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Review Article

Environmental Triggers' Involvement in the Development of Type 1 Diabetes Mellitus

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Abstract

The huge burden of type 1 diabetes mellitus (T1DM) has been a source of concern globally since the Industrial Revolution in the 18th–19th centuries. To this end, studies have shown that certain environmental changes that accompanied the Revolution may have increased the risk and burden of the disease in genetically predisposed individuals. However, documented studies that synthesize these environmental triggers are scarce. As a result, the current study was conceived to synthesize the environmental triggers of T1DM to boost public awareness. Relevant information was retrieved from reputable academic databases; namely, Scopus, PubMed, SpringerLink, and Embase. The results showed that chemical exposure, viral infection, gut microbiome disruption, vitamin and mineral deficiencies, inadequate or exclusive breastfeeding, as well as early exposure to infant feeding formulas could increase the risk and burden of T1DM in genetically predisposed individuals. As a consequence, these triggers could compromise the expression of certain genes involved in insulin synthesis and immune function, such as the human leukocyte antigen (*HLA*), insulin (*INS*), cytotoxic T lymphocyte-associated antigen 4 (*CTLA-4*), and protein tyrosine phosphatase non-receptor type 22 (*PTPN22*) genes. This would result in a dysfunctional immune system in which immune cells, such as T-cells and B-cells and molecules, such as cytokines would attack self-tissues, thus causing autoimmunity of the pancreatic beta cells. Environmental triggers could also induce the T1DM pathophysiology by modifying the epigenome of the mentioned genes. Furthermore, some epigenetic changes could be reversed, which would infer that treatment procedures that would include the pathophysiology of the environmental triggers could be more effective.

Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder that is characterized by insulin insufficiency.[1] Insulin is a hormone synthesized in the pancreas' islet of Langerhans and normalizes blood glucose by ferrying it into the cells that need it. T1DM is mediated by autoimmunity in which the immune system is tricked into destroying the insulin-producing beta cells. It often affects children and adolescents, but can affect people of other ages, too.[2] Excessive urine excretion, thirst, persistent hunger, emaciation, eyesight abnormalities, and weariness are some of the clinical features of T1DM that might appear unexpectedly.[1] Uncontrolled T1DM can also cause long-term health problems like retinopathy, nephropathy, neuropathy, and vascular diseases.[3]

In addition, the mortality of diabetes mellitus (DM) is high. This disease, together with respiratory diseases, cardiovascular diseases, and cancers, is responsible for at least 80% of all premature deaths resulting from non-communicable diseases.[4] Furthermore, DM affects approximately 422 million people globally, the majority of whom live in low- and middle-income countries.[5]

Keywords: B-cells; beta cells; cytotoxic T lymphocyte-associated antigen 4; epigenome; type 1 diabetes mellitus; T1DM.

Abbreviations: CTLA-4, cytotoxic t lymphocyte-associated antigen 4; DM, diabetes mellitus; HLA, human leukocyte antigen; INS, insulin; PDX1, pancreatic and duodenal homeobox 1; PTPN22, protein tyrosine phosphatase non-receptor type 22; RNA, ribonucleic acid; T1DM, type 1 diabetes mellitus; TLRs, toll-like receptors.

