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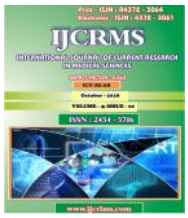

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Review on Human Microbiome and their implication in Type 1 Diabetes

V. Poorna Pushkala
Reader, Sri Sairam Siddha Medical College and Research Centre, Sai Leo Nagar, Poonthandalam, West Tambaram, Chennai, 600044, Tamil Nadu, India
E-mail: *poorna.mku@gmail.com*

Abstract

Type 1 diabetes (T1D) is characterized by progressive pancreatic beta-cell loss resulting in insulin deficiency and hyperglycemia. It not only involves genetic predisposition, but the environmental factors and human microbiome also plays a major role in inducing T1D. Some viruses are diabetogenic in animals and the pathogenesis of various viruses like *Enteroviruses, rubella viruses, cytomegaloviruses* and *Epstein-Barr* viruses in the pathogenesis of human IDDM (Insulin-dependent diabetes mellitus) has been studied widely. It is very much true that human microbiome correlates highly with diabetes and several studies prove this correlation. A study conducted in 2012 showed that *Human Enterovirus (HEV)* infections rank high as an environmental risk factor for triggering T1D through observational studies in humans and experimental studies in mice. It has also been reported that *HEV* exposure prior to development of autoimmune insulitis, can help in preventing T1D onset. Another study proves that *Enterovirus* infections can serve as a major trigger for T1D in the young, as it involves the induction of islet-cell antibodies. These results have been proved by numerous epidemiological surveys and also using PCR methods and HLA-typing. Moreover, besides *Enterovirus* infections, several other viruses have also been proved to be associated with diabetes like *Coxsackie virus* and *Echo virus*. The pathogenesis of viral infection in inducing T1D is reported to be either directly by altering beta cell function thereby leading to the activation of apoptotic pathways or indirectly by the expression of proinflammatory cytokines and chemokines, proves a study. Bacteriology of the cases of cellulitis and cutaneous abscess shows that gram-negative pathogens were not more common among diabetics than non-diabetics; however they were more likely than non-diabetics to be exposed to broad gram-negative therapy. In conclusion, genetics, diet and Diabetes always go hand in hand according to the common world. The main aim of the present review is to provide detailed description on pathogenesis and current scenario on human microbiome and their role in T1D.

Keywords: Type-1 Diabetes, IDDM, Human Enterovirus, Proinflammatory cytokines, Microbiome, PCR method, HLA-typing.

Scope and Background

Diabetes mellitus (DM) may be caused by insulin deficiency, insulin resistance, or by a combination of both. Insulin deficiency can be caused by pancreatectomy, pancreatitis, alcoholic chronic pancreatitis, hemochromatosis, cystic fibrosis, mitochondrial DNA mutations, or by drugs/toxins. Insulin deficiency may lead to type 1 diabetes mellitus (T1DM) which may be autoimmune or idiopathic in nature and is present in 9% cases of insulin deficiency. Insulin resistance may also be caused by leprechaunism, autoimmune diseases, lipoatrophy, or endocrinopathies including glucagonoma, pheochromocytoma, acromegaly, Cushing's syndrome, and thyroid disease [1].

T1D is a heterogeneous disorder characterized by destruction of pancreatic beta cells, culminating in absolute insulin deficiency. The majority of cases are attributable to an autoimmune-mediated destruction of beta cells (type 1a) while a small minority of cases results from an idiopathic destruction or failure of beta cells (type 1b). T1D accounts for 5–10% of the total cases of diabetes worldwide [2]. A second and more prevalent category, type 2 diabetes (T2D), is characterized by a combination of resistance to insulin action and inadequate compensatory insulin secretory response[1]. T1D has been historically, and continues to be, the most common type of diabetes in children and adolescents, although type 2 diabetes (T2D) is increasingly diagnosed in youth [3-4].

Prevalence of T1D

The worldwide trend of increased T1D prevalence likelihood has multiple etiologies, which may act through multiple mechanisms. By assessing the T1D prevalence rate data for 118 countries we have shown that globally and regionally population which had greater value of T1D prevalence and secondly, that newborn life expectancy was significantly associated with T1D prevalence rate at population level.

Overall, the operation of natural selection on contemporary populations is declining due to modern medicine [5], but the magnitude of the decline may differ between countries due to their specific level of sanitation, medical interventions and public health measures. Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. [6,7] In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively. According to Wild et al [8], the prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India. It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India, while China (42.3 million) and the United States (30.3 million) will also see significant increases in those affected by the disease [9]. India currently faces an uncertain future in relation to the potential burden that diabetes may impose upon the country. Many influences affect the prevalence of disease throughout a country, and identification of those factors is necessary to facilitate change when facing health challenges.

