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Environmental risk factors for type 1 diabetes

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Abstract

The incidence of type 1 diabetes has risen considerably in the past 30 years due to changes in the environment that have been only partially identified. In this Series paper, we critically discuss candidate triggers of islet autoimmunity and factors thought to promote progression from autoimmunity to overt type 1 diabetes. We revisit previously proposed hypotheses to explain the growth in the incidence of type 1 diabetes in light of current data. Finally, we suggest a unified model in which immune tolerance to β cells can be broken by several environmental exposures that induce generation of hybrid peptides acting as neoautoantigens.

Introduction

The incidence of type 1 diabetes has increased by several times over the past 30 years.[1] This increase can only be explained by changes in environment or lifestyle. Supporting the impact of environment or lifestyle on risk, migrants tend to acquire the same risk of type 1 diabetes as the population in their new area of residence.[2, 3] In Europe, the risk of type 1 diabetes differs substantially in people who are genetically close but separated by socioeconomic borders.[4] This risk has become more homogeneous within populations with free movement of people and trade.[5] Improved understanding for the environmental determinants of type 1 diabetes could make it possible to prevent or delay the disease.

Type 1 diabetes is diagnosed after onset of overt hyperglycaemia;[6] however, evidence is mounting that islet autoimmunity is the first stage of the disease.[7] Islet autoimmunity is defined by the persistent presence of autoantibodies to pancreatic islet antigens. Islet immunity usually starts in early childhood, with incidence peaking in the second year of life,[8–10] and can have a remitting-relapsing course before onset of diabetes.[11] Development of two or more islet autoantibodies (to insulin, glutamic acid decarboxylase [GAD],

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Contributors

MR carried out literature search, provided figures and wrote parts of the Review. JL outlined the structure of the paper, added some references and contributed to data interpretation and writing.

Declaration of interests

We declare no competing interests.

insulinoma-associated antigen 2, or zinc transporter-8 [ZnT8]) marks a point of no return from which 70% of children progress to diabetes over the next 10 years.[12] Prospective birth cohorts[9, 10, 13–15] have helped to identify potential triggers of islet autoimmunity and the natural history of progression to diabetes. Candidate triggers include infections, diet, and toxins that affect children in utero, perinatally, or during early childhood. These triggers need to be recorded prospectively in studies rather than recalled retrospectively at the time of diabetes diagnosis, several years later.

In paper one of this Series on development of type 1 diabetes, Pociot and Lernmark[16] summarise factors for genetic susceptibility and resistance to type 1 diabetes. In this paper, we discuss candidate triggers of islet autoimmunity and factors thought to promote progression from autoimmunity to overt type 1 diabetes (figure 1). These factors seem to have their effect mainly in the genetically predisposed individuals. We also review data for candidate environmental factors that have not yet been confirmed to predict islet autoimmunity or type 1 diabetes or might have weak or confounding effect.

Infections

Early ecological reports,[17] seroepidemiological studies,[18] and case reports[19] have drawn attention to viral infections as a potential cause of type 1 diabetes. Bacterial infections are rarely discussed, although bacteria as a cause of pancreatic lesions cannot be excluded. Several viruses have been implicated, with enteroviruses having the strongest evidence from studies in animal models[20] and in human beings.[21] These viruses have a tropism to human pancreatic islets in vivo and in vitro,[19, 22] and have been detected in the pancreas of patients recently diagnosed with type 1 diabetes. Recent findings consistent with a persistent enteroviral infection in patients at diagnosis of type 1 diabetes include: more frequent detection of enteroviral VP1 protein immunoreactivity in the β cells of children with type 1 diabetes than in age-matched controls;[23, 24] VP1 expression in β-cells that also produce elevated levels of PKR consistent with degradation of myeloid cell factor 1 (MCL1) and higher susceptibility of the cells to apoptosis;[25] and that double-stranded RNA (dsRNA) and elevated levels of MDA5 in the β cells of patients with type 1 diabetes.[26] An intriguing line of evidence suggests that enteroviral infections during pregnancy might result in persistent infection and islet autoimmunity in the mother[27] and off spring.[28, 29] A plausible mechanism for persistence of enteroviruses in the pancreatic islets has been proposed from studies of enteroviral myocarditis.[30, 31] A spontaneous deletion of 22–36 nucleotides in the 5′ non-translated region of the virome resulted in lowgrade persistence of the defective virus that was unable to cause cytopathic damage, but was able to slowly replicate. Evidence for a similar pathomechanism in islet autoimmunity has yet to be reported. Whether enteroviruses act as triggers of islet autoimmunity, promoters of progression to type 1 diabetes, or non-specific precipitating stressors is an unsettled issue.[32–37] Interestingly, an in-vitro study suggested that persistent enteroviral infection of human pancreatic ductal cells might diminish their ability to transdifferentiate into β cells, thus slowing down β-cell mass decline due to autoimmunity.[38]