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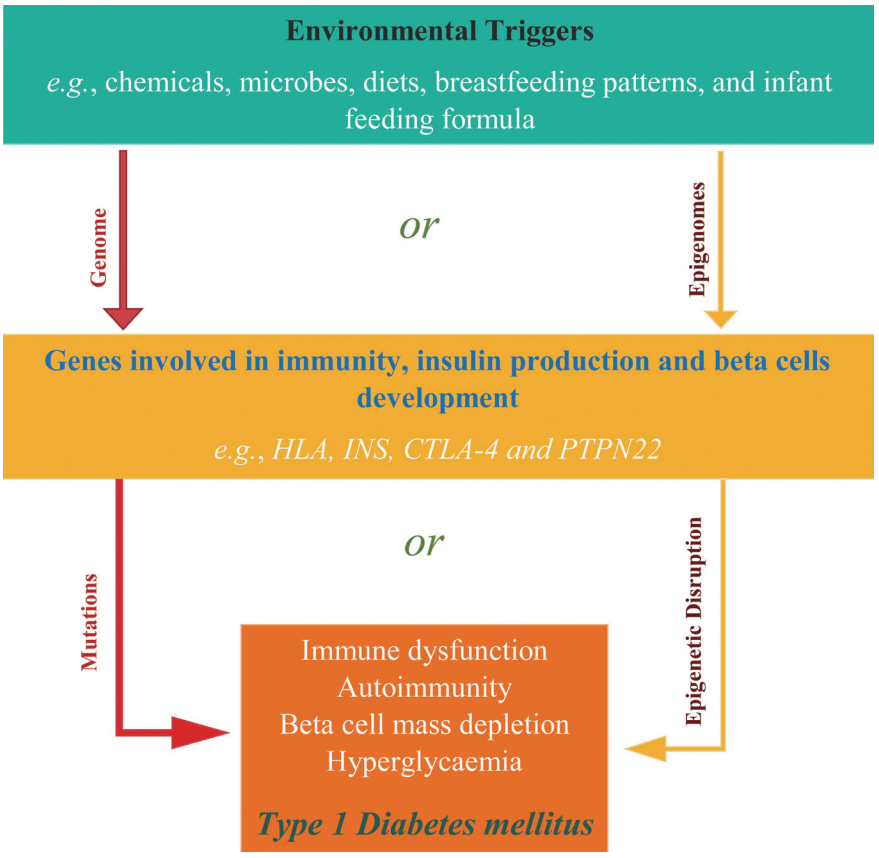

Fig. 1. Etiologies of type 1 diabetes mellitus. HLA, human leukocyte antigen; INS, insulin; CTLA-4, cytotoxic t lymphocyte-associated antigen 4, and PTPN22, protein tyrosine phosphatase non-receptor type 22.

Of this figure, over nine million people live with T1DM, mostly in high-income nations, and only 1.2 million of them are children and adolescents (0–19 years).[6,7] Hence, this would indicate that the disease is becoming more prevalent among older adults. In the United Kingdom, about 8% of the populace lives with T1DM;[8] however, T1DM only affects 0.5% of the population in the United States.[9] Additionally, the prevalence of T1DM is 7.7% in Africa.[10] Globally, the incident rate of T1DM is 9.5%.[11] These figures show that the threat posed by T1DM is significant, so there is an urgent need to reverse it. The widely used treatment option for T1DM is insulin therapy, and this has resulted in a huge economic burden due to the high cost. Moreover, the treatment is painful and stressful because the patient has to receive daily insulin injections.

Considering the mortality and burden of T1DM, a better understanding of the disease is needed to develop complementary novel treatment procedures. T1DM has a strong genetic etiology. However, genetic susceptibility does not account for all cases of the disease, as observed in several studies and clinical manifestations. Evidence from several studies, including Yahaya *et al*.[12] and Yahaya *et al*.,[13] have shown that certain environmental triggers may increase the risk and burden of T1DM in genetically predisposed individuals. Exposure to some environmental triggers may also cause reconfiguration or destruction of beta cells, thus predisposing to T1DM. This shows that the identification and understanding of these triggers may improve the treatment outcome of the affected individuals. Additionally, several environmental triggers of T1DM have been mentioned in the literature, but there is a dearth of documented studies synthesizing these triggers. This current study, therefore, compiled and synthesized the diabetogenic activities of certain environmental triggers.