Impact of diabetes mellitus in India

Preliminary results from a large community study conducted by the Indian Council of Medical research (ICMR) revealed that a lower proportion of the population is affected in states of Northern India (Chandigarh 0.12 million, Jharkhand 0.96 million) as compared to Maharashtra (9.2 million) and Tamil Nadu (4.8 million) [10]. The National Urban Survey conducted across the metropolitan cities of India reported similar trend: 11.7 per cent in Kolkata (Eastern India), 6.1 per cent in Kashmir Valley (Northern India) [11], 11.6 per cent in New Delhi (Northern India), and 9.3 per cent in West India (Mumbai) compared with (13.5 per cent in Chennai (South India), 16.6 per cent in Hyderabad (south India), and 12.4 per cent Bangalore (South India) [12].

Pediatric implication of T1D in India

India accounts for most of the children with T1DM in South-East Asia. According to the 6th edition of the International Diabetes Federation diabetes atlas, India has 3 new cases of T1DM/100,000 children of 0–14 years [13]. The prevalence of diabetes in India is variable, and three sets of data show 17.93 cases/100,000 children in Karnataka, 3.2 cases/100,000 children in Chennai, and 10.2 cases/100,000 children in Karnal (Haryana) [14-16]. The bottom line remains that T1DM is quite prevalent and common.

Environmental Factors Contributing to T1D

The following environmental factors have been suspected to contribute to the development of T1DM: dietary factors, such as cow's milk proteins[17-18], vitamin D deficiency[19-20] and gluten[21]; pancreatic toxins[22-23], such as streptozotocin and nitrites; psychological factors[24]; and viral infection factor[25]. Viruses are among the most probable environmental factors in the development of T1DM, including rubella virus[26], rotavirus[27], mumps virus, cytomegalovirus and enteroviruses[28-30]. Recent studies using different approaches have suggested that the most promising candidates for viral triggers with clinically significant associations with T1DM development are enteroviruses[31-34].

Viral infection

However, it has been difficult to establish viruses as the inducers of T1DM. First, the link between infections and autoimmunity is multifactorial[35]. Several infections may act together or in an appropriate temporal sequence to trigger clinical autoimmunity. Furthermore, the particular virus that is involved in triggering T1DM may be hard to detect systemically or in the target organ after the initiation of the autoimmune response[36]. Second, the long duration of time between the possible triggering effect and the onset of the clinical symptoms of diabetes makes it difficult to establish a direct relationship. Third, T1DM patients and healthy individuals undergo multiple viral infections during their lifetime, and several of these viruses may even protect individuals from autoimmune disease[37-38]. Fourth, the "fertile field hypothesis" suggests that viral infections render tissue a "fertile ground" for autoaggressive lymphocytes to invade and expand, which leads to T1DM[39-40]. Therefore, the activation of the immune system may have a role in the pathogenesis of this disease[41].

Enterovirus infections

Enterovirus infections are transmitted from person to person by fecal-oral and, less commonly, respiratory routes, which indicates that these infections usually begin in the gastrointestinal or respiratory mucosa. After replicating in the mucosa, the virus spreads through the lymphatic system into the circulation after a brief viremic phase at secondary replication sites, which determines the types of symptoms[42].In humans, *enterovirus* infection has been suspected to be involved in the pathogenesis of T1DM since the late 1960s, when Gamble et al described a seasonal variation in the incidence of T1DM following *enterovirus* infection[43] and demonstrated that the frequency of neutralizing antibodies against the *CVB4* serotype was increased in newly diagnosed T1DM patients[44]. A *CVB4* virus was subsequently isolated from the pancreas of a child who died from diabetic ketoacidosis, and this virus strain caused diabetes in a susceptible mouse strain[45].

Enteroviruses are perhaps the most well studied environmental factor in relation to type 1 diabetes. A possible link was first reported by Gamble et al in 1969,[46] with many subsequent studies, in humans and animal models of diabetes, showing an association, particularly with coxsackievirus B-4. Higher rates of enterovirus infection, defined by detection of enterovirus IgM or IgG, or both, viral RNA with reverse transcription polymerase chain reaction (RT PCR), and viral capsid protein, have been found in patients with diabetes at diagnosis compared with controls [47-53]. Prospective studies have also shown more enterovirus infections in children who developed islet autoantibodies or

subsequent diabetes, or both; as well as a temporal relation between infection and autoimmunity [54-56].