Intestinal microbiota

Some of the candidate environmental factors for type 1 diabetes (eg, caesarean delivery, early childhood diet, and use of antibiotics) are intertwined with the development and function of the human microbiome. Gut microbes influence lipid and glucose metabolism, as well as immunity and systemic inflammation outside of the intestine.[39–41] Commensal microbiota might modulate the risk of type 1 diabetes,[39, 42–48] but studies so far have been underpowered and focused on taxa diversity. Some have reported lower microbial diversity in children with islet autoimmunity before progression to diabetes, compared with healthy controls.[42, 43, 48] Larger studies are needed that use whole-genome sequencing of the microbiome at multiple timepoints before diagnosis and use carefully selected controls.

Vaccines

There has been speculation that vaccines might trigger autoimmunity, but no association has been detected with islet autoimmunity[49, 50] or type 1 diabetes.[51, 52] A recent meta-analysis of 23 studies investigating 16 vaccinations[53] concluded that childhood vaccines do not increase the risk of type 1 diabetes. The BCG vaccine has attracted some interest as a potential immune-modulator that could theoretically reduce the incidence of autoimmunity. Clinical data have shown no association between BCG vaccination and type 1 diabetes or islet autoimmunity. A 20 year follow-up of the 1974 Canadian birth cohort, of which 45% were given BCG in the first year of life, showed no association with type 1 diabetes,[54] nor did case-control studies from Canada[55] and Sweden.[56] The German BABYDIAB study[57] reported no association between BCG vaccination and development of islet autoimmunity. In addition, in two clinical trials, vaccination with BCG at diagnosis of type 1 diabetes did not preserve β-cell function.[58, 59]

Hygiene hypothesis

The hygiene hypothesis posits that incidence of autoimmune diseases might be rising because of a decreasing frequency of childhood infections due to improved hygiene.[60–62] However, a UK population-based study showed that infections in early life, routinely recorded by family doctors, were not associated with subsequent childhood type 1 diabetes.[63] On the other hand, prospective studies have reported a significant increase in the risk of islet autoimmunity with more frequent respiratory infections during the first 6 months of life; the association was weaker for infections age 6–12 months and absent for those beyond 1 year of age.[64] Similar results were reported from Norway,[65] whereas the DAISY study[37] in Colorado reported an association between islet autoimmunity and early childhood gastrointestinal infections, but not respiratory infections. In summary, prospective studies generally do not support the hygiene hypothesis for type 1 diabetes. It has been hypothesised that in countries with the highest incidence of type 1 diabetes, increased hygiene and sanitation resulted in a decline in herd immunity to enteroviruses among pregnant women, exposing fetuses and newborn babies to prenatal or infant enteroviral infections.[66] Although direct evidence for this effect in human beings is not established, in animal models virus-induced diabetes can be prevented in off spring by infecting mothers with the same virus before pregnancy.[67]

Dietary factors

Breastfeeding

Although some retrospective studies showed a small reduction in the risk of type 1 diabetes with breastfeeding, all but one, ABIS in Sweden,[68] of the prospective birth cohort studies failed to find a protective effect.[13, 14, 69, 70] Nevertheless, children who were still breastfed at the time of introduction to cereals had a reduced risk of islet autoimmunity,[13] and type 1 diabetes.[71] These findings suggest that breastfeeding might play a protective role in the relationship between dietary factors and type 1 diabetes.