Environmental triggers of type 1 diabetes mellitus

The genetic constitution of an organism, often referred to as a genome, contains the basic information for the organism to grow and function, but other factors also shape organisms. Phenotypes are shaped by an organism's genome, epigenome, and environmental factors. Environmental factors can thus be described as a collective term for all factors that affect the phenotypes apart from the genetic and epigenetic factors. Environmental factors may act alone to modify the phenotypes and may also influence the phenotypes by interacting with the genes that control the phenotypes or chemical tags above the gene (epigenome), such as the methyl or ethyl groups. Chemicals, microorganisms, micronutrients (vitamins and minerals), breastfeeding, lifestyle, and seasonal changes are some of the environmental factors that may be involved in the onset of T1DM (Fig. 1).

Chemical exposure and development of type 1 diabetes mellitus

Chemical pollutants are diverse, of which the majority are known to cause disease pathologies, including T1DM. Some of the chemi-

cals whose exposure has been linked with T1DM include phthalates, bisphenol A, perfluorinated compounds, polybrominated diphenyl ethers, perfluorinated alkyl substances, and heavy metals.[10] Some others are dichlorodiphenyltrichloroethane, triclosan, polychlorinated piphenyls, dioxins, N-Nitroso compounds, and organotin compounds.[10] Particulate matter and traffic-related pollutants, such as nitrogen dioxide and sulfur dioxide, are also thought to increase the risk of T1DM.

Nevertheless, several mechanisms have been proposed through which chemical exposure (via food, air, or skin) could initiate T1DM. Chemicals could directly destroy beta cells or disrupt the immune cells by binding to important receptors, such as scavenger receptors that would clear lipoproteins, pathogens, and some other molecules that could disrupt immune function.[14,15] Chemicals could also increase mucosal permeability, reduce microbiome diversity, or cause a hormonal imbalance; all of which could result in the dysfunction of the immune system and thus predispose to T1DM.[14] In addition, chemicals could induce epigenetic changes in genes important in beta cell proliferation, maturation, and differentiation, as well as in the immune cells and genes. Some chemicals induce oxidative stress, consequently resulting in altered immune function or immunosuppression, apoptosis, and impaired insulin response.[14] Some may elicit molecular mimicry, thus causing autoimmunity.[14] Airborne chemicals like benzo (a) pyrene (emitted by smoking) and polychlorinated biphenyls have been shown to overexpress programmed cell death protein-1 (*PD-1*) by activating aryl hydrocarbon receptors, which stimulate the body's response to these chemicals.[16] Ozone exposure during the first trimester of pregnancy has been shown to reprogram the fetus and predispose to pediatric diabetes.[17] Furthermore, heavy metals, such as cadmium, nickel, zinc, lead, chromium, mercury, and arsenic, among others could induce oxidative stress causing inflammation as well as beta and islet cell dysfunction and apoptosis.[18,19] An animal study found that hydrogen peroxide (H_2O_2) created a reactive oxygen species and damaged hemoglobin, which made beta cell autoimmunity and T1DM more likely.[20]

Microorganism exposure and development of type 1 diabetes mellitus

Microorganisms, such as bacteria, protozoa, fungi, and viruses, have evolved a wide range of strategies to establish themselves in the host, obtain nutrients, and, in the process, cause damage and initiate disease. These microorganisms have been linked to a lot of different diseases, but bacteria and viruses are the most often linked to T1DM.