Enterovirus mediated beta cell destruction

Beta cell destruction/dysfunction in T1D would result from an autoimmune process [57] and the role of EV in the scenario should not be thought as a massive lytic replication in islets. The implication of the virus relies on the immune response, and especially the production of type 1 interferons (IFNs) and other pro-inflammatory cytokines. Indeed, the terms of the interaction between the virus and the innate immune system determine the susceptibility to this EV-mediated autoimmune diabetes, and could justify why such infection do not trigger T1D in every patient. The scenario leading to the disease is thought to include the production of significant amounts of IFNs, through activation of pathogen recognition receptors (PRRs). This inflammatory environment contributes to the initiation of autoimmune destruction of beta cells.

Common identification techniques of Ev infection in T1D

In situ hybridization

Primary screening of enterovirus was carried out on formalin-fixed and paraffin-embedded biopsy samples (5-µm sections) using an in situ hybridization (ISH) assay as previously described [58-60]. This is based on a single enterovirus-specific probe targeting a highly conserved, group-common sequence in the 5′-noncoding region of the enteroviral genome.

Immunohistochemical staining

Formalin-fixed paraffin-embedded biopsy samples (5-µm sections) were stained with antienterovirus VP1 antibody.

RT-PCR Method

For RT-PCR, unfixed biopsy samples were stored frozen in optimal cutting temperature medium at −70°C. The biopsy samples were removed from the optimal cutting temperature medium and homogenized using a SilentCrusher S homogenizer (Heidolph, Schwabach, Germany). RNA was extracted with the RNeasy Mini Kit (Qiagen, Hilden, Germany). RT-PCR was performed using two independent methods: a previously described method amplifying a sequence common to all known enterovirus serotypes [61] and a real-time RT-PCR using the same primers and probes.

Clinical Management

Insulin therapy

Insulin therapy is the cornerstone of management of T1D as beta cell dysfunction or destruction progressively leads to absolute insulin deficiency. Physiologic insulin replacement that aims to mimic normal pancreatic insulin secretion is the preferred method of treatment of T1D patients. Basal insulin is the background insulin required to suppress hepatic glucose production overnight and between meals. Prandial (bolus or meal-time) insulin replacement, provides enough insulin to dispose of glucose after eating. Such a therapeutic insulin regimen providing both basal and bolus insulin allows flexibility of dosing. Older twice-daily combination of regular and NPH regimens generally should not be used in T1D as they are less effective since the time-action profile of these two standard insulins do not readily allow for the clear separation of basal and prandial insulin action. However, it may be necessary to use such regimens in patients who cannot otherwise afford insulin. It also should be pointed out that for newly diagnosed patients with T1D, transient use of once- or twice-daily basal injections is sometimes adequate [62].

Insulin pumps

Insulin pumps and continuous glucose monitors (CGM) are advanced diabetes management devices that may lead to improved glycemic control compared to traditional insulin injections with self-monitoring of blood glucose (SMBG) [63-68]. Compared to injections, insulin pump therapy offers a more physiologic method of insulin delivery by simulating the normal diurnal

pattern of basal insulin secretion in conjunction with prandial or correction boluses [69]. CGM is an emerging technology that provides a continuous measure of interstitial fluid glucose levels to provide real-time trends and alerts to glucose excursions [70]. Despite their potential benefit for improving glycemic control, uptake of these technologies has been limited with 60% of T1D Exchange Registry participants use an insulin pump and a mere 11% using CGM [71].

Whole pancreas transplant

Despite developments in closed loop systems and encouraging results from insulin gene therapy, completely mimicking the beta cells still remained a distant dream. Thus, pancreas transplant was considered as a viable option. Whole pancreas transplant was tried initially in patients requiring kidney transplant but complications were galore like pseudocyst, fistula, thrombosis and pancreatitis. Moreover, transplanting the whole pancreas when the patients were only in need of the islets of Langerhans which constitute a meagre 2% of the pancreatic mass was like losing the battle for want of a horse shoe nail[72].