Cows' milk

Most prospective birth cohort studies have not shown any link between early exposure to cows' milk and either islet autoimmunity[13, 14, 68, 69] or type 1 diabetes.[71] In a double-blind, randomised trial (TRIGR Pilot II), 230 infants at genetically increased risk for type 1 diabetes who received a casein hydrolysate formula whenever breastmilk was not available had lower risk of islet autoimmunity than had those given cows' milk-based formula during the first 6–8 months of life.[72] Unfortunately, the larger phase 3 TRIGR study could not confirm this effect on islet autoimmunity;[73] follow-up of the study participants for type 1 diabetes continues.

Studies exploring the role of cows' milk consumption later in childhood on the risk for islet autoimmunity and type 1 diabetes have also produced contradictory results. Cows' milk intake in childhood has been associated with both an increased risk of islet autoimmunity[74, 75] and type 1 diabetes,[76, 77] as well as a decreased risk of type 1 diabetes.[78] A higher cows' milk intake might promote progression to type 1 diabetes in children with islet autoimmunity,[79] an effect that could be mediated by certain fatty acids present in cows' milk and meats—eg, myristic, penta-decanoic, monounsaturated palmitoleic acid isomers 16:1 omega-7 and 16:1 omega-9, and conjugated linoleic acid.[80] If confirmed, this observation could inform a new line of dietary interventions to prevent type 1 diabetes.

Solid foods and cereals

In DAISY, the timing of introduction of any type of cereal (gluten and non-gluten containing) was associated with an increased risk of islet autoimmunity in a U-shaped relationship with nadir at introduction at 4–6 months of life.[13] BABYDIAB showed association only with early exposure to gluten,[14] ABIS with gluten introduced late,[74] and the Finnish DIPP study found no clear association with gluten.[70] In Finland, DIPP reported that introduction of root vegetables by age 4 months doubled the risk of islet autoimmunity compared with later introduction and also that first exposure to egg before age 8 months was associated with an increased risk of islet autoimmunity.[70] ABIS showed that less than daily consumption of vegetables (3–5 times per week) in the mothers' diet was associated with increased risk of islet autoimmunity.[81] Cross-study differences might be related to country differences in infant nutrition, and there is a risk of false positive associations caused by multiple comparisons. Therefore, results of these studies must be interpreted with caution.

Examination of dietary exposures and clinical type 1 diabetes also gives divergent results. In DAISY,[71] young (<4 months) exposure to fruit and late (age ≥6 months) first exposure to any solid food, including rice, predicted development of type 1 diabetes. However, BABYDIAB[82] found only weak associations to early gluten introduction. In aggregate, these studies lend support to the idea that general antigenic stimulation is more important than is the actual antigen in this disease process. This association might be due to immature immune response and the gut. The increased risk by late exposure to solid foods might be related to the larger amounts given at initial exposure to older children, nutrient deficiencies, or the cessation of breastfeeding before solid foods are introduced, resulting in a loss of the protective effect of breastmilk at the introduction of foreign food antigens. A randomised trial of gluten-free diet at 6–12 months of age did not reduce the development of islet autoimmunity in genetically high-risk infants[83] and it did not decrease the levels of islet autoantibodies in children with established islet autoimmunity.[84]