Viral infection and type 1 diabetes mellitus

T1DM and viral diseases occur more commonly in the winter, which suggests a link between viral infection and T1DM.[13] Viruses that are associated with T1DM include enteroviruses, such as Coxsackievirus B, as well as cytomegalovirus, adenovirus, rubella, and mumps.[21] A virus may initiate T1DM through molecular mimicry in which the virus mimics self-peptide. Mimicking causes an immune response against self-tissues, therefore causing inflammation and cell death via endoplasmic reticulum stress, which would result in the release of autoantigens and activation of autoreactive T cells.[13] Alternatively, some human enteroviruses (transmitted through food and beverages), including polioviruses, echoviruses, and rhinoviruses, could reach the pancreas where they would be attacked by the immune system along with the beta cells. However, under certain conditions, viral infection may be protective, thus suggesting that viruses would play a dual role in T1DM development.[22] In a study in which coxsackievirus B type 4 isolated from human islets was inoculated into mice and a rat insulinoma cell line, the repression of the *URI* and *PDX1* genes was observed, which affected the β-cell function and identity.[23] In the mentioned study, the *URI* gene was depleted, which caused endoplasmic reticulum nuclear translocation and activated DNA methyltransferase 1 (DNMT1), thus causing *PDX1* promoter hypermethylation and silencing. When the mice were treated with a demethylating agent called procainamide, the *PDX1* expression was restored and protected against diabetes. In another study, inoculating young nonobese and non-insulitis diabetic mice with any strains of coxsackieviruses B increased the interferon expression by the beta cells, which decreased the risk of T1DM.[24] However, when the same virus was given to older, nonobese, and insulitis mice, all of their islets became severely infected, which led to T1DM.

Gut microbiome and type 1 diabetes mellitus

In healthy individuals, the gut microbiome is diverse and contains mainly millions of bacteria species that maintain homeostasis in the body. The gut microbiota diversity is influenced by many factors, including diet and the delivery mode during childbirth. Infants that are delivered naturally inherit gut microbiomes from the mother's vagina, while the bacteria on the mother's skin populate the gut microbiome of infants delivered via C-section.[25] According to Han *et al*.[26] and Zheng *et al*.,[27] cesarean delivery and certain dietary intakes reduced or disrupted gut microbiome diversity. A healthy gut microbiota produced several molecules that were absorbed by the body for several physiological processes, consequently indicating that their disruption could cause diseases.[26] Among other diseases, disrupted intestinal microbiome was linked to the pathophysiology of insulin failure and T1DM, hence suggesting that maintenance of gut microbiota diversity could be a treatment option for diabetics expressing such an etiology.[26] In an experiment, disruption of the gut microbiota preceded the development of T1DM in diabetes-prone bred rats.[28] In particular, Roesch *et al*.[29] noticed a decline in the population of health boosting bacteria, such as *Bryantella*, *Lactobacillus*, *Turicibacter*, and *Bifidobacterium* and an increase in pathogenic bacteria, such as *Bacteroides*, *Ruminococcus*, and *Eubacterium*, in bred diabetic-prone rats compared with diabetes-resistant bred rats. Similarly, in a human study, the guts of healthy children had greater numbers of health boosting bacteria, such as *Lactobacillus*, *Bifidobacterium*, and *Prevotella*, while children expressing T1DM had higher proportions of pathogenic bacteria, including *Clostridium*, *Bacteroides*, and *Veillonella*.[30] In another study, people who had pathogenic bacteria and lacked butyrate-producing bacteria in their fecal microbiota were more likely to have beta-cell autoimmunity and T1DM.[31]

Several mechanisms through which the gut microbiota predisposes to T1DM have been proposed. Toll-like receptors (TLRs), which actively defend the host from pathogenic microorganisms, are derived from gut microbiota.[27] Specifically, TLRs initiate the maturation of dendritic cells, a form of antigen presenting cell which is important in the adaptive immune system. As such, TLRs dysfunctioning through gut microbiota disruption may cause an abnormal immune response, as such predisposing to autoimmunity and T1DM. In another mechanism, gram-negative bacteria may release endotoxin (also called lipopolysaccharide), which would raise the concentrations of pro-inflammatory cytokines, disrupt the pancreatic beta cell function, and cause T1DM.[27] Alternatively, an

altered gut microbiome could increase the permeability of the intestinal mucosal barrier resulting in leaking endotoxin and fatty acids, which would activate TLR4, a member of the toll-like receptor family that would signal the production of inflammatory cytokines. Overall, these mechanisms have shown the importance of a balanced gut microbiome in the maintenance of blood glucose levels and are being used as therapeutic strategies. For instance, daily intake of *Lactobacillus reuteri* was shown to increase the secretion of both insulin and incretin in glucose-tolerant humans.[32] Two separate studies have also shown that the ingestion of VSL#3, a mixture of many probiotics, prevented diabetes in nonobese diabetic mice when administrated from four weeks of age.[33,34]

