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Infant and Childhood Diet and Type 1 Diabetes Risk: Recent Advances and Prospects

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Abstract Type 1 diabetes is a chronic autoimmune disease characterized by a preclinical period of autoimmunity. It is well accepted that both genetic and environmental factors contribute to disease risk. Given that type 1 diabetes, and its preclinical autoimmunity, appear early in life, infant and childhood diet have been implicated as potential initiating exposures in the etiology of the disease. Several publications in the past year have provided further evidence for existing hypotheses regarding the roles of wheat, cow's milk, omega-3 fatty acids, and the maternal diet during pregnancy. However, inconsistencies in findings between studies suggest the need for collaboration and standardization of study methods to move forward in research in this area. One such example of this is the TEDDY (The Environmental Determinants of Diabetes in the Young) study, which is an international, multicenter birth cohort study with standardized recruitment, dietary collection methodologies, and analytic approaches.

Keywords Infant diet · Childhood diet · Maternal diet · Autoimmunity · Type 1 diabetes · Omega-3 fatty acids · Wheat · Gluten · Microbiota · Cow's milk · Intestinal permeability

Introduction

For decades, researchers have been actively investigating the role of infant and childhood diet in type 1 diabetes. Much of this work is comprehensively summarized in two review articles that were recently published [1, 2•]. Most of the recent focus has been on investigating the role of cow's milk, wheat/cereals/gluten, omega-3 fatty acids, and vitamin D, as well as the overall role of the gut immune system. Papers published in the last year (2009–2010) further elucidate a number of these research areas, as reviewed below. Type 1 diabetes is an autoimmune disease characterized by the destruction of the insulin-producing β cells in the pancreatic islets. Islet autoimmunity precedes and is strongly predictive of type 1 diabetes development [3], and is therefore a useful intermediate end point when examining the role of environmental risk factors, such as diet. Therefore, this review includes research studies using type 1 diabetes or islet autoimmunity, where appropriate.

Cow's Milk

Prospective studies of high-risk children show that autoimmunity can appear as early as the first year of life [4, 5], suggesting that the putative environmental factor must occur very early in life in many situations. Therefore, infant diet behaviors, including breast-feeding and age at first exposure to non–breast milk substitutes (eg. cow's milk formula), are likely candidate exposures. Numerous studies have been conducted examining the association between age at introduction of cow's milk and type 1 diabetes or islet autoimmunity, as reviewed in Knip et al. [2•], and they have been inconsistent. One meta-analysis of case–control studies [6] and a nested case–control study of a cohort study [7] suggest an increased risk; a second meta-analysis [8] and the majority of the prospective cohort studies show no association [9–13]. Although there can be several explanations for this inconsistency, including

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methodologic differences in population selection and data collection, one alternative explanation is gene-environment interaction, with differences in the observed exposure association driven by differences in gene allele frequency across populations. Lempainen et al. [14] genotyped polymorphisms in three type 1 diabetes candidate genes (*INS*, *PTPN22*, and *CTLA4*) and tested whether their effect on risk of islet autoimmunity differed by whether children had been exposed to cow's milk formula before or after 6 months of age. The investigators found that the association between *PTPN22* and islet autoimmunity was only significant in children exposed to cow's milk formula prior to 6 months of age, suggesting that the effect of certain environmental exposures, such as early exposure to milk, may not be involved in the disease process in all cases, and that this gene-environment interaction may explain the contradictory observations on this topic across different populations.

Virtanen et al. [15] set out to investigate whether serum fatty acids differed between children developing islet autoimmunity and those remaining autoantibody negative. Myristic acid, pentadecanoic acid, monounsaturated palmitoleic acid isomers 16:1 n-7 and 16:1 n-9, and conjugated linoleic acid were positively associated with the risk of islet autoimmunity at or before the time of seroconversion. Because these serum fatty acids are biomarkers of milk and ruminant meat fat consumption [16, 17], this suggests that higher current consumption of milk and meat may be associated with risk of islet autoimmunity. Linoleic acid, which reflects vegetable oil intake [18], was inversely associated with the risk of islet autoimmunity, suggesting that current consumption of vegetable oil may be protective.