Islet Cell transplant

In addition to transplanting only the endocrine component, islet cell transplantation is minimally invasive and is associated with lower morbidity. After pancreas retrieval, the islets are isolated and cultured which is the most formidable step in the whole procedure. The most commonly used anatomical site for islet transplant is the liver due to the convenience of access and good entrapment and engraftment in the sinusoids though spleen, renal capsule and the gonads have been tried[73]. Islet cell transplantation done in animals resulted in universal reversal of diabetes but reproduction of these results in human beings was a Himalayan task in the 1990s as only 11% achieved insulin independence. However, in 2009, the Collaborative Islet Transplant Registry reported that the overall incidence of sustained graft function was 77% after first 6 mo, 66% after 1 and 45% at 3 years[74]. Though independence from exogenous insulin can be achieved, extrapolation of results from studies done in adults to children with type 1 diabetes mellitus (T1DM) would be a precocious decision and awaits more research.

Stem cell therapy

The interest stem cell therapy created in almost all chronic diseases is also reverberating in type 1 diabetes. Generation of sufficient mass of beta cells, releasing insulin in response to physiological signals and protection from autoimmunity is the most important challenges. Stem cells can be converted to beta cells by sequential transient activation of specific transcription factors like Pa x 4, Nk x 6.1 and Nk x 2.2[75]. The possibility of teratogenicity with embryonal stem cells makes mesenchyme derived stem cells a better option. An alternative approach is by neogenesis of beta cells from mature beta cells with the use of GLP analogue (Exendin), Epidermal Growth Factor and gastrin. The common endodermal origin of pancreas, liver and small intestine allows trans-differentiation of any of these cell types to beta cells[76]. Trans-differentiation involves reprogramming mature cells by certain transcription factors into alternate developmental lineages.

Summary

Type 1 diabetes (T1D) is an autoimmune disease with a strong genetic component [77-78]. It can occur at any age, but tends to develop in childhood,[79] so it has long been called ‘juvenile diabetes’. T1D is characterized by destruction of pancreatic β-cells, culminating in absolute insulin deficiency [80]. As of 2014, an estimated 387 million people have diabetes worldwide, [81] of which T1D accounts for between 5% and 10% [82]. Diabetic complications continue to be a major cause of morbidity and mortality in persons with T1D [83]. Great efforts have been made to assess the incidence and prevalence of T1D. Unfortunately, the exact etiology and pathogenesis of T1D is still unknown. Generally, longitudinal or cross-sectional studies are often locally or regionally performed. Consequently, it is difficult to access generalizable results because

the epidemiology of T1D is known to be heterogeneous regarding geography and ethnicity. Genetic predisposition to T1D is only alleged to explain some of the geographic variability in T1D occurrence, but it cannot account for its rapidly increasing frequency [84].

The incidence of type 1 diabetes varies among different countries, which reflects the roles played by genetic and environmental factors in the ultimate expression of the disease. It varies from 57.4 cases/100000 per year in Finland to 0.6 cases/100000 per year in India[85]. The fact that there is a rising trend in the number of children diagnosed to have type 1 diabetes is supported by a number of studies. Whether this can be attributed to an absolute increase in the incidence of the disease is still under speculation because the proportion of children with highest risk human leukocyte antigen haplotypes have decreased and hence, the changing environmental patterns may rather be uncovering the latent genetic factors to cause earlier expression of the disease[86]T1D was thought only to be of genetic and environmental origin in early days. The viral etiology of T1D onset has been proved to be important in recent researches and studies. Both human gut microbiome and viral infections play a major role in T1D development. EV infections and other viruses like Mumps, Rubella, CMV, EBV, etc. were found to be the causes of T1D onset.

T1D incidence was very rare in the history but has increased in recent years. The reason for this rise is believed to be the constant microbial stimulation in early days and lack of this exposure to microbes in the modern world. The steps involved in viral infection and the role of viruses in T1D pathogenesis showed that EV viral infections alter the beta cell function by modulating the genes responsible for glucose oxidation and thereby leading to the development of T1D. These studies suggests that viral infection causes damage to beta cells either directly by causing functional impairment and damage of beta cells or indirectly by inducing the expression of proinflammatory cytokines and chemokines. These viral infections need to be prevented or treated to prevent T1D onset and development [87].Clinicians may be targeted to facilitate the implementation of screening and early detection programmes, diabetes prevention, self-management counselling, and therapeutic management of diabetes in accordance with the appropriate local guidelines form the backbone of controlling the predicted diabetes epidemic.

Diabetes is an expensive illness to treat even in developing countries, although the pattern of costs was quite different from that of developed ones. There is a need to increase awareness of these facts among all health professionals involved in the care of diabetes in developing countries as well as health policy makers of these countries. This work also makes it clearly evident that the largest share of costs was being borne by patients and their families. Any efforts at cost reduction should, therefore, have the family as its focus, and relieving the family of this financial burden needs to be prioritized.