Vitamin deficiencies and development of type 1 diabetes

Vitamins are necessary for healthy living and their deficiency or excess has been linked with several diseases, including T1DM. Vitamin deficiencies can cause pancreatic cell malfunction, B-cell mortality, diminished islet cell populations, faulty tyrosine kinase activity, and oxidative stress among other physiological and metabolic issues.[35] Among vitamins, vitamin A, B-complex, C, D, and E deficiencies are the most commonly thought to be the causes of T1DM.[36]

Vitamin A is involved in cell growth and differentiation, epithelial cell integrity, and antimicrobial activities, and it promotes antioxidant enzymes and immunological processes.[37] Vitamin A inhibits Teff cells and increases the Treg cell mass, so preventing islet inflammation and thus T1DM.[36] This would suggest that the disruption of vitamin A metabolism could induce autoimmunity, thus leading to T1DM.[37] Vitamin B6 is required for cellular metabolism and functions as an antioxidant, prevention of reactive oxygen species, and advanced glycation end products.[38] Deficiency of vitamin B6 would impair T-cell function, consequently contributing to pancreatic islet autoimmunity in T1DM.[39,40] Folate (Vitamin B9) aids in the completion of essential metabolic processes, the maintenance of a healthy immune system, and the development of healthy neural tubes. Defects in the folate pathway would reduce the immune responses to viral infection or reactivation interfering with signaling and antigen presentation and amplifying CD8+ lymphocyte proliferation and cytotoxicity; all of which are hallmarks of T1DM.[40] Vitamin B12 is required for the formation of red blood cells, DNA, and the development of the nervous system.[41] Oxidative stress, autoimmunity, insulin resistance, beta-cell dysfunction, systemic inflammation, obesity, and endothelial dysfunction are all exacerbated by a vitamin B12 deficiency.[35] Vitamin C protects islet cells from free radical attacks by reducing free radical-mediated oxidation processes.[42] Vitamin C aids in the immune defense by increasing B- and T-cell differentiation and proliferation, as well as enhancing many cellular processes of both the innate and adaptive immune systems.[43] A vitamin C deficiency results in oxidative stress, which impairs immunity and predisposes it to higher susceptibility to infections.[43] Vitamin D receptors are embedded in immune cells (B-cells, T-cells, and antigen-presenting cells), where they use chemical signals to influence innate and adaptive immune responses.[44] As a result, vitamin D reduces the errors committed by the immune cells.[44] Furthermore, particular receptors in pancreatic beta cells turn on only when they receive adequate vitamin D, thus implying that vitamin D has a role in beta-cell function and insulin release.[45] Vitamin D binds to these receptors, so preventing beta-cell death, increasing insulin production, and reducing inflammation.[45] Depletion of vitamin D contributes to beta-cell autoimmunity, insulin insensitivity, and glucose malabsorption.[44] Vitamin E is an antioxidant, which stops free radicals and reactive oxygen species from forming when vitamin A and unsaturated fatty acids are oxidized.[46] Vitamin E protects cells, particularly pancreatic islet cells, by scavenging free radicals and inhibiting invading toxins and cytokines.[47] A vitamin E deficiency causes oxidative stress, which could damage beta cells.[48]

