* , *Akkermansia* (17, 18), *Finegoldia* , *Anaerococcus* , *Faecalibacterium* and *Roseburia* are drastically decreased in HIV patients . Butyrate is produced by *Anaerococcus. This product is* anti-inflammatory, improves insulin sensitivity and decrease risk of diabetes. The Kynurenine/tryptophan ratio is increased when the number of *Anaerococcus decreased* . *This ratio indicates* tryptophan catabolism (15). Tryptophan belongs to essential amino acids and serves a lot of important purposes. Tryptophan is catabolized into kynurenine through kynurenine pathway. At first the indole ring of tryptophan is oxidatively cleaved and forms N-formyl-kynurenine. Later it decomposed by indoleamine 2,3-dioxygenase (IDO) to kynurenine. IDO can induce immune activation and inflammation. Sodium butyrate is down-regulating transcription of IDO and decrease inflammation. That's why the rate of systemic inflammation is increased during *Anaerococcus low concentration* (14, 15). Such changes alert metabolism and might cause metabolic disturbances, including insulin resistance and type 2 diabetes (14, 15, 17, 18) .

Combined ART is given to patients with HIV/AIDS . They are associated with insulin resistance, glucose intolerance and type 2 diabetes, especially PIs and NRTIs. Duration of ART has big influence on hyperglycemia . The increased glucose level during ART is connected to pancreatic beta-cell lipotoxicity and insulin inhibition . Insulin resistance by protease inhibitors (PI) is increased via GLUT4-dependent or/and independent mechanisms. They interfere GLUT4 translocation from the cell cytosol to the cell's surface and inhibit adipocyte differentiation. PIs also suppress insulin release and decrease sensing of glucose (19).

Nucleoside reverse transcriptase inhibitors (NRTIs) can cause mitochondrial dysfunction. They affect mitochondrial oxidative phosphorylation. The mitochondrial ATP synthase expression is reduced. Also the number, size and activity of mitochondrias are decreased. Reduction of the mitochondrial function is reason of increased intramyocellular lipid accumulation, reduced lipid oxidation and increased insulin resistance. It was found that Mitochondrial toxicity during NRTIs treatment is caused by γ-polymerase inhibition. Also mitochondrial RNA is depleted , adipose differentiation genes are down-regulated, fatty acid oxidation transcriptional regulators and genes are up-regulated. All of these changes might lead insulin resistance and T2D (20) .

Cytomegalovirus induced diabetes

Human herpes virus 5 is known as Cytomegalovirus (CMV), which is associated with development of diabetes. It could cause T1D in children and T2D in adults(21). Some studies have reported, that CMV accelerated development of T1D in genetically predisposed people(4, 6, 7). A lot of theories and mechanisms have been suggested, how CMV could cause T1D and T2D. First, CMV could specifically recognise and infect islet's Beta cells(4, 6, 21). Viral infection stimulated production of many apoptotic factors and cause destruction of pancreas Beta cells(6, 7, 21).Beta cell apoptosis was accelerated by TNF-α, which could cause not only destruction of Beta cells, but also lead to insulin resistance and problems in insulin signaling pathway by CMV initiated adipocyte lipolysis or loss function of insulin receptor. This dysfunction was reason of both T1D and T2D(21).
Second mechanism was that, CMV caused destruction of Beta cells with cross reactivity. DNA-binding protein pUL57 had homology with GAD65 and Hsp60. With molecular mimicry CMV activated cytotoxic T cells, which leaded pancreatic Beta cell destruction(4, 6, 21). Third, viral infection initiated clonal activation of T cells (4), which stimulated production of pro inflammatory cytokines and chemokines. It initiated development of T1D and T2D(21). Some authors suggest, that activation of macrophages and their motion to the pancreas induce inflammation, insulitis and development of T1D(4, 7).

Hepatitis C virus induced diabetes

A lot of studies reported, that hepatitis C virus (HCV) increased risk to develop insulin resistance and T2D(8, 22,

23, 30). HCV patients had 2-10 fold higher risk to develop T2D(8, 30).It has been discovered, that 25% of HCV patients had T2D(23).Also T2D was found in 47million HCV patients. Large cohort studies have reported, that 20-50% of chronic HCV patients had HCV associated T2D (22).HCV positive patients had a higher chance of developing T2D compared to HBV(hepatitis B virus) positive patients. Both HCV and HBV could replicate in the pancreatic Beta cells, damage them and insulin signaling pathway, causing insulin resistance and lead T2D. Lower risk of T2D during HBV infection had two explanations. First is Vaccination program of HBV, which avoided chronic form of HBV and virus induced complications. Second reason, that HBV had a fast progression and few patients had HBV associated cirrhosis, which could induce inflammation and T2D(30).