Vitamin D

Vitamin D has been examined as a potentially protective factor because it has an active role in the regulation of the immune system, as well as metabolic pathways relevant to diabetes. Vitamin D has also been shown to shift the balance of the body's T-cell response toward downregulation of the T-helper-1 immune response. The seasonality of birth in children with type 1 diabetes and the seasonal pattern at diagnosis of type 1 diabetes could be explained by seasonal variation in vitamin D production from exposure to the sun. In Belgium, the monthly averages of daily hours of sunshine were inversely related to the number of new patients with type 1 diabetes per month.[85] However, meta-analysis of observational studies of vitamin D intake during pregnancy showed no effect on the incidence of type 1 diabetes.[86] A Norwegian study found an association between higher serum 25-hydroxyvitamin D in late pregnancy and lower risk of type 1 diabetes in off spring,[87] but a Finnish study found no such association between concentrations of the molecule in the first trimester of pregnancy and the risk of type 1 diabetes in babies.[88]

Two meta-analyses of retrospective studies showed that the risk of type 1 diabetes was lower in infants who were supplemented with vitamin D (calcitriol) compared with those who were not supplemented (pooled odds ratio 0·71).[88, 89] DAISY examined plasma 25-hydroxyvitamin D concentrations in infancy and throughout childhood and found no association with islet autoimmunity or progression to type 1 diabetes.[90] Dietary intake of vitamin D (from food and supplements) was also not associated with islet autoimmunity or progression to type 1 diabetes[90] and the ABIS prospective study found no association between an intermediate dose of vitamin D supplementation during infancy and development of islet autoimmunity.[78] Two clinical trials reported no effect of vitamin D supplementation on sustained insulin production in new-onset type 1 diabetes.[91, 92] In summary, despite continuing interest in vitamin D supplementation as a potential intervention to prevent islet autoimmunity and type 1 diabetes, there is surprisingly little supporting evidence from prospective birth cohort studies.

Polyunsaturated fatty acids

Long-chain polyunsaturated fatty acids, specifically omega-3 fatty acids, affect inflammatory responses. A relative deficiency of omega-3 fatty acids, characteristic of many western diets, might predispose to inflammatory reactions. In Norway, a prospective study found no association between risk of type 1 diabetes in babies and docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and other fatty acid concentrations in the phospholipid fraction of maternal serum collected in late pregnancy.[93] Among Finnish children, lower serum linoleic acid (an omega-6 fatty acid) concentrations, but not DHA or EPA concentrations, were associated with increased risk of islet autoimmunity.[80] Interestingly, in a US study, higher omega-3 fatty acid intake during childhood and higher omega-3 fatty acid in the erythrocyte membrane predicted a lower risk of islet autoimmunity.[94] However, it can be noted that the omega-3- fatty acid intake is even lower in the diet of certain areas of the world (eg, India), than in western diets, without any observed relation to development of type 1 diabetes.

Toxins and chemical compounds

Toxins in foods or water might activate autoimmune mechanisms in genetically susceptible individuals, and exposure to toxins might result in pancreatic islet cell death. The list of elements, man-made chemicals, and naturally occurring mycotoxins associated with type 1 diabetes is long and the evidence too preliminary to review here. Some circumstantial and ecological[95] evidence suggests a connection between type 1 diabetes and water containing nitrates, nitrites, or nitrosamines, although other studies show no or contradictory associations.[96–98] In a case-control study in Sweden, type 1 diabetes was associated with consuming higher amounts of foods containing nitrosamines and nitrates or nitrites[99] and in the ABIS, water samples from families with a child with type 1 diabetes had higher concentrations of nitrate than did water samples from control families.[100] However in Germany, water concentrations of nitrate and nitrite were not associated with risk of either islet autoimmunity or progression to type 1 diabetes.[101]

Birthweight and infant growth

Higher birthweight[102, 103] and rapid weight gain during age 12–18 months[104, 105] have been linked to type 1 diabetes. The magnitude of effect is modest and the associations have been noted in Scandinavian countries, but not in the USA or Germany.[106, 107] The accelerator hypothesis proposes that excess weight gain leads to insulin resistance in early childhood and could initiate islet autoimmunity, eventually leading to type 1 diabetes.[108] Although there is little evidence for the hypothesis,[109] insulin resistance and rising blood glucose (glucotoxicity) might accelerate β-cell apoptosis directly or by inducing β-cell neoautoantigens in genetically predisposed people; rapid growth might increase insulin demand causing β-cell stress and increased presentation of autoantigens.