Mineral deficiencies and development of type 1 diabetes

Minerals are essential in maintaining health, and the disruption of their nutritional composition has been linked to several health issues, including T1DM. Among minerals, zinc boosts metabolism and controls several enzymes involved in gene expression, protein folding, and the generation and neutralization of reactive oxygen species.[49] Zinc is also involved in cell signaling, cell division, as well as cytokine production.[49] Zinc deficiency impairs the immunological function, which increases cytokine-induced damage during an autoimmune response, consequently leading to islet cell death in T1DM.[50,51] Physiological calcium (Ca^{2+}) signaling is important for normal β-cells to release insulin effectively.[52] Deficiency of calcium, often called hypoglycemia, impairs the β-cells' ability to secrete insulin, thus resulting in T1DM.[53,54] Selenium mimics insulin, but a prolonged high selenium intake reduces the intracellular reactive oxygen species, which would disrupt the key regulators of the β-cells and insulin production and release.[55] Vanadium complexes mimic insulin and assist the macrophages to produce free radicals free of nitrogen oxide to be used against pathogens, thereby preventing beta-cell autoimmunity and T1DM.[56,57] Omega-3 fatty acids boost cell receptors in cell membranes throughout the body and are necessary for making hormones that regulate inflammation.[12] They also bind to receptors in cells that regulate genetic function.[12] Islet autoimmunity is reduced when omega-3 fatty acids are consumed between the ages of one and six years.[58] Fatty acids are usually linked to islet autoimmunity, except for those that come from fish, which are protective.[59]

Breastfeeding styles and infant feeding formulas and development of type 1 diabetes

Breastfeeding methods and infant feeding formulas may contribute to T1DM pathogenesis. Several bioactive molecules are present in breast milk, which include insulin, cytokines, immunoglobulins, lysozyme, oligosaccharides, lactoferrin, cytokines, health-boosting microorganisms, and several vitamins and minerals, among others.[47] All the mentioned molecules improve the immune system of a breastfeeding infant both directly and indirectly by increasing the gut microbiome diversity and combating pathogenic bacteria and pro-inflammatory compounds.[47] As a result, inadequate or negligent breastfeeding may expose babies to a variety of autoimmune diseases, including T1DM.[47] However, exclusive breastfeeding devoid of vitamin ingestion could lead to a vitamin D deficiency in newborns, especially if the mother's vitamin intake is insufficient. As a consequence, exclusive breastfeeding could also result in a vitamin E deficiency because the vitamin E levels in the breast milk would diminish with the maturation of colostrum.[47] It has also been stated earlier that T1DM could be caused by a lack of both vitamins.[47]

Complementary or total feeding, which includes nutritional formulas having certain complex proteins could also increase the T1DM risk of infants.[60,61] Bovine insulin in cow's milk, for example, varies from human insulin by three amino acids and can induce immunological reactions in infants.[12] Some proteins in cow's milk,

especially the beta-casein A1 molecule, differ significantly from those in human breast milk. These proteins are tightly bonded and are difficult for mammals with only one stomach to digest.[12] As such, the digestive system of infants may not be mature enough to handle cow's milk proteins, thus provoking autoimmunity.[12] Gluten-containing foods, such as wheat and barley, may alter immune cell populations proportionally or affect cytokine and chemokine patterns to favor an inflammatory profile.[12] Active estrogenic endocrine disruptors are also found in concentrated soya-based formulations. Fruits, berries, roots, and vegetables may be contaminated with harmful microorganisms, which could trigger autoimmunity.[12] Furthermore, feeding formulas are frequently fed from containers that are often coated with toxic chemicals, such as bisphenol A (BPA), which has a T1DM risk factor.[12] T1DM susceptibility could also be influenced by the length of breastfeeding or the age at which supplemental foods would be introduced. T1DM is linked to short-term breastfeeding (less than three months) and the early (less than four months) or late introduction (greater than or equal to six months) of complementary foods.[62] The mother's age, lifestyle, such as drinking and smoking habits, and psychological state could also make her child more likely to have T1DM.[44]

