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Type 1 diabetes: a disease of developmental origins

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ABSTRACT

The incidence of type 1 diabetes globally has increased dramatically over the last 50 years. Proposed environmental reasons for this increase mirror the modern lifestyle. Type 1 diabetes can be viewed as part of the non-communicable disease epidemic in our modern society. Meanwhile rapidly evolving new technologies are advancing our understanding of how human microbial communities interface with the immune system and metabolism, and how the modern pro-inflammatory environment is changing these communities and contributing to the rapid rise of non-communicable disease. The majority of children who present with clinical type 1 diabetes are of school age; however 80% of children who develop type 1 diabetes by 18 years of age will have detectable islet autoantibodies by 3 years of age. The evolving concept that type 1 diabetes in many children has developmental origins has directed research questions in search of prevention back to pregnancy and early life. To this end the world's first pregnancy to early childhood cohort study in at-risk children has commenced.

The incidence of type 1 diabetes in the Western World

The incidence of type 1 diabetes in the Western World has increased dramatically over the last 50 years with geographical differences, as illustrated by a two fold increase reported in Australia (1) a five fold increase in Finland (2). In parallel with the rise in type 1 diabetes is the emergence of childhood overweight and obesity and an increased incidence of other immune mediated disease: coeliac disease, inflammatory bowel disease, and allergy. The epidemics have occurred in our modern pro-inflammatory environment, which is notable for its obesogenic influences, changes in the perinatal environment and increased use of antibiotics and environmental pollutants (table 1).

The majority of children who present with clinical symptoms and signs of type 1 diabetes are of school age; however 80% of children who develop type 1 diabetes by 18 years of age have detectable islet autoantibodies by 3 years of age (3). The percentage is even higher in children who develop type 1 diabetes before puberty (4). Initiators of the autoimmune process leading to beta cell destruction and dysfunction in child and adolescent onset cases must therefore frequently occur early in life, possibly as early as pregnancy.

The developmental origins of health and disease

The developmental origins of health and disease (DOHaD) paradigm arose from the original seminal observation in the 1980s that lower birth weight predicts late cardio-metabolic disease in adulthood, the Barker Hypothesis (5,6). The concept has been

extended to propose that metabolic, immune and physiological adaptations to antenatal life modify later health and disease risk, in childhood and adulthood, and in subsequent generations. It has been applied to understand the origins of cardiovascular, metabolic and allergic disease.

The impact of the 'omes

In the last 10 years rapidly expanding new technologies in the 'omic sciences have advanced our understanding of how the environment alters genetic material and how microbial communities and their metabolites interface with the immune system and metabolism. The genome, epigenome, microbiome, metabolome and lipidome have provided new avenues to investigate gene –environment interactions and interactions between metabolism, physiology and immunology. Transcriptome and proteome sequencing identify gene activity at a given time and suggest possible function. Metagenome and metatranscriptome sequencing of the whole microbiome nucleotide pool uses more sophisticated computational and bioinformatics skills, and can generate a functional profile. These new sciences are revolutionizing our capacity to investigate how the modern pro-inflammatory environment influences adaption *in utero* and physiology to change disease susceptibility in future generations and to drive the rapid rise of non-communicable diseases. They hold the potential to discover early biomarkers, pathogenic mechanisms and intervention targets.

The microbiome in early life

The microbiome defines the micro organisms that reside as commensals in our bodies and their collective genome. Nominally, the term microbiome refers to the bacterial communities and to a lesser extent fungi and archaea with the term virome used to describe the viral component of the complete microbiota. The microbiome is influenced by the site in the body, life-stage, living environment and geographical location. It changes rapidly after birth and during the first two years of life (7) underscoring the importance of prospective studies from early life. The largest numbers of microbes reside in the gut. The maternal gut microbiome is influenced by pre-pregnancy weight, pregnancy weight gain, antibiotics, hygiene, smoking gestational complications and her partner's microbiome (7). The fetus was thought to grow in a sterile environment, but this has been challenged by the description of a placental microbiome that most closely resembles the mother's mouth microbiome (8). The infant's gut microbiome is influenced by the maternal microbiome, mode of delivery, infant feeding, birth weight, gestational age, antibiotics, and intensive care at birth (9). For example, children born by Cesarean section and children born prematurely have reduced diversity of their gut microbiome throughout infancy.