β-cell stress

Although the accelerator hypothesis mainly relates to rapid growth, the β-cell stress hypothesis proposes that factors causing increased insulin demand, such as rapid growth,

overweight, puberty, low physical activity, trauma, infections, and glucose overload,[110] might play an important role in development of type 1 diabetes.[111] Serious life events (eg, divorce or death in the family) as shown in the ABIS study, might increase the risk of islet autoimmunity[112, 113] and type 1 diabetes.[15] Psychological stress not only increases insulin resistance leading to increase demand on the β cells, but stress (eg, via increased cortisol concentrations) might also directly influence the immune response.

Prolonged endoplasmic reticulum stress impairs insulin synthesis and causes pancreatic β-cell apoptosis.[114] In turn, reduced insulin production relieves endoplasmic reticulum stress and induces β-cell proliferation.[115] Furthermore, endoplasmic reticulum stress might increase abnormal post-translational modification of endogenous β-cell proteins (figure 2).[116] The findings summarised in the next section might provide the link between multiple environmental stressors of β cells and initiation of the autoimmune process.

Post-translational modification and neoautoantigens

Physiological states related to oversecretion of insulin might promote generation of neoautoantigens via post-translational modification of islet proteins (eg, proinsulin, chromogranin A, islet amyloid polypeptide [IAPP], and GAD; figure 2). Although post-translational modification plays a role in other autoimmune diseases, such as coeliac disease, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, or berylliosis,[117] it has only recently become the subject of systematic studies of type 1 diabetes.[118–124] One of the strongest lines of evidence for the primary role of post-translational modification in development of type 1 diabetes in non-obese diabetic (NOD) mice, as well as in human beings, comes from the discovery of a new class of naturally occurring autoantigens called hybrid insulin peptides (HIPs).[121–124] HIPs are formed through transpeptidation of the C-terminal carbonyl groups of C-peptide fragments with N-terminal amino groups of peptides derived from chromogranin or IAPP, other β-cell prohormonal secretory granule proteins. HIP-reactive CD4 cells have been identified in both NOD[123, 124] and human[124] pancreas cells, suggesting that this mechanism might be responsible for the loss of self-tolerance in type 1 diabetes.

Molecular crowding of peptides derived from proinsulin, chromogranin A, and IAPP in secretory granules might promote formation of HIPs. In addition to the products of natural processing of these proteins by prohormone convertases and carboxypeptidase E, products generated by lysosomal proteases during granule turnover could also be involved.[123] The role of IAPP in type 1 diabetes is unclear at present. Increased plasma concentrations of IAPP have been noted at diagnosis in some patients with type 1 diabetes;[125] intra-β-cell amyloid formation commonly seen in type 2 diabetes can also be found in patients with type 1 diabetes.[126]

Heterogeneity of type 1 diabetes

The patterns of insulitis (ie, infiltration of the islets by CD8, CD4, and CD20 lymphocytes) in people with type 1 diabetes seem to differ by age at diagnosis. Insulitis shows high proportion of CD20 B cells in patients diagnosed before the age of 7 years, mixed pattern at

age 7–13 years, and low CD20 content after age 13 years.[127, 128] Importantly, patients diagnosed when older than 13 years retain about 40% of residual insulin-containing islets at diagnosis, consistent with the observed higher rates of partial remission of insulin dependency and the favourable results of immunomodulatory interventions. The reasons for spontaneous remission and reactivation of the autoimmune process are unclear. Reactivations of persistent viral infection or recurrent infections of the islets[24, 26, 129] and of the exocrine pancreas[38, 130] might be a plausible mechanism. Increases in insulin resistance due to puberty, weight gain, infections, or stress could also play a role.[15, 109] In addition to age of diagnosis, HLA-DR-DQ genotype, pattern of islet autoantibodies development, and ethnic origin have been reported to be associated with variable diabetic phenotypes,[8–10] although there seems to be a large overlap between potential categories. The process of systematic aetiological classification of subtypes of type 1 diabetes has just begun.[131, 132]