There were different theories how HCV could cause T2D. Reason of HCV associated T2D was defect of AKT (protein kinase B), phosphatidylinositol3-kinase(PI3-kinase) and IRS1(insulin receptor substrate)(8, 23). A lot of pro inflammatory cytokines were produced during HCV infection, including TNF- α and IL-6 (8, 22, 23). IRS1/IRS2 signaling pathway was inhibited by pro inflammatory cytokine stimulated IRS1/IRS2 phosphorylation, which caused insulin resistance and leaded T2D (8, 23).

It has been found, that concentration of TNF-α, IL-8 and IFN-γ has been increased during HCV infection. IFN-γ stimulated macrophages and monocytes, which leaded chronic inflammation in the liver. Also macrophages activated pro inflammatory cytokines and damaged liver (22). Pro inflammatory cytokines, including IL-6 stimulated cytokine signaling protein suppressors, which resulted insulin resistance by IRS1 and IRS2 degradation(8, 22). Free fatty acids(FFA), released by liver steatosis during HCV could cause insulin resistance. FFA activated reactive oxygen species(ROS), increased diacylglycerol and acylCoA concentration. This process stimulated protein kinase C (PKC) and c-Jun N terminal kinase(JNK), which increased IRS1 serine phosphorylation, hepatic glucose production, gluconeogenesis, decreased glycogenesis, resulted insulin resistance and T2D(22).

Encephalomyocarditis virus induced diabetes

Studies have reported, that Encephalomyocarditis virus-D (EMC-D) induced pancreatic Beta cell destruction and development of diabetes in mice(5, 25). During EMC-D macrophages were activated. They stimulated production of nitric oxide(NO), TNF-α, IL-1beta ,caused inflammation, destroyed Beta cells and reduced insulin secretion(24, 25).Signaling pathway of tyrosine kinase was initiated by macrophages during EMC-D infection. This process was induced by following mitogen activated protein kinases (PKs): JNK, p38 and extracellular regulated kinase ½. EMC-D activated macrophages, triggered p59/p56Hck, Src tyrosine kinase, stimulated expression of iNOS (inducible nitric oxide synthase) and TNF-α, which leaded Beta cell destruction(5).After macrophages, T cells, NK (natural killers) cells and B cells caused pancreas infiltration(5, 25). EMC-D initiated Bax protein, Bak and Bax mRNA expression in the pancreas islets. Increased expression of Bak and Bax in the islets by EMC-D induced Beta cell apoptosis(25). EMC-D induced diabetes was prevented by block of macrophage stimulated mediators, including iNOS, TNF-α and IL-beta (5, 25). Incidence of diabetes was reduced during EMC-D infection, when mice got the treatment of iNOS inhibitors. iNOS deficit during EMC-D decreased expression of TNF-alpha and IL-1β, down regulated NF-ϰB and prevented Beta cells from apoptotic death. This process avoided the development of diabetes (25). Also the risk of diabetes was reduced in EMC-D infected mice, when mice were treated by tyrosine kinase inhibitor AG126 (5).

H.pylori induced diabetes

A lot of studies have reported, that H.pylori could induce development of diabetes(11, 26, 31). H.pylori seropositive patients had an increased risk of T2D compared to people who were seronegative on H.pylori (26).Patients with H.pylori infection had an increased level of HbA1c. It has been discovered, that patients who had T2D and high levels of HbA1c were infected with H.pylori .HbA1c was significantly high in people older than 65 years. In young patients insufficient of insulin secretion was detected during H.pylori infection(31). H.pylori caused inflammation, released inflammatory factors, including CRP(C reactive protein), IL-6, TNF-α. During inflammation insulin interaction with insulin receptors were inhibited by phosphorylation of serine on IRS, which leaded insulin resistance and development of T2D.Also H.pylori stimulated accumulation of the fat, activated TLR and initiated immune system response (26). Cellular macromolecules were damaged during H.pylori induced oxidative stress, which stimulated hyper production of ROS. This process lead to lipid peroxidation, protein modification and DNA damage (11). Macrophages and neutrophils activation, infiltration and inflammation was initiated by H.pylori infection (11, 26). In H.pylori patients OX-LDL was increased by oxidative stress. Also, glucose oxidation and AGE (advanced glycation end products) formation, caused by oxidative stress could trigger hyperglycemia. ROS generation was increased by leptin and FFA during H.pylori. Growth factors and inflammatory cytokines and chemokines were activated by OX-LDL. Guanine in DNA was attacked by RIS, which caused formation of 8-OHdG (8-hydroxydeoxy guanosine). It has been shown, that 8-OHdG was mutagenic and could cause a lot of diseases, including diabetes. Increased 8-OHdG was detected in T1D and T2D patients. On the other hand, H.pylori could cause insulin resistance and T2D with lipotoxicity, glucotoxicity, lead Beta cell dysfunction and chronic inflammation(11).