Maternal Diet during Pregnancy

Two papers published in the past year investigated dietary exposures in the maternal diet during pregnancy and risk of islet autoimmunity. Brekke and Ludvigsson [19] used a 22-item food frequency questionnaire collected just after delivery to examine the maternal diet collected from 5724 mother-infant pairs in Sweden. The investigators found that a low consumption of vegetables (<1 time/week) in the maternal diet was associated with a higher risk of islet autoimmunity in the child compared with daily consumption of vegetables (OR, 2.89; 95% CI, 1.18–7.05). No other factors in the maternal diet were found to be associated with islet autoimmunity in this analysis, which is contradictory to previous studies that have suggested that greater consumption of potatoes was associated with a lower risk of islet autoimmunity in children at increased risk for type 1 diabetes [20].

A Finnish study examined the maternal diet during pregnancy in 4297 mothers whose children are at increased risk for type 1 diabetes, recently reporting data concerning vitamin D intake [21]. Using an 181-item food frequency questionnaire, which asked about intake during the 8th month of pregnancy and was collected 1 to 3 months after delivery, the investigators found that vitamin D intake was not associated with risk of islet autoimmunity nor type 1 diabetes in the child, which contradicts previous studies that found that maternal vitamin D intake was associated with a decreased risk of islet autoimmunity in the child overall [22] or in the first year of life [23].

Wheat

In the biobreeding diabetes-prone (BB-DP) rat, it has been shown that gluten precipitates the onset of autoimmunity and diabetes [24]. Moreover, MacFarlane et al. [25] identified a wheat storage protein, which was subsequently identified as Glo-3A that may be associated with islet damage, by observing that antibodies to this protein were detectable in patients with diabetes but not in nondiabetic patients. Two prospective studies of high-risk infants and children showed an increased risk for islet autoimmunity associated with first introduction of cereals or gluten in the first 3 months of life when compared with first introduction in the 4th to 6th month of life [9, 10]. These data suggest that there are specific times in infancy wherein gluten or cereal exposure is associated with an increased risk of developing islet autoimmunity. The risk associated with early exposure may suggest a mechanism involving an aberrant immune response to cereal, gluten, or wheat antigens in an immature gut immune system among susceptible individuals.

Two studies were published in the past year that investigated what the aberrant immune response to wheat might be. Simpson et al. [26] compared levels of antibodies to a wheat storage globulin homologue of Glo-3A, which is a nongluten component of the wheat protein matrix, in children with and without islet autoimmunity. Although Glo-3A antibody levels did not differ between children with and without islet autoimmunity, the Glo-3A antibody levels were correlated with gluten intake, and inversely correlated with breast-feeding duration, but only in the children who developed islet autoimmunity. This suggests that Glo-3A antibodies may be markers of dietary exposure and may represent a unique response to exposure that is specific to children developing autoimmunity.

Mojibian et al. [27•] compared the immune response to wheat polypeptides between patients with type 1 diabetes and healthy control subjects. Diabetic patients showed a marked T-cell proliferation response to wheat polypeptides and, to a lesser extent, other dietary antigens such as ovalbumin and gliadin. These data suggest a general impairment of oral tolerance in some diabetic patients with the strongest response induced by a mixture of wheat polypeptides. One potential mechanism is that wheat polypeptides or perhaps gliadin (the fraction of gluten that is the most antigenic) pass through the gut epithelial barrier of the intestine, possibly during an episode of increased intestinal permeability for some as yet unknown reason. In susceptible individuals, this then triggers an immune response that leads to an inflammatory reaction, and then eventually autoimmune disease. Additional work needs to be done to provide evidence for this hypothesis; nonetheless, these two recently published papers as well as previous work suggest that the gut is an active player in the disease process leading to diabetes.

Gut Microbiome/Gut Permeability/Mucosal Immunity

In 2008, Vaarala et al. [28••] published a review of the evidence that type 1 diabetes results from a complex interrelationship between the gut microbiome, gut permeability, and mucosal immunity. Although there are no studies showing that animals or humans with type 1 diabetes or at risk for diabetes have a different microbiome than nondiabetic individuals, a study in nonobese diabetic mice showing that probiotic administration prevented the development of diabetes is suggestive that the microbiome might be important [29]. A study published this year adds evidence to this hypothesis. Valladares et al. [30] isolated two *Lactobacillus* strains from BB diabetes-resistant (BB-DR) rats, and then injected them into BB-DP rats to investigate their effect on the development of diabetes. BB-DR rats given *Lactobacillus johnsonii* but not *Lactobacillus reuteri* post-weaning developed diabetes at a reduced rate. These rats showed higher levels of the tight junction protein, claudin, suggesting that the feeding of *L. johnsonii* may have increased the gut barrier, thus inhibiting the passage of inflammatory antigens. This hypothesis is supported by a number of animal and human studies suggesting that the gut is more permeable in type 1 diabetic patients and that this may be true even before the diagnosis of type 1 diabetes [28••]. And finally, observations that dietary exposures, particularly during infancy, can modulate the gut microbiota [31, 32] suggest one mechanism by which diet may have an important role in the etiology of type 1 diabetes.