Diabetes mellitus is reaching potentially epidemic proportions in India. The level of morbidity and mortality due to diabetes and its potential complications are enormous, and pose significant healthcare burdens on both families and society. Worryingly, diabetes is now being shown to be associated with a spectrum of complications and to be occurring at a relatively younger age within the country. In India, the steady migration of people from rural to urban areas, the economic boom, and corresponding change in life-style are all affecting the level of diabetes.

References

1. Ashok Kumar Das. Type 1 diabetes in India: Overall insights. Indian J EndocrinolMetab. 2015 ; 19:31-33.
2. Diagnosis and classification of diabetes mellitus. Diab care. 2009;32 (Suppl 1):S62–S67.
3. Liese AD, D'Agostino RB, Jr, Hamman RF, et al. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. peds. 2006;118:1510–1518.

4. Dabelea D, Bell RA, D'Agostino RB, Jr, et al. Incidence of diabetes in youth in the United States. JAMA. 2007;297:2716–2724.
5. Stephan CN, Henneberg M. Medicine may be reducing the human capacity to survive. Med Hypotheses 2001;57:633–7
6. Joshi SR, Parikh RM. India - diabetes capital of the world: now heading towards hypertension. J Assoc Physicians India. 2007;55:323–4.
7. Kumar A, Goel MK, Jain RB, Khanna P, Chaudhary V. India towards diabetes control: Key issues. Australas Med J. 2013;6(10):524–31.
8. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes-estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(3):1047–53.
9. Whiting Dr, Guariguata L, Weil C, Shawj. IDF Diabetes atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res ClinPract. 2011;94:311–21.
10. Anjana RM, Ali MK, Pradeepa R, Deepa M, Datta M, Unnikrishnan R, Rema M, Mohan V. The need for obtaining accurate nationwide estimates of diabetes prevalence in India - rationale for a national study on diabetes. Indian J Med Res. 2011;133:369–80.
11. Zargar AH, Khan AK, Masoodi SR, Laway BA, Wani AI, Bashir MI, Dar FA. Prevalence of type 2 diabetes mellitus and impaired glucose tolerance in the Kashmir Valley of the Indian subcontinent. Diabetes Res ClinPract. 2000;47(2):135–46.
12. Ramachandran A, Snehalatha C, Kapur A, Vijay V, Mohan V, Das AK, Rao PV, Yajnik CS, Prasanna Kumar KM, Nair JD. Diabetes Epidemiology Study Group in India (DESI). High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. Diabetologia. 2001;44(9):1094–101.
13. Aguiree F, Brown A, Cho NH, Dahlquist G, Dodd S, Dunning T, et al. 6th ed. Brussels, Belgium: International Diabetes Federation; 2013. IDF Diabetes Atlas.
14. Ramachandran A, Snehalatha C, Krishnaswamy CV. Incidence of IDDM in children in urban population in southern India. Madras IDDM Registry Group Madras, South India. Diabetes Res ClinPract. 1996;34:79–82.
15. Kalra S, Kalra B, Sharma A. Prevalence of type 1 diabetes mellitus in Karnal district, Haryana state, India. Diabetol Metab Syndr. 2010;2:14.
16. Kumar P, Krishna P, Reddy SC, Gurappa M, Aravind SR, Munichoodappa C. Incidence of type 1 diabetes mellitus and associated complications among children and young adults: Results from Karnataka Diabetes Registry 1995-2008. J Indian Med Assoc. 2008;106:708–11.
17. Gerstein HC. Cow's milk exposure and type I diabetes mellitus. A critical overview of the clinical literature. Diabetes Care. 1994;17:13–19.
18. Couper JJ, Steele C, Beresford S, Powell T, McCaul K, Pollard A, Gellert S, Tait B, Harrison LC, Colman PG. Lack of association between duration of breast-feeding or introduction of cow's milk and development of islet autoimmunity. Diabetes. 1999;48:2145–2149.
19. Jankosky C, Deussing E, Gibson RL, Haverkos HW. Viruses and vitamin D in the etiology of type 1 diabetes mellitus and multiple sclerosis. Virus Res. 2012; 163:424–430.
20. Hyppönen E, Läärä E, Reunanen A, Järvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet. 2001; 358:1500–1503.
21. Sarmiento L, Galvan JA, Cabrera-Rode E, Aira L, Correa C, Sariego S, Fonseca M, Cubas-Dueñas I, Hung LH, Resik S, et al. Type 1 diabetes associated and tissue transglutaminase autoantibodies in patients without type 1 diabetes and coeliac disease with confirmed viral