Parvovirus induced diabetes

It has been reported, that bio breeding diabetes-resistant rats (BBDR) developed diabetes after Parvovirus infection (9). It has been found ,that during Parvovirus 569 genes were up regulated (29). Parvovirus could cause diabetes by TLR signaling pathway. Immune response during Parvovirus infection was activated by TLRs (9). After virus recognition, TLRs were expressed on macrophages, DCs and B lymphocytes, which activated MHC and leaded production Parvovirus activated pro inflammatory chemokines and cytokines, including IL-12, IL-12p40, IL-23p40, IL-6, IFN-γ, IL-1β, IL-1α and TNF-α (9, 29). IFNs, IFN-γ induced chemokines and IL-1 pathways were the most active during Parvovirus immune response. IL-1 superfamily cytokines expression was increased by peripheral blood mononuclear cells(PBMCs). Parvovirus mainly up regulated two chemokines: CC and CXC. From CXC the highest concentration of CXCL9, CXCL10 and CXCL11 was found. NK cells and T cells were activated by CXCL10, which triggered development of T1D. It has been discovered, that Parvovirus infection up regulated STATS (signal transducers and activators of transcription), CD86, MHC-II, CD40, TLRs, B cells and DCs. When STATs were blocked T1D was prevented (29).

Echovirus induced diabetes

Echovirus(E) has been associated with development of T1D (12, 27, 28). In Cube was meningitis epidemic in 1986, 2000 and 2001 years, which was caused by E4, E16, E30. During meningitis epidemic in 2000 and 2001 islet cell antibodies and GADA (glutamic acid decarboxylase autoantibodies) were detected in 92,1% (2000 year) ,87,5%(2001 year) and 36,1%(1986 year) of infected people. The number of circulated autoantibodies during E16 and E30 were high, it was moderate during E4(28). E infected different lines of Beta Cells Outcome was depending on E strain. E30 and E16 replicated in NIT1, INS, MIN6, had cytopathic effect(CPE) within 3days (12) and also cytolytic effect, which caused islet Beta cell destruction (28). CPE appeared within 24 hours with E16 and E30 infection, when CEP was not detected during E4. Morphological changes during E30 and E16 was detected after 2-3 days. A lot of Beta cells and Beta cell lines were dead from 3 to 6 days (12). It has been reported, that E4 infected children had an increased number of insulin cell antibodies(ICA) and neutralising antibodies(NtAb), so their pancreas secreted insufficient amount of insulin. ICA was significantly increased during E16. Because ICA has been known as a main marker to detect Beta cell destruction, it means that E could induce and cause T1D(27). Concentration of other autoantibodies were increased too, including GADA (27, 28)and IAA (27).E16 could induce autoimmunity against Beta cell antigens(12, 27). During E16 NtAb was connected with increased level of circulating autoantibodies. It has been described, that maternal E6 infection caused neonatal T1D. Neonate had high levels of ICA and GADA (27). E4 did not have cytolytic effect, but they could cause chronic inflammation, which leaded insulin resistance and induce T2D (12). Insulin secretion was significantly decreased during E4, E16 and E30 infections. It has been suggested that E induced diabetes with several mechanisms. First was cross-reactivity with beta cells and it's antigenes. Second was direct cytolytic effect (27). Third, TLR3, MDA5 and RIG-I were activated in response of virus sensing process(28). E caused Beta cell destruction with pro inflammatory cytokines and chemokines, including TNF-α, IL-1β, IL-1alpha, IFN-β (27, 28). So E damaged Beta cells, caused their destruction, decreased secretion of insulin and initiated T1D (12).

Do viral or bacterial infections accelerate the development of Type 1 or Type 2 Diabetes?