Discussion

There is no shortage of hypotheses to explain the rise in the incidence of type 1 diabetes in most of the world. The accelerator and β-cell stress hypotheses propose that several unspecific environmental factors, for example, overweight, fast growth, infections, dietary deficiencies or psychological stress, alone or in combination, might make pancreatic β cells exhausted and eventually fail due to a secondary autoimmune destruction. For a long time, these models lacked a convincing biological mechanism linking β cell stress to autoimmunity. The recent discovery of HIPs might provide such a link. The peptides are likely to be produced by exhausted β cells and can act as powerful neoantigens that initiate β-cell-specific autoimmunity in a susceptible host. There are similarities between this model and the aetiology of coeliac disease for which the immune-dominant peptides are also post-translationally modified. However, these peptides originate from among hundreds of proteins (gliadins, glutenins, hordein, secalins, and avenins) present in wheat, rye, barley, and oats, whereas HIPs are thought to be byproducts of degradation of insulin and other β-cell hormones and thus are truly neoautoantigens.

The hygiene hypothesis postulates that fewer early childhood infections and infestations and less diverse symbiotic gut flora deviate the immune system towards autoimmunity and atopy. A variant of the hygiene hypothesis specifically blames decreased herd immunity to enteroviruses for the rise in incidence of type 1 diabetes. The detection in pancreatic biopsies and post-mortem samples of material consistent with slowly-progressing persistent enteroviral infection of the β cells has provided new credence to this scenario.

The evidence is growing to support heterogeneity of type 1 diabetes by age, genotype, the autoimmune phenotype, and pathomorphology of the pancreatic islet. The combination or sequence of the causal environmental exposures might vary among individuals as well as over time within a population. This heterogeneity might explain inconsistent, sometimes even contradictory, observations from different populations. Importantly, environmental factors that trigger islet autoimmunity might differ from those that promote progression from autoimmunity to overt diabetes.

Continuing and future studies to define environmental causes of type 1 diabetes will benefit from wide representation of children from different areas of the world, with and without first-degree relatives with diabetes, and a large sample size that allows for stratified and pooled analyses to understand what local genetic and environmental factors are important and which are universal. In addition to the current focus on genomics and metagenomics, studies are beginning to evaluate metabolomics and proteomic markers that could reveal novel pathways involved in pathogenesis of type 1 diabetes and inform future interventions. The rise in type 1 diabetes is compatible with an epigenetic effect amplified over generations, but so far evidence is scant. Additional opportunities might lie in increased understanding of β-cell biology, including nerve supply, vascular supply, islet cell interplay, and the relationship to the exocrine pancreas.

Prevention of type 1 diabetes will be more feasible if modifiable checkpoints are shared by most pathways to diabetes. For instance, if β-cell stress-generated neoautoantigens are the major mechanism of loss of tolerance, intervention at this point might be more feasible than eradication of some causes of β-cell stress. If persistent viral infection of β cells is one of the common pathways, then vaccination might confer only partial benefit. Addition of antiviral or immune interventions might be needed to stop or delay the autoimmune process and preserve more β-cell function. Combined with modern devices and advanced insulins, these advances would lessen the heavy burden associated with type 1 diabetes.

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Search strategy and selection criteria

We identified papers through searches of PubMed with search terms “type 1 diabetes”, “autoimmunity”, “environmental”, “trigger”, and “promoter” and also from references from relevant articles. We did not include abstracts and reports from meetings. We included only articles published in English between 1960 and Jan 31, 2016.