Omega-3 Fatty Acids

Factors in the diet may also play a protective role in the etiology of type 1 diabetes. In a longitudinal observational study following otherwise healthy children who are at increased risk for developing type 1 diabetes, investigators reported that higher omega-3 fatty acid intake was associated with a lower risk of islet autoimmunity (hazard ratio [HR], 0.45), and likewise, that higher omega-3 fatty acid levels in the erythrocyte membrane were associated with a lower risk of islet autoimmunity (HR, 0.63) [33]. This finding is supported by a case–control study from Norway that showed that children with type 1 diabetes were less likely to have been given cod liver oil during infancy than controls [34]. A paper published in the past year sheds light on the possible mechanism behind these observations. Wei et al. [35•] developed a transgenic mouse model that overexpressed the *mfat-1* gene, which converts omega-6 fatty acids to omega-3 fatty acids, with the end result being higher endogenous production of omega-3 fatty acids. This enabled the investigators to examine the effect of higher omega-3 fatty acid levels on the insulin-producing β cells of the pancreas. They showed that higher cellular production of omega-3 fatty acids enhances insulin secretion and confers resistance to cytokine-induced β-cell destruction [35•]. At the moment, it is unclear how changes in polyunsaturated fatty acid levels impact insulin secretion and survival of the β cells. The production of omega-3 fatty acids in the β cells and islets via *mfat-1* activity is achieved by using omega-6 fatty acids as substrates, thus bringing down the ratios of omega-6 to omega-3 fatty acids. Because the eicosanoid products derived from omega-6 fatty acids are more proinflammatory than those derived from omega-3 fatty acids, this would reduce the inflammatory state in the β cell, and may explain mechanistically why increased intake of omega-3 fatty acids or a decreased ratio of omega-6 to omega-3 fatty acids may reduce the risk of type 1 diabetes.

Prospects: The Environmental Determinants of Diabetes in the Young (TEDDY)

Although quite a bit of interesting research regarding diet and risk of type 1 diabetes has been published in the past year, there are still a number of holes and a troubling lack of consistency in the findings to date. It is likely that the results from previous studies have been confounded by imprecise assessment of dietary exposure, recall bias, failure to assess dietary exposures at very early ages, differing definitions of exposures, and small sample sizes. While many of these issues will be worked out with time as the scientific process takes place, an impressive development that is likely to facilitate this area of research in the near future is the collaborative study, TEDDY (The Environmental Determinants of Diabetes in the Young). The TEDDY study is a multicenter, multinational, epidemiologic study aimed at identifying environmental exposures that are associated with increased risk of autoimmunity and type 1 diabetes [36]. Maternal diet during pregnancy is assessed with a short food frequency questionnaire, concentrating on the intakes of fish, milk, and cereals. The duration of total and exclusive breast-feeding, age at introduction of various foods during the first 2 years of life, type of infant formulas used, source of drinking water (eg, local waterworks, bottled water, and private wells), elimination diets, and use of dietary supplements are recorded prospectively. Infant and childhood diet are assessed by 3-day diet records at 3-month intervals during the first year of life and biannually thereafter. In addition, plasma, erythrocytes, and toenail clippings are stored for future dietary biomarker analyses. TEDDY will provide an opportunity to fill important gaps in our understanding of the role of diet in the etiology of type 1 diabetes by studying from birth over 7000 high-risk children using an extensive arsenal of prospective dietary exposure assessments.

Conclusions

Evidence is building that infant and childhood diet play an important role in the etiology of type 1 diabetes and diabetes autoimmunity, and recent studies have started to explore the mechanism behind this relationship. Newly formed collaborative studies will help us to elucidate and interpret these exciting findings.

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