Enterovirus accelerated the development of diabetes

Studies have suggested, that autoimmunity, which caused T1D could not be induced by viral infections, but they could accelerate already triggered process (32). It has been shown, that viral infections accelerated development of the T1D by cytolysis of pancreas Beta cells or loss self-tolerance. Losing self-tolerance was activated by molecular mimicry between viral epitopes and islet Beta cells' auto antigens (33). A lot of studies have reported, that Enterovirus(EV) infection accelerated development of T1D (32, 34-37). Pregnant women who had EV infection had an increased rate to develop T1D in their offspring (38). Boys had higher risk of EV associated T1D than girls. Children who had EV infection, diabetes associated antigens were found during 6 month period and had an increased risk of T1D development (36).T1D was developed faster in children who had EV RNA in blood, compared to children who did not have viral RNA (32).Studies have found, that patients who had T1D, their intestinal mucosa was infected by EV (32, 37).EV infection increased inflammation in gut mucosa and induced antibody mediated and cell-mediated inflammation. EV could persist in the intestinal mucosa and spread later to the pancreas via vascular and lymphatic system (37). EV could accelerate development of T1D by several mechanisms. First, was directly destroy of beta cells by cytolysis. Second, was molecular mimicry to Beta cell antigens. Some viral and self-antigens are sharing same protein sequence, which can induce auto reactive T cells, because of cross reactivity. It was found, that GAD65(glutamic acid decarboxylase 65)and CVB protein P2C had cross reactivity, which activated effector T cells and accelerated development of T1D.Third mechanism was bystander activation by inflammatory mediators ,that leaded insulitis and Beta cell death (34, 38-40).Patients who had genetic predispose to T1D,EV accelerated process by stimulation of MHC ,increased secretion of IFN-γ and PKR, which leaded inflammation and Beta cell destruction (35). CCR2 which was expressed on CD4+ and CD8+ T cells has been decreased significantly in children with T1D.Also they had low level of IL-12Rβ, IL-18R, CXCR6 and suppression of Tbet (38).Patients who had metabolic disturbance EV infection could accelerate development of T2D.Underlying mechanism was inflammation

of Beta cells, which increased insulin resistance and leaded T2D (35).

It has been found that EV infection could initiate and accelerate Beta cell destruction autoimmune mechanism during fulminant T1D.EV induced the CXCL10(CXC chemokine ligand 10) expression in Beta cells. CXCL10 receptor activation triggered CXCR3, which stimulated T cell migration. On the other hand,CXCL10 activated macrophages (41). IFN-γ and other inflammatory cytokines were released in the islets by macrophages and T cells. This mechanism did not cause only damage of Beta cells, but it also speeded upCXCL10 generation in beta cells. After some time it caused Beta cell destruction by activation of cell-mediated immune mechanism (35, 41). It has been discovered, that LPG2 expression was significantly increased in patients' Beta cells with fulminant T1D.For Picornavirus recognition, including EV, meningovirus and EMC LPG2 has been known to be very important. During viral recognition LPG2 was regulating RIG-I(retinoid acid inducible gene I) and MDA5(melanoma differentiation associated protein 5) (41). EV detecting pathway was activated by LPG2, which enhanced MDA5 and RIG-I. This process accelerated Beta cell destruction (40, 41). Mutation of MDA5 gene decreased rate of T1D development (41, 42).During EV replication dsRNA (double-stranded RNA) was generated, which activated MDA5,RIG-I and Toll like receptor 3(TLR3).This process initiated secretion and production of pro inflammatory chemokines and cytokines, which leaded inflammation (40).

Coxsackie virus accelerated the development of diabetes

Studies have reported, that Coxsackie virus B4(CVB4) more in 60% of NOD mice caused acceleration of T1D.To develop T1D Treg (regulatory T cells) defect was important. It has been found in the mice, that Tregs moderately lost ability to down regulate proliferation of effector T cells. This process weakened tolerance toward Beta cell antigens and progression of disease had begun. Beta cell antigen was presented to T cells during defect of Tregs. After noninvasive peri insulitis period destruction of Beta cells had begun.CVB4 infection triggered auto reactive T cells, that leaded pancreas to insulitis and inflammation, which resulted T1D (47).

It has been discovered, that CVB5 caused acceleration of T1D.CVB5 initiated Beta cell death by activation of PKR (protein kinase R), it decreased Mcl-1(myeloid leukemia cell-1) expression, which is antiapoptotic protein. CVB3, CVB4 and CVB5 could cause death of Beta cells with pyknosis, without apoptosis. CVB infections increased expression of pro inflammatory cytokines, including TNF-α, IL-1β, and IL-1α, also level of ATP was decreased in mitochondria. During CVB IFN-α, IFN-β, TNF-α,IL-6,IL-8,IL- α and IL-beta were detected in the islets (40, 42).MHC was activated by IFNs, which found viral antigen on cell surface and programmed cell death by triggering immune system cells (40, 48).