infections. J Med Virol. 2012;84:1049–1053.
22. Ganda OP, Rossini AA, Like AA. Studies on streptozotocin diabetes. Diabetes. 1976;25:595–603.
23. Myers MA, Mackay IR, Rowley MJ, Zimmet PZ. Dietary microbial toxins and type 1 diabetes--a new meaning for seed and soil. Diabetologia. 2001;44:1199–1200.
24. Hägglöf B, Blom L, Dahlquist G, Lönnberg G, Sahlin B. The Swedish childhood diabetes study: indications of severe psychological stress as a risk factor for type 1 (insulin-dependent) diabetes mellitus in childhood. Diabetologia. 1991;34:579–583.
25. Filippi CM, von Herrath MG. Viral trigger for type 1 diabetes: pros and cons. Diabetes. 2008;57:2863–2871.
26. Gale EA. Congenital rubella: citation virus or viral cause of type 1 diabetes? Diabetologia. 2008;51:1559–1566.
27. Blomqvist M, Juhela S, Erkkila S, Korhonen S, Simell T, Kupila A, Vaarala O, Simell O, Knip M, Ilonen J. Rotavirus infections and development of diabetes-associated autoantibodies during the first 2 years of life. Clin Exp Immunol. 2002;128:511–515.
28. Coppieters KT, Boettler T, von Herrath M. Virus infections in type 1 diabetes. Cold Spring Harb Perspect Med. 2012; 2:a007682.
29. Roivainen M, Klingel K. Virus infections and type 1 diabetes risk. CurrDiab Rep. 2010;10:350–356.
30. Hober D, Alidjinou EK. Enteroviral pathogenesis of type 1 diabetes: queries and answers. Curr Opin Infect Dis. 2013;26:263–269.
31. Hober D, Sauter P. Pathogenesis of type 1 diabetes mellitus: interplay between enterovirus and host. Nat Rev Endocrinol. 2010;6:279–289.
32. Tracy S, Drescher KM, Chapman NM. Enteroviruses and type 1 diabetes. Diabetes Metab Res Rev. 2011;27:820–823.
33. Diaz-Horta O, Baj A, Maccari G, Salvatoni A, Toniolo A. Enteroviruses and causality of type 1 diabetes: how close are we? Pediatr Diabetes. 2012;13:92–99.
34. Jaïdane H, Sauter P, Sane F, Goffard A, Gharbi J, Hober D. Enteroviruses and type 1 diabetes: towards a better understanding of the relationship. Rev Med Virol. 2010;20:265–280.
35. Filippi C, von Herrath M. How viral infections affect the autoimmune process leading to type 1 diabetes. Cell Immunol. 2005;233:125–132.
36. Sané F, Moumna I, Hober D. Group B coxsackieviruses and autoimmunity: focus on Type 1 diabetes. Expert Rev ClinImmunol. 2011;7:357–366.
37. Christen U, Hintermann E, Holdener M, von Herrath MG. Viral triggers for autoimmunity: is the ‚glass of molecular mimicry' half full or half empty? J Autoimmun. 2010;34:38–44.
38. Rook GA. Hygiene hypothesis and autoimmune diseases. Clin Rev Allergy Immunol. 2012;42:5–15.
39. Veld P. Insulitis in the human endocrine pancreas: does a viral infection lead to inflammation and beta cell replication? Diabetologia. 2011;54:2220–2222.
40. Fujinami RS, von Herrath MG, Christen U, Whitton JL. Molecular mimicry, bystander activation, or viral persistence: infections and autoimmune disease. ClinMicrobiol Rev. 2006;19:80–94.
41. vonHerrath MG, Fujinami RS, Whitton JL. Microorganisms and autoimmunity: making the barren field fertile? Nat Rev Microbiol. 2003;1:151–157.
42. Roivainen M. Enteroviruses: new findings on the role of enteroviruses in type 1 diabetes. Int J Biochem Cell Biol. 2006;38:721–725.
43. Craig ME, Nair S, Stein H, Rawlinson WD. Viruses and type 1 diabetes: a new look at an old story. Pediatr Diabetes. 2013;14:149–158.