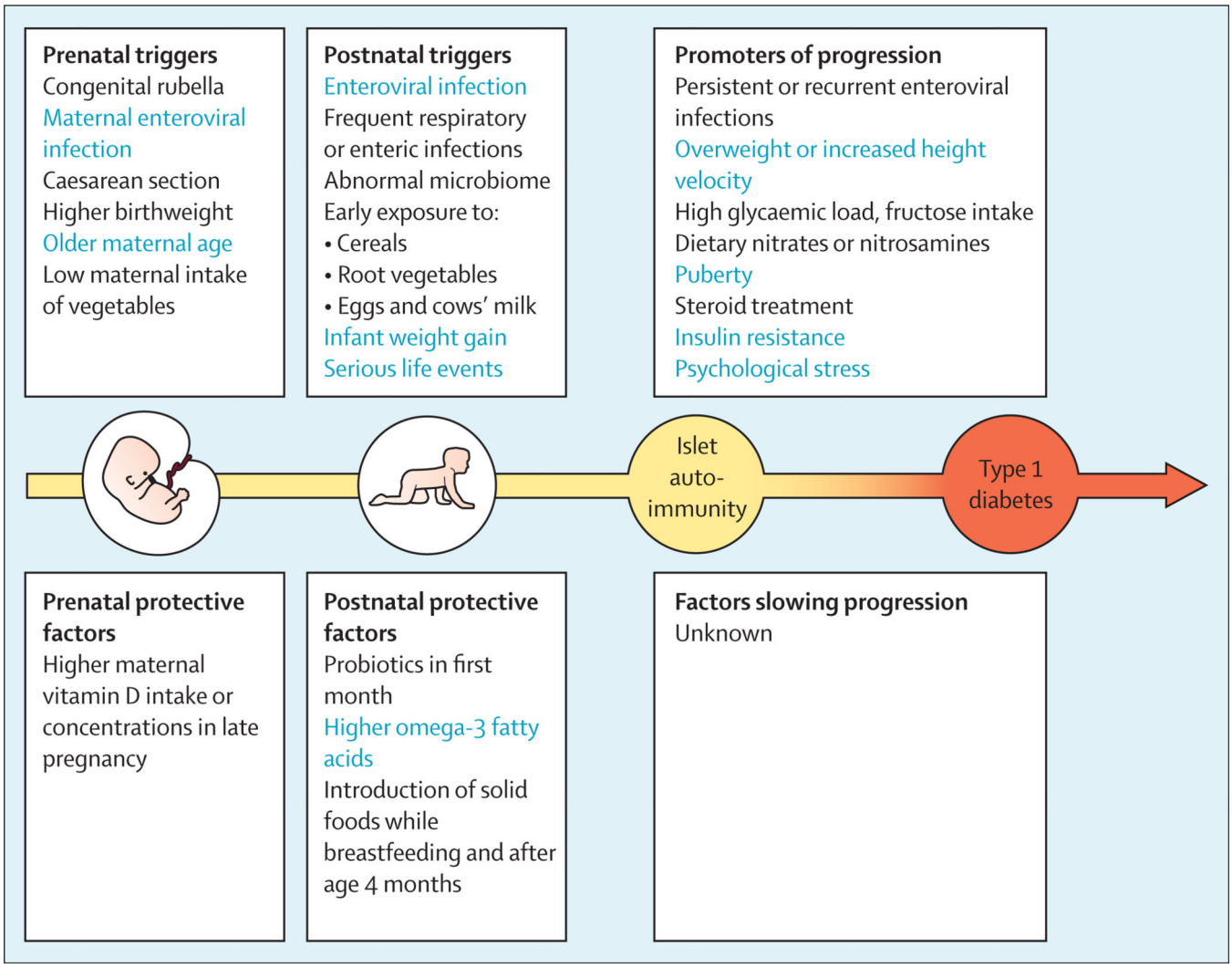

Figure 1.

Environmental triggers and protective factors for islet autoimmunity and promoters of progression to type 1 diabetes for which an association has been suggested

Triggers and factors with the strongest evidence base are shown in blue.