Mumps and Rubella accelerated the development of diabetes

Some studies have reported that mumps and rubella were associated with T1D.They could accelerate development of T1D, but could not cause it (6, 43). Rubella virus infected beta cells and had cross reactivity with GAD, but it did not have cytolytic effect on Beta cells. Mumps infected Beta cells without cytolytic effect too, but increased HLA-I, HLA-II expression on Beta cells, which leaded Beta cell destruction with auto reactive T cells (43).

Rotavirus accelerated the development of diabetes

Rotavirus was associated with T1D acceleration (44, 49).T1D development was accelerated in Rotavirus RRV strain infected NOD mice, when it was delayed in infant NOD mice. Molecular mimicry has been found between Intrinsic protein of insulin granulates(IA/ICA512),GAD65 and rotavirus VP7protein, which was reason on T1D development (33, 40, 44, 45).

Rotavirus could accelerate development of T1D in children, who have already been genetically predisposed to T1D. T1D is accelerated by T cell immune response and infect of regional lymph nodes, including mesenteric lymph nodes (MLN) and pancreatic lymph nodes (PLN) (46). Rotavirus RRV activated macrophages, DCs, B cells and T cells (45). Granzyme B and pro inflammatory cytokine levels were increased in the pancreas, MLN and PLN by cytotoxic T lymphocytes (45, 46). Also, MHC I were expressed on the B cells and number of antigen presenting cells were increased (33, 46). Up regulation of MHC I made Beta cells more detectable, which caused pancreas insulitis and Beta cell destruction (33).On the other hand, molecular mimicry affected not only Beta cell infection and lysis, but it also triggered auto reactive T cells by T cell receptor(TCR).TCR independently activated B and T cells via DC stimulated pro inflammatory cytokines (45). DCs has been very important to produce IFN-γ and induce immune response. Plasmacytoid dendrite cells (pDCs) activated CD8+ T cells, which happened via TLR7 and IFN-I (46). During RRV infection CD8+ T cells had autoimmunity toward IGRP(islet specific phosphate catalytic subunit related protein), which accelerate development of T1D (45). It has been found, that diabetic patients have a increased number of both conventional DC (cDC) and pDCs during rotavirus infection (46). pDCs with T cytotoxic cells and APCs stimulated secretion of TNF,IFN and other cytokines in PLN, which weakened self-tolerance (45, 46). Because IFN-γ and TNF were main markers for T helper immune response and CD4+ with CD8+ were important for this process, it proved, that cytotoxic T cells with T helpers played major role in T1D acceleration and development during Rotavirus infection (45).

Are diabetic patients more susceptible to viral or bacterial infections?

Diabetes and Tuberculosis

It has been reported, that patients with T2D had an increased risk to develop Tuberculosis (TB) faster and had more complications compared to non-diabetic patients (50). T2D patients had 2.44 to 8.33 fold higher risk to develop TB compared to non-diabetic patients (50, 51).

Insulin dependent diabetic patients'(IDDM) , who used more than 40 unites per day had twice the risk of developing tuberculosis. Study from 1959 to 1982 had found that ,24% of IDDM patients from all IDDM and 4,8% of NIDDM from all NIDDM developed tuberculosis during 10 years. In Hispanics study discovered, that 25% of diabetic people aged 25-54 had tuberculosis. Study from Spain had reported, that 69(42%) diabetic patients from 163 had positive tuberculin skin test. Another study from Philadelphia found out, that 3106 diabetic patients' had two fold increased prevalence of tuberculosis, compared to 70767 non diabetic patients. Studies from the UK from 1990 to 2001 have found that diabetic patients had 3.8% higher risk to develop TB. Study in Hong Kong during 5 years has discovered, that diabetic patients had 7% increased risk to develop TB compared to non-diabetic patients (51).

LL-37 has been known to be the strongest host defensive peptide. It is regulated by D3 and plays significant role to defend organism from infection diseases including m. tuberculosis and eliminate them. LL-37 showed two immunomodulatory effects: anti-inflammatory and pro inflammatory (50).Phagocytosis index, percentage of phagocytosis and macrophages viability has been decreased by evaluated level of glucose. High glucose level down regulated LL-37 expression, which weaken immune system's defence ability (50, 52). M.tuberculosis growing index in diabetic patients increased, because of LL-37 suppression. Down regulation LL-37 decreased production of TLR2,TLR4 and myeloid cells(TREM-1),which had inflammatory effect, also this process triggered macrophages' anti-inflammatory responses, by increased level of TGF-β and IL-10 and inhibited antimicrobial activity (50).