Recent comparison of early life gut microbiomes in Finland and Estonia, and those in neighbouring Russian Karelia with its contrasting low incidence of childhood autoimmune disease, showed a distinct difference. *Bacteroides* species, particularly *B. dorei*, were dominant in Finnish and Estonian infants, but low in Russian Karelian infants. *Bacteroides* lipopolysaccharide (LPS), higher in Finnish and

Estonian microbiomes, did not activate innate immunity and, in contrast to E. Coli LPS which does activate innate immunity, did not decrease the incidence of autoimmune diabetes in non-obese diabetic mice. These findings may provide a mechanism for the “hygiene hypothesis” whereby reduced frequency of early life infections (Table 1) contributes to the increasing incidence of autoimmune disease in Western countries. (10)

There are few studies of the human gestational gut microbiome. One study during normal human pregnancy shows major changes between the first and third trimesters, with an increase in pro-inflammatory and a decrease in anti-inflammatory bacteria, and with increasing differences in the diversity between the mothers’ gut microbiomes that persist for one month post-partum (11). Neither gestational diabetes nor obesity in the mother increases these inflammatory changes further. When transferred to germ-free mice, human microbiota from the third trimester induce adiposity and insulin insensitivity (11). There are no data to our knowledge from the second trimester of human pregnancy, and none on the human gestational virome.

The effect of nutrition on the microbiome during pregnancy and early life

The short term effect of nutrition and fibre on the composition and diversity of both the adult human gut microbiome and the murine gestational microbiome is well documented (12,13). The component of dietary fibre that consists of non-digestible oligosaccharides and resistant starches (prebiotics) escapes digestion in the small

intestine and is fermented by colonic bacteria to the anti-inflammatory short chain fatty acidss acetate, butyrate and propionate. Higher dietary fibre intake in late human pregnancy is associated with higher maternal serum acetate levels (14). There is otherwise minimal information as to the effect of nutrition on the human gestational microbiome. Yet nutrition is one factor that has changed dramatically over the last 50 years. One third of Australian woman begin pregnancy overweight or obese (15) and few attain recommended dietary intakes of fibre. Optimising gestational nutrition is a potential intervention strategy, if the effect of diet on the gut microbiome also occurs during pregnancy, and if the gestational gut microbiome alters immune regulation in early life. Pregnancy is a time when motivation to change lifestyle is high.

The gut microbiome in type 1 diabetes

The role of the gut microbiome in type 1 diabetes is a particular focus of research because of the known major impact of the modern environment on the microbiome and the known interactions between gut microbes and immune regulation (16). Altered balance of the gut microbiota (gut dysbiosis) is reported in children with islet autoimmunity and type 1 diabetes at both taxonomic and functional levels. Lactate- and butyrate-producing bacteria support mucin production to maintain intestinal integrity in health. Children with islet autoimmunity who progress to type 1 diabetes have shown an increased Bacteroidetes: Firmicutes Phyla ratio, a lower proportion of butyrate-producing bacteria, and reduced bacterial diversity (17,18). Despite the considerable differences conferred by geographical locations and ethnicities, dysbiosis with

perturbations in composition and diversity can be detected widely in children with islet autoimmunity and type 1 diabetes from different countries and continents (17,19). The gut dysbiosis can be detected early, before 2 years, in those children who later develop islet autoimmunity and type 1 diabetes. Metagenomic sequencing has identified one species in particular, *Bacteroides dorei*, that peaks around the time when solids are introduced in genetically at-risk Finnish infants, who later develop islet autoimmunity (20,21). This is the same species that is dominant in the gut microbiomes of Finnish and Estonian infants in contrast to Russian infants, as discussed above (10). These findings support an early life role of the microbiome in the immune dysregulation leading to islet autoimmunity and type 1 diabetes. Studies outside Europe are needed to clarify whether these spikes of *B dorei* in children who develop islet autoimmunity are specific to Finland or more universal, because of the substantial geographic-specific differences in the microbiome in children at risk of type 1 diabetes(22) .

Maintenance of a balanced healthy gut microbiome and intestinal integrity from birth therefore appears critical, but how dysbiosis of the microbiome disturbs immune regulation to initiate or progress islet autoimmunity remains unknown. There are no gestational data in humans but in experimental models antibiotics provide NOD mice with the greatest protection from diabetes development, through alterations in the gut microbiome, when they are given prenatally (23).

Significantly, for the future development of primary prevention strategies, the early life microbiome is potentially modifiable, through changes in diet, prebiotics and probiotics. The Environmental Determinants of Diabetes in the Young (TEDDY), a large prospective cohort study following children at risk of type 1 diabetes from 3 months of age in the US and Europe, recently reported that early probiotic supplementation in the first 27 days of life, documented retrospectively, was associated with a decreased risk of islet autoimmunity in children with the highest risk HLA DR 3/4 genotype (24).