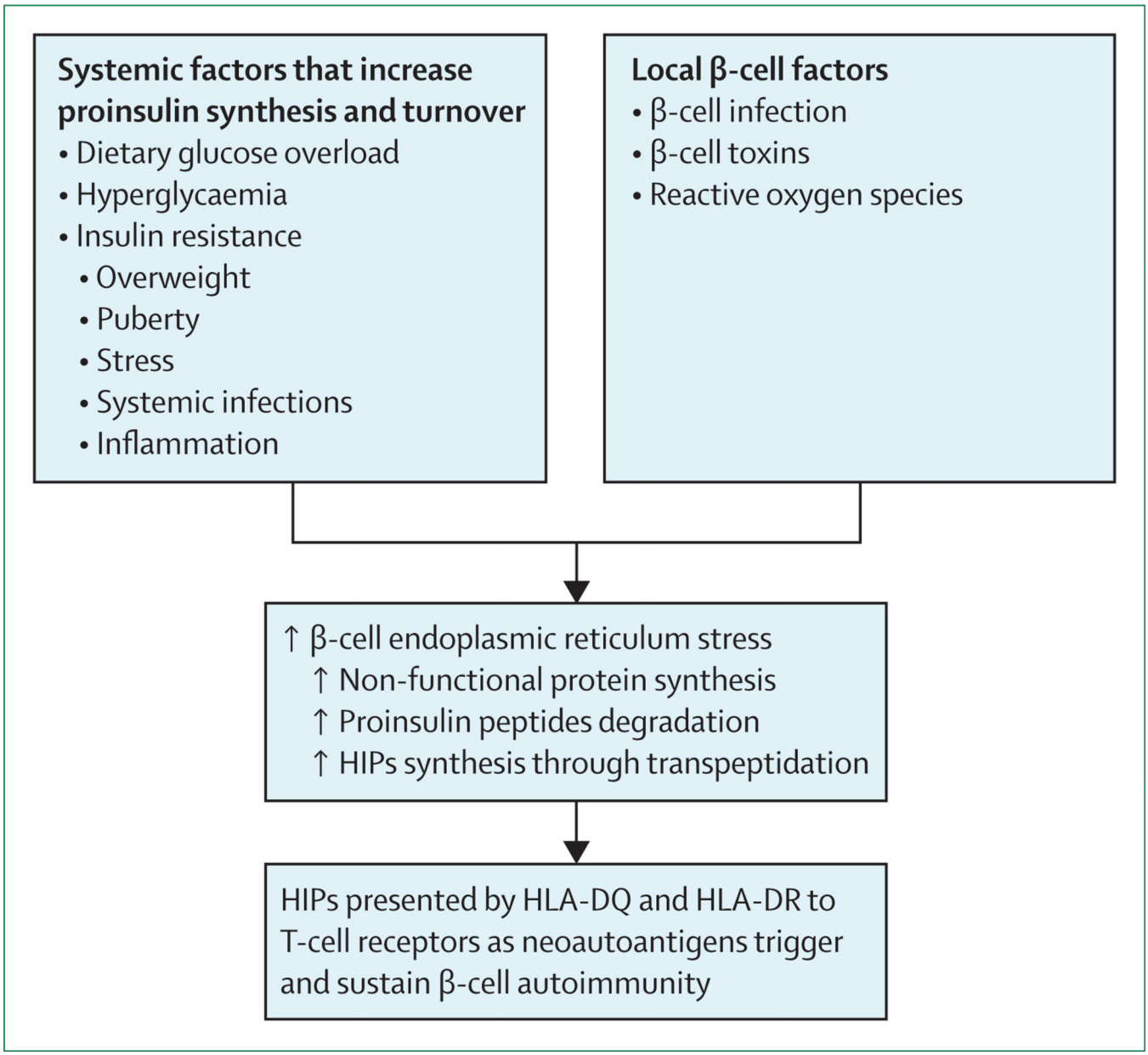

Figure 2.

A unified model of the relationship between environmental factors, β-cell endoplasmic reticulum stress, generation of neoautoantigens (HIPs), and loss of immune tolerance that triggers islet autoimmunity

HIP=hybrid insulin peptide.