T2D patients with TB had down regulation of inflammatory cytokines (52, 53). Short-chain fatty acids(SCFAs) has been known to regulate inflammatory responses and immune system. They affected different cells, including macrophages, neutrophils and lymphocytes.IL-17 was inhibited stronger with SCFAs butyrates, including C2, C3 and C4 compared to IL-1beta and TNF-α during TB infection in T2D patients. Also C4 stimulated production of IL-10, which had anti-inflammatory effect. In T2D patients IL-10 blocked M.tuberculosis killing process, suppressed inflammatory cytokines production and prevented formation of protective immunity (53).

On the other hand, M.tuberculosis decreased expression of alveolar macrophages, IFN-γ mRNA,IL-12,IL-18 and TNF-α in patients with T2D, which leaded poor glycemic control (52).

Reduced intercellular glutathione(GSH) was reason of low IL-12. It happened because GSH concentration was low in PBMCs. Supplementations of GSH improved TB control by GSH's cytolytic effect on bacteria, which leaded better T cell control. Bad TB outcome was determined by the GSH/GSSG (oxidised GSH) imbalance, which down regulated IL-12 production .Low levels of intracellular GSH increased susceptibility of disease, weaken immune response, increased rate of bad results from infection and determined T2D progression and outcome. There were three mechanisms of reduced GSH levels during T2D. First, glucose decreased activity of γ glutamylcystein ligase, which affected GSH synthesis. Second, glucose used NADPH to be converted into sorbitol. NADPH was necessary to regenerate GSH from GSSG. Third, AGE(advanced glycation end products) stimulated production of hydrogen peroxide and superoxide, which affected GSH (54).

TB increase mortality rate during T2D.T2D mice had higher expression of inflammatory and pro inflammatory chemokines and cytokines compared with non T2D mice. During M.tuberculosis infection NK cells activated CD11c+ cells, which stimulated IL-6 production.IL-6 weakened immune response, lowered the rate of good outcome and increased risk of mortality during TB in T2D mice (55).

Diabetes and Pseudomallei Burkholderia

Studies have discovered, that patients with T2D have increased risk to develop melioidosis, which is caused by infection Burkholderia pseudomallei. Half of the patients with melioidosis had diabetes. In Northeastern Thailand T2D was detected in more than 60% of melioidosis patients. In Malaysia 57% of patients with melioidosis had T2D.PBMCs were infected by B.pseudomallei, that down regulated IL-12p70 and IL-12p35 production, it lead to reduced level of IFN-γ and decreased ability to kill bacterial infection.The rate of T2D was increased, because B.pseudomallei is antibiotic resistance and hard to treat (54).

Diabetes and H. pylori

A lot of studies have reported, that poor glycemic control during T1D was connected to H.pylori. H.pylori positive patients with T1D had higher levels of HbA1c compared to H.pylori negative patients with T1D.During H.pylory infection poor glycemic control could be reason of pro inflammatory cytokines, which were initiated by H.pylori. Connection has been found among H.pylori,T1D and autoimmune thyroiditis. T1D patients with H.pylory had higher concentration of anti-thyroid antibodies ,including anti-Tg and anti-TPO compared to H.pylori seronegative patients (56).

Diabetes prevented by viral and bacterial infections

It has been reported, that some viral and bacterial infections initiate process, which damages Beta cells and cause T1D, when others can avoid the development of diabetes. It has not been fully understood why different viral or bacterial infections have opposite effects (48).Some studies suggested, that infections and inflammatory signaling could prevent development of T1D.Immunity caused by viral infections could enhance resistance against diabetic infections, which controlled T cells by immunoregulatory mechanisms (13). Immunoregulatory mechanism, caused by viral infections included suppressor cytokines production, activation of Tregs, Foxp3, CD25+, and CD4+,up regulation of PD-L1.To maintain peripheral tolerance and have full protection from T1D Tregs, Foxp3, CD25+ and CD4+ has been shown to have the most important role for this process (48).

Studies reported, that TLR2(Toll like receptors) had both immunoregulation and autoimmunity effect. So, balance of immunoregulation and autoimmunity determined prevention or initiation if T1D. It has been suggested, that some viral and bacterial infections could induce HSPs, which up regulated CD4+CD25+ Tregs by TLR2.This process helped organisms to control immunity and prevent T1D (13).