Association between environmental triggers and epigenetic changes in T1DM

Epigenetic changes are biological processes that control the gene expression without affecting the DNA sequence. Epigenetic changes are controlled by environmental triggers and are necessary for cellular activities and phenotypic presentations in living systems.[47] However, epigenetic changes other than normal biological functions or reactions to environmental stimuli could lead to heritable epigenetic mutations, including disease pathologies such as T1DM.[63] There are several epigenetic mechanisms, but the most common are DNA methylation, histone post-translational modifications (PTM), and non-coding RNA gene silencing.[63] Environmental triggers induce epigenetic changes by altering the chemical tags (such as methyl and ethyl groups) on the epigenome or by causing the reconfiguration of histones following translation. Environmental triggers may also cause epigenetic changes by overexpressing or repressing the non-coding RNAs, hence affecting gene expressions. In some cases of T1DM, environmental triggers cause epigenetic changes in genes that control immunity, insulin secretion, and glucose metabolism.[47] Notable among these genes are human leukocyte antigen (*HLA*), insulin (*INS*), cytotoxic T lymphocyte-associated antigen 4 (*CTLA-4*), and protein tyrosine phosphatase non-receptor type 22 (*PTPN22*).[47] Aberrant epigenetic modifications in these genes may cause foreign antigens to trick the immune cells (*e.g.* T-cells and B-cells) into attacking self-antigens and causing the autoimmunity of beta cells, therefore resulting in insulin insufficiency and thus T1DM.

Certain epigenetic mechanisms are reversible by activating or deactivating the modulating enzymes, as a result suggesting that some cases of T1DM could be treated by reversing the epigenetic mechanisms. To this end, certain drugs, called epigenetic drugs or epidrugs, have been formulated and demonstrated to be effective in the treatment of T1DM. These drugs include I-BET151[64] and RGFP966.[65] A variety of dietary compounds, such as sulforaphane found in broccoli sprouts and dialyl disulfide in garlic, have also demonstrated to reverse epigenetic changes in diabetics.[66,67] Some other compounds, such as methione, choline, and betaine, found in dietary substances, have also shown some promising outcomes in T1DM treatment.

Future directions

Considering the high mortality and financial burden of DM, it is obvious that a new and effective procedure would be necessary to complement the existing treatment options. Preventive measures are always the best approach, so the environmental triggers highlighted in this review could be monitored by individuals to reduce their risk of developing the disease. Government agencies, especially the Ministry of Health and Environment, should introduce policies and enlightenment campaigns on the reduction of exposure to the mentioned triggers. Periodic genetic testing for the early detection of biomarkers of the disease would assist in preventing the disease or reducing its severity in genetically predisposed humans. Though genetic tests are costly, they could be made accessible through government or corporate funding. Scientists and medical practitioners should also develop drugs and administer therapies based on each trigger and its mechanisms.

Conclusions

This review has shown that certain environmental triggers, such as chemical exposure, viral infection, gut microbiome disruption, vitamin and mineral deficiencies, inadequate or exclusive breastfeeding, as well as early exposure to infant feeding formulas, could trick the immune cells into attacking the self-tissues, thus causing the autoimmunity of the beta cells and T1DM. These triggers could achieve this by directly disrupting the genes involved in insulin production and immune regulation, such as the leukocyte antigen (*HLA*), insulin (*INS*), cytotoxic T lymphocyte-associated antigen 4 (*CTLA-4*), and protein tyrosine phosphatase non-receptor type 22 (*PTPN22*) genes, or indirectly by disrupting the epigenome of the mentioned genes. Each trigger has a specific pathophysiology, thereby suggesting that personalized medicine that would tailor treatment to the health needs of individuals could result in better T1DM treatment outcomes. To this end, some drugs, mainly epigenetic drugs that target epigenetic changes in diabetics, have been formulated and demonstrated to be effective.

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Conflict of interest

The authors have no conflict of interest to declare.

Author contributions

Study design and manuscript writing (TOY), critical revision (DA, COB), literature search (UUL, ZZI), and article sorting (CBG, BMM). All authors made a significant contribution to this study and approved the final manuscript.

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