The Epigenome

Environment -gene interactions are mediated by epigenetic modifications that underlie the complex and dynamic control of gene expression. Epigenetic modifications provide a mechanism for environmental cues to integrate and impact at the cellular level (25). DNA methylation is determined partly genetically but also by many environmental factors implicated in T1D (dietary components, antibiotics, environmental pollutants and microbiome products e.g. short chain fatty acids). In addition to DNA methylation, histone modifications are also involved in T1D pathogenesis, (26) but our present understanding of epigenetic dynamics in autoimmune disease is limited. Certainly epigenetic modifications are more reversible and dynamic than previously thought. Dynamic epigenetic modifications control the development, differentiation, and activation of immune cells (25).

Periconceptional development may be the most critical time when the environment can induce epigenetic changes in reproductive cells that are associated with a higher risk of disease in future generations. Father's BMI may in fact have a greater impact than mother's BMI on body fat in children in the normal population (27). The impact of paternal obesity or type 2 diabetes on the incidence of type 2 diabetes in the offspring has also been established in the high risk population of the Pima Indians (28). In experimental models this transgenerational risk from the father occurs via epigenetic changes in sperm (29). Such paternally-derived epigenetic effects might also contribute to the higher risk of T1D in the offspring of paternal as opposed to maternal probands (30,31).

New epigenetic-immune signatures are potential biomarkers of risk for T1D and umbilical cord blood may reveal signatures that predict risk of T1D, if the pathogenic processes begin prenatally. An example of an epigenetic-immune biomarker in early development is our recent report of an immune signature of food allergy in human cord blood (32). Dynamic epigenetic modifications indicate gene regulatory mechanisms that are reversible, so they provide targets for novel therapies. The enzymes catalyzing epigenetic modifications, for example, could be developed into therapeutic drugs.

The metabolome and lipidome

If the origins of type 1 diabetes are prenatal, metabolomic analysis of cord blood may also identify children at increased risk for islet autoimmunity and/or progression to type 1 diabetes. Cord-blood phosphatidylcholines and phosphatidylethanolamines were significantly decreased in children diagnosed with type 1 diabetes before 4 years of age (33,34). In a further Scandinavian study, children who progressed from islet autoimmunity to T1D had a cord blood lipidomic profile with low choline-containing phospholipids (35).

The overlap between type 1 and type 2 diabetes

The separation of type 1 diabetes and type 2 diabetes, with the implication that they are unique pathogenetically, has come under recent scrutiny (36,37). Clinicians caring for children with diabetes are aware of the frequent overlap in patients who present as overweight and insulin resistant but also have islet autoimmunity. Similarly patients with a classical type 1 diabetes presentation may also be overweight with insulin resistance. The DOHaD model fits comfortably with this observed clinical overlap. There is substantial evidence that the human gestational milieu affects weight, insulin resistance, and type 2 diabetes in the offspring (38–40). Children born during the Dutch Famine at the end of World War II had a greater incidence of obesity, type 2 diabetes and dyslipidaemia as they aged (35,41). Both paternal and maternal nutrition can affect the metabolic health of the offspring (42) Ground breaking work shows that adverse paternal nutrition can alter beta cell function (43) or DNA methylation of genes that are expressed in lipid metabolism in rodent models (44). It is very possible that similar

influences in the modern inflammatory environment during conception and gestation are driving both overweight and insulin resistance, and immune dysregulation, thus impacting the incidence of both type 1 and type 2 diabetes.

ENDIA (Environmental Determinants of Islet Autoimmunity)

The growing evidence that type 1 diabetes has developmental origins directs research questions to pregnancy and early life. The world's first pregnancy to early childhood cohort study in at-risk children began in 2014 (ACTRN12613000794707) (45). The ENDIA cohort follows at-risk children from early pregnancy through childhood, to determine the relationship between genome, epigenome, microbiome, and metabolome and the environment, and the development of islet autoimmunity. Maternal and paternal health before conception is also detailed. ENDIA aims to complement established large international prospective birth cohorts following infants at risk from infancy (46–49), by focusing on the earliest life determinants of type 1 diabetes.

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APPENDIX

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TABLE

Table 1: Candidate environmental risk factors for type 1 diabetes (15,50–56)

Prenatal and perinatal factors	Increased rates of C-section*
	Reduced frequency and duration of breast feeding*
	Maternal overweight and obesity*
	Older parents
Obesogenic factors	More calories*
	Poorer food quality*
	Food additives*
	Less physical activity*
	Less thermoregulation*
Other environmental factors	Less sleep*
	Less infections*
	More antibiotics*
	Enteroviruses
	Less sunlight and lower Vitamin D status *
	More pollution

* Factors -associated with increased innate immune inflammation with or without demonstrated changes in the microbiome

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