It has been discovered, that during viral infections NO, FAS/FAS-L, IL-1beta, TNF-alpha, IFN-gama, CD4+ and CD8+ were required for Beta cell destruction and development of T1D (13, 57, 58). Some viral infections caused insufficient antiviral response, which activated SOCS (suppressor of cytokine signaling). Cytokine signaling and growth factors were down regulated by SOCS-1, which is known as member of the SOCS protein family. Also IL-6 and IFN-γ were suppressed and JAK-STAT signaling way were inhibited by SOCS-1. Up regulation of SOCS significantly reduced damage of Beta cells, which was caused by direct cytotoxic T cell attack on Beta cells and cytokine mediated cell killing. Concentration of IP-10, IL-1β and IFN-γ outstandingly decreased by SOCS-1. Down regulation of cytokines with SOCS suppressed MHC molecules' expression on Beta cells, which increased survival rate of Beta cells and prevented development of T1D (58).

Diabetes prevented by CVB and LCMV

T1D incidences were reduced or delayed, when NOD mice were infected with Lymphocytic choriomeningitis virus(LCMV) or Coxsackie virus B3(CVB3) (48) and Coxackie virus B4 (CVB4) (47).Reason of T1D delay during CVB3 and LMCV was increased expression of CD4+CD25+ Tregs and programmed cell death ligand 1 (PD-L1),which suppressed diabetic CD8+T cells. CD4+CD25+ Tregs increased production of TGF-β, retained tolerance and reduced incidence of T1D.Synergy of Tregs,C D25+,CD4+ and PL-L1 fully prevented T1D (13, 48). On the other hand, CVB4 induced Tregs with TGF-β avoided development of T1D too. TGF-beta caused up regulation of Tregs and Foxp3, which is specific transcription factor of Tregs. This process delayed T1D.Gene therapy of TGF-beta increased the number of Tregs in pancreas and grew the rate of survival pancreas islet cells (47).

Diabetes prevented by Salmonella

Studies have reported that Salmonella infection prevented development of T1D by dendritic cells (DCs). salmonella activated DCs, which influenced migration of auto-reactive T cells to the pancreas and avoided T1D.DCs activated CD4+CD25+Tregs, that produced TGF-β and suppressed pathogenic T cells, which mediated tolerance. DCs also could prevent T1D by induce indoleamine 2,3 dioxygenase (IDO) and inhibit activity of diabetic T cells (59).

Diabetes and Herpes simplex virus

In the research of 2005 1566 patients were tested to find a connection between T2D and Herpes simplex virus 1 (HSV1). Also they had a control of 1360 patients. In patients with T2D HSV1 infection's prevalence was outstandingly higher compared to control group. In diabetic group HSV1 IgG seropositive patients were significantly more, than HSV1 seronegative patients. HSV1 infection of pancreas leaded initiation of Fas in Beta cells, which caused apoptosis by mediate of Fas/Fas ligand. Also this viral infection caused hemorrhagic necrosis in pancreas, triggered cytokines production and inflammation. During HSV1 infection potential of mitochondrial membrane, level of lactate and ATP were significantly decreased.HSV1 could cause insulin resistance, lose regulation of intramolecular fatty acid metabolism, which was the reason for progressively decreasing phospholipid synthesis and mitochondrial protein synthesis in mitochondria (57).

Diabetes and CMV

Study of 2014 reported, that CMV increased mortality rate in diabetic patients. High level of islet cell autoantibodies, anti-CMV IgG and CMV genome has been found in patients with T1D, who have never got any organ transplant (21). A Cross-sectional study has reported, that during T2D increased level of non-fasting glucose and HbA1c was associated with CMV seropositivity in 549 person aged 85 years (21, 60). CMV increased rate of metabolic disturbance, induced hyperglycemic hyperosmolar state and diabetic ketoacidosis, which increased risk of mortality (21).

Rotavirus prevented diabetes

It has been found, that in infant NOD mice rotavirus with RRV strain increased number of T cells, intraperipheral lymphocytes (IEL), TCR-α,TCR-β,CD8-α,CD8-β in mesenteric lymph nodes. During Rotavirus RRV strain infection thymus grew ratio of CD4+Tregs to Teff (CD4+T effector cells).This process decreased expression of inflammatory T cells response in PLN (pancreatic lymph nodes) and delayed development of T1D (49).

Conclusion

A lot of studies have been conducted to find out if infectious diseases could induce, accelerate or prevent the development of diabetes. Scientists have tested different molecular mechanisms and found out some mediators, genes and molecules, which were connected to initiation of diabetes. The most common reason for diabetes's development was inflammation induced by Infections . They trigger autoimmunity and cause destruction of pancreatic Beta cells. Researches has found out, that different mechanisms, including direct cytolytic effect , Beta cell infection , bystander activation and molecular mimicry was accelerating progression of diabetes. In contrast some studies suggest, that infections and inflammatory signaling could prevent the development of T1D.Immunity caused by viral infections could enhance resistance against diabetic infections. During this process T cells are controlled by multiple immunoregulatory mechanisms. In conclusion more research is needed for clarification of the immunopathogenic mechanisms linking infections and diabetes .