44. Gamble DR, Taylor KW, Cumming H. Coxsackie viruses and diabetes mellitus. Br Med J. 1973;4:260–262.
45. Yoon JW, Austin M, Onodera T, Notkins AL. Isolation of a virus from the pancreas of a child with diabetic ketoacidosis. N Engl J Med. 1979;300:1173–1179.
46. Gamble D, Kinsley M, Fitzgerald M, Bolton R, Taylor K. Viral antibodies in diabetes mellitus. BMJ 1969;3:627.
47. Helfand RF, Gary HE Jr, Freeman CY, Anderson LJ, Pallansch MA. Serologic evidence of an association between enteroviruses and the onset of type 1 diabetes mellitus. Pittsburgh Diabetes Research Group. J Infect Dis 1995;172:1206-11.
48. Nairn C, Galbraith DN, Taylor KW, Clements GB. Enterovirus variants in the serum of children at the onset of type 1 diabetes mellitus. Diabet Med 1999;16:509-13.
49. Lönnrot M, Korpela K, Knip M, Ilonen J, Simell O, Korhonen S, et al. Enterovirus infection as a risk factor for beta-cell autoimmunity in a prospectively observed birth cohort: the Finnish Diabetes Prediction and Prevention Study. Diabetes 2000;49:1314.
50. Andreoletti L, Hober D, Hober-Vandenberghe C, Belaich S, Vantyghem MC, Lefebvre J, 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;52:121-7.
51. Craig ME, Howard NJ, Silink M, Rawlinson WD. Reduced frequency of HLA DRB1*03-DQB1*02 in children with type 1 diabetes associated with enterovirus RNA. J Infect Dis2003;187:1562-70.
52. Sarmiento L, Cabrera-Rode E, Lekuleni L, Cuba I, Molina G, Fonseca M, et al. Occurrence of enterovirus RNA in serum of children with newly diagnosed type 1 diabetes and islet cell autoantibody-positive subjects in a population with a low incidence of type 1 diabetes. Autoimmunity 2007;40:540-5.
53. Richardson S, Willcox A, Bone A, Foulis A, Morgan N. The prevalence of enteroviral capsid protein vp1 immunostaining in pancreatic islets in human type 1 diabetes. Diabetologia 2009;52:1143-51.
54. Hyöty H, Hiltunen M, Knip M, Laakkonen M, Vähäsalo P, Karjalainen J, 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;44:652.
55. Hiltunen M, Hyöty H, Knip M, Ilonen J, Reijonen H, Vähäsalo P, et al. Islet cell antibody seroconversion in children is temporally associated with enterovirus infections. J Infect Dis1997;175:554-60.
56. Salminen K, Sadeharju K, Lönnrot M, Vähäsalo P, Kupila A, Korhonen S, et al. Enterovirus infections are associated with the induction of beta-cell autoimmunity in a prospective birth cohort study. J Med Virol 2003;69:91-8.
57. Roep B.O., Tree T.I.M. Immune modulation in humans: implications for type 1 diabetes mellitus. Nat. Rev. Endocrinol. 2014;10:229–242.
58. Oikarinen M, Tauriainen S, Honkanen T, et al. Analysis of pancreas tissue in a child positive for islet cell antibodies. Diabetologia 2008;51:1796–1802.
59. Oikarinen M, Tauriainen S, Honkanen T, et al. Detection of enteroviruses in the intestine of type 1 diabetic patients. Clin ExpImmunol 2008;151:71–75
60. Oikarinen M, Tauriainen S, Penttilä P, et al. Evaluation of immunohistochemistry and in situ hybridization methods for the detection of enteroviruses using infected cell culture samples. J Clin Virol 2010; 47:224–228
61. Lönnrot M, Sjöroos M, Salminen K, Maaronen M, Hyypiä T, Hyöty H. Diagnosis of enterovirus and rhinovirus infections by RT-PCR and time-resolved fluorometry with lanthanide chelate labeled probes. J Med Virol 1999;59:378–384.