Table 1— infections which can cause diabetes

Infections	Mechanism	References
Cytomegalovirus	1.Beta cell infection; 2.Clonal activation of T cells; 3.Cross-Reactivity between CMV protein pU57 and GAD65, Hsp60; 4.Bystander activation ;	(4, 7, 21)
Hepatitis C	Bystander activation	(8, 22, 23)
Encephalomyocarditis virus	1.Direct destruction of Beta cells; 2.Bystander activation	(5, 24, 25)
H.pylori	1.Bystander activation; 2.Activation of macrophages and neutrophils, which leads infiltration and inflammation ;	(11, 26)
Echovirus	1.Direct cytolytic effect; 2.Beta cell infection; 3.Bystander activation; 4.Molecular mimicry ;	(12, 27, 28)
Parvovirus	1.Disbalance between T effector and T regulatory cells; 2.TLR signaling pathway induced immune response 3.Bystander activation ;	(9, 29)
HIV	1. Systemic inflammation 2. Gut microbiota	(14, 15)

Table 2– infections which accelerate development of Diabetes

Infection	Mechanism	References
Enterovirus Coxsackie virus	1.Direct cytolytic effect on Beta cells; 2.Molecular mimicry; 3.Bystander activation	(33-35, 37-39, 41)
Mumps	1. Beta cell infection without cytolytic effect; 2.Increased HLA I, HLA II expression on Beta cells ;	(43)
Rubella	1.Beta cell infection without cytolytic effect; 2.Molecular mimicry, cross reactivity between GAD and Rubella antigens	(6, 43)
Rotavirus	1.Molecular mimicry; 2.initiation of auto reactive T cells	(33, 40, 44-46)

Table 3– infections which prevent development of diabetes

Infections	Mechanism	References
CVB	Up regulation of PD-L1, which suppressed cytotoxic T cells ;	(13, 47, 48)
LMCV	Up regulation of PD-L1, which suppressed cytotoxic T cells ;	(13, 47, 48)
Salmonella	Activation of DCs and suppression of pathogenic T cells ;	(59)
Rotavirus	Virus increased number of T regulatory cells ;	(49)

Figure 1– Parvovirus induced diabetes

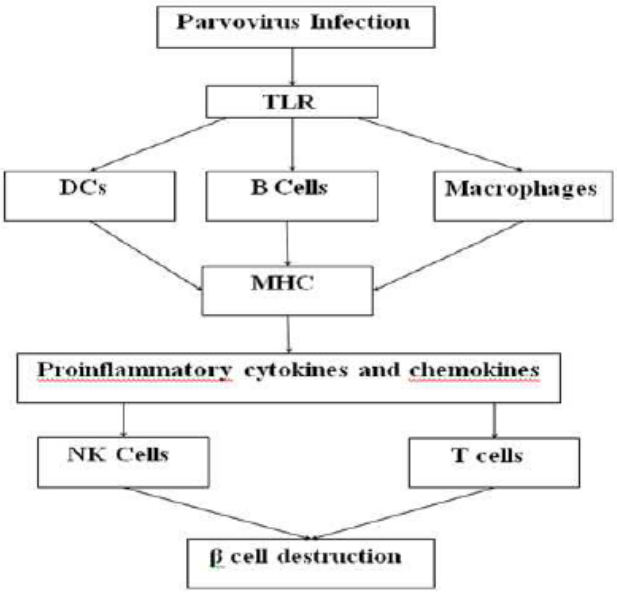
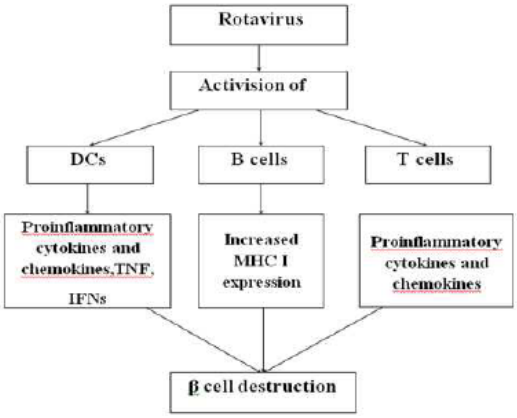


Figure 2– Mechanism how Rotavirus Accelerate development of diabetes



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