62. Savitha Subramanian. The Management of Type 1 Diabetes. De Groot LJ, Chrousos G, Dungan K, et al., editors.South Dartmouth (MA): MDText.com, Inc.; 2000.
63. Johnson S. R., Cooper M. N., Jones T. W., Davis E. A. Long-term outcome of insulin pump therapy in children with type 1 diabetes assessed in a large population-based case-control study. *Diabetologia*. 2013;56(11):2392–2400.
64. Pickup J. C., Sutton A. J. Severe hypoglycaemia and glycaemic control in type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabetic Medicine*. 2008; 25(7): 765–774.
65. Beck R. W., Hirsch I. B., Laffel L., et al. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care*. 2009;32:1378–1383.
66. Deiss D., Bolinder J., Riveline J. P., et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. *Diabetes Care*. 2006; 29(12): 2730–2732.
67. Rachmiel M., Landau Z., Boaz M., et al. The use of continuous glucose monitoring systems in a pediatric population with type 1 diabetes mellitus in real-life settings: the AWeSoMe study group experience. *Acta Diabetologica*. 2015;52(2):323–329.
68. Karges B., Schwandt A., Heidtmann B., et al. Association of insulin pump therapy vs insulin injection therapy with severe hypoglycemia, ketoacidosis, and glycemic control among children, adolescents, and young adults with type 1 diabetes. *JAMA*. 2017;318(14):1358–366.
69. Pickup J. C. Insulin-pump therapy for type 1 diabetes mellitus. *The New England Journal of Medicine*. 2012;366(17):1616–1624.
70. DeSalvo D., Buckingham B. Continuous glucose monitoring: current use and future directions. *Current Diabetes Reports*. 2013;13(5):657–662. doi: 10.1007/s11892-013-0398-4.
71. Miller K. M., Foster N. C., Beck R. W., et al. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D exchange clinic registry. *Diabetes Care*. 2015;38(6):971–978.
72. Jahansouz C, Kumer SC, Ellenbogen M, Brayman KL. Evolution of β-Cell Replacement Therapy in Diabetes Mellitus: Pancreas Transplantation. Diabetes TechnolTher. 2011;13:395–418.
73. Bellin MD, Kandaswamy R, Parkey J, Zhang HJ, Liu B, Ihm SH, Ansite JD, Witson J, Bansal-Pakala P, Balamurugan AN, et al. Prolonged insulin independence after islet allotransplants in recipients with type 1 diabetes. Am J Transplant. 2008;8:2463–2470.
74. Vantyghem MC, Kerr-Conte J, Arnalsteen L, Sergent G, Defrance F, Gmyr V, Declerck N, Raverdy V, Vandewalle B, Pigny P, et al. Primary graft function, metabolic control, and graft survival after islet transplantation. Diabetes Care. 2009;32:1473–1478.
75. Takeuchi H, Nakatsuji N, Suemori H. Endodermal differentiation of human pluripotent stem cells to insulin-producing cells in 3D culture. Sci Rep. 2014;4:4488.
76. Berneman-Zeitouni D, Molakandov K, Elgart M, Mor E, Fornoni A, Domínguez MR, Kerr-Conte J, Ott M, Meivar-Levy I, Ferber S. The temporal and hierarchical control of transcription factors-induced liver to pancreas transdifferentiation. PLoS One. 2014; 9: e87812.
77. Noble JA, Erlich HA. Genetics of type 1 diabetes. Cold Spring HarbPerspect Med 2012;2:1–15.

78. Steck AK, Rewers MJ. Genetics of type 1 diabetes. ClinChem 2011;57:176–85.
79. Frese T, Sandholzer H. The epidemiology of type 1 diabetes mellitus. In: Escher S, Li A., eds. type 1 diabetes. InTech, 2013:1–22.
80. Maahs DM, West NA, Lawrence JM et al. Epidemiology of type 1 diabetes. EndocrinolMetabClin North Am 2010;39:481–97.
81. International Diabetes Federation. Key findings 2014.
82. Melmed S, Polonsky SK et al. Williams textbook of endocrinology. 12th edn Philadelphia: Elsevier/Saunders, 2011.
83. Libby P, Nathan DM, Abraham K et al. Report of The National Heart, Lung, and Blood Institute—National Institute of Diabetes and Digestive and Kidney diseases working group on cardiovascular complications of type 1 diabetes mellitus. Circulation 2005;111:3489–93 93.
84. Borchers AT, Uibo R, Gershwin ME. The geoepidemiology of type 1 diabetes. Autoimmun Rev2010;9:A355–65.
85. Patterson CC, Dahlquist GG, Gyürüs E, Green A, Soltész G. 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; 373:2027–2033.
86. Weets I, De Leeuw IH, Du Caju MV, Rooman R, Keymeulen B, Mathieu C, Rottiers R, Daubresse JC, Rocour-Brumioul D, Pipeleers DG, et al. The incidence of type 1 diabetes in the age group 0-39 years has not increased in Antwerp (Belgium) between 1989 and 2000: evidence for earlier disease manifestation. Diabetes Care. 2002; 25: 840–846.
87. Kumar A, Goel MK, Jain RB, Khanna P, Chaudhary V. India towards diabetes control: Key issues. Australas Med J. 2013;6(10):524–31.

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