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Review Article

A review of association between early exposure to infant-feeding formulas and Type 1 diabetes among children

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Abstract

The increasing incidence of type 1 diabetes among children calls for a thorough understanding of the disease to stem its growth. Early exposure to infant-feeding formulas has been linked with the disease and several mechanisms of action have been proposed. However, it is unclear the exact mechanism by which infant-formulas aid in the pathogenesis of type 1 diabetes. This paper reviewed and articulated several hypotheses proposed as the mechanisms of action of infant formulas in the onset of type 1 diabetes. The Google search engine was used to search for relevant information on the internet from reputable sources such as PubMed, Google Scholar, among others. The majority of the studies reviewed overwhelmingly agreed early exposure to infant-feeding formulas may contribute to the pathogenesis of type 1 diabetes among children. Cow milk, for example, contains bovine insulin, which differs from human insulin with 3 amino acids, and can cause immune reactions in children. Gluten-containing diets such as wheat may cause proportional changes in immune cell populations or modify the cytokine/chemokine pattern towards an inflammatory profile. Concentrated soy-based formulas contain active estrogenic endocrine disruptors. Fruits, berries and roots may be infected with toxic antibiotics, which can start off autoimmunity. Nursing moms are therefore advised to breastfeed their babies for a long time before introducing infant-feeding formulas, especially those with a family with a history of diabetes.

Keywords: Type 1 diabetes, Infant-feeding formulas, bovine insulin, Gluten, Pathogenesis.

1. Introduction

Diabetes is a metabolic disorder which occurs when the intake of energy (from sugars or protein) is different from the need for that energy [1]. This can happen through many mechanisms among which is dietary intake. For instance, some processed foods such as milk and wheat products contain addictive substances which can stimulate food consumption regardless the physical need for energy [1]. This explains why obesity often comes with diabetes, but diabetes also occurs in lean people. The body has two types of energy at its disposal, fat-like substances and sugar-like substances. Consuming too little fat de-stabilizes blood-sugar levels, which can eventually cause diabetes. So, consuming protein or sugars can only cause diabetes in the relative absence of fat. This is because the body needs fat (fatty acids) to be able to deposit redundant blood-sugar (glucose) into the fat-depots as glycerol [1]. Evidences from several studies have proven this and other exogenous factors play a critical role in the pathogenesis of diabetes in genetically predisposed individuals.

Among the evidences is the fact that less than 10% of people with *HLA*-conferred diabetes susceptibility; do progress to manifest the disease. A pair wise concordance of type 1 diabetes of less than 40 % among monozygotic twins also shows there are risk factors other than genetics. Moreover, about10-fold difference in the disease's incidence has been observed among whites who live in

Europe, indicating non-genetic factors. Environmental pollution has also been suspected as one of the risk factors due to the increasing incidence of the disease over the past 50 years in many industrialized countries. Migration studies indicate that the disease incidence has increased in population groups who have moved from a low-incidence to a high-incidence region [2]. People are also sometimes diagnosed with type 1 diabetes during or after a viral infection, most often during winter when viral infections are more common [3].

The development of type 1 diabetes among children starts with beta cell autoimmunity, which is usually induced early in life [4,5]. The first autoantibodies may appear before the age of 3 months as markers of the induction of the disease process and the affected becomes positive at around 2 years [5]. Progression to full-blown type 1 diabetes occurs between the age of 5 and 10 years, especially among children in developed countries [6,7]. These successive processes show that the exogenous factors that contribute to the pathogenesis of type 1 diabetes must be operative in the first 2 years of life. Early exposure of a baby to infant-feeding formulas which is synonymous with partial or total suspension of breastfeeding has long been implicated in diabetes pathogenesis of type 1 diabetes. However, there are diverse opinions on their involvement or otherwise in the onset of type 1 diabetes. Consequently, this paper was intended to articulate evidences linking infant feeding formulas with the pathogenesis of type 1 diabetes.

2. Information search method

Reputable websites such as Google scholar, PubMed and some scientific Blogs were surfed for information on the subject using the Google search engine. Criteria used for selection of articles include authors' affiliation and educational background, the journal's reputation, accuracy and technicality of the research, sponsors of the research, among others. Many articles were retrieved, but some were rejected for failing the selection test. The selected articles were reviewed, compared and contrasted, and their findings summarized and articulated in this paper.

3. Results and discussion

Many studies overwhelmingly support association exists between early baby exposure to infant-feeding formulas and the development of type 1 diabetes. Some of the infant-feeding formulas suspected in the pathogenesis of diabetes are cow milk-based formula, soy-based formula, gluten-containing formulas as well as solid foods like fruits, berries and roots [8].

3.1 Cow Milk-based Formulas

The hypothesis that early exposure to cow milk or a lack of breastfeeding may predispose a baby to type 1 diabetes dates to the 1980s [9]. In 1994, the American Academy of Pediatrics (AAP) began recommending that infants with a strong family history of type 1 diabetes be breast-fed and that the introduction of cow milk be delayed [10]. Since then, many researchers have examined the association between early exposure to cow milk and development of type 1 diabetes in infants. Cow milk contains bovine insulin, which is similar to human insulin, but differs with 3 amino acids, and can cause immune reactions in humans. The body recognizes bovine insulin as an antigen, secretes antibodies against it, and may mistakenly attack own insulin-producing beta cells, culminating in type 1 diabetes [11]. Other factors such as viral infections may play a role in 'deceiving' the immune system to attack self while reacting to bovine insulin in cow milk [12]. Some scientists also propose that the proteins present in cow milk, particularly the beta-casein A1 molecule, are radically different from that found in human breast milk. These proteins have strong bonds and are exceedingly hard to digest for mammals with only one stomach, unlike ruminants which have many. This underscores the danger of consumption of foods designed for other species (and even for that species only during early development as a calf), will usually produce adverse effects [13]. Another hypothesis is that a baby's digestive system is too immature to process milk protein and this can cause an autoimmune response by the body, attacking the beta cells in the pancreas [14].

Cow milk proteins' involvement in the pathogenesis of diabetes was first reported in children with type 1 diabetes for the first time in 1988 by Savilahti *et al*.[15] The researchers observed that the diabetic children had significantly higher concentrations of serum immunoglobulin (Ig)A antibodies to cow milk and β-lactoglobulin and of IgG antibodies to β-lactoglobulin than age-matched controls. The scientists offered three alternative explanations for the observed enhanced humoral immune response to cow milk proteins in the diabetic children. First, increased consumption of cow milk before the presentation of clinical type 1 diabetes is a risk factor for the disease. Second, immune response to cow milk proteins may be enhanced in children who later developed type 1 diabetes. The third explanation is that the gastrointestinal permeability to cow milk proteins might be increased in such children. However, based on other research by the same authors, the scientists were much more comfortable with the latter two options.

In the other study, the pre-diabetic children who subsequently progressed to type 1 diabetes had elevated concentrations of IgG antibodies to β-lactoglubulin from 3 to 18 months of age. The children also had an increased concentration of IgA antibody titers to cow milk formula at the age of 9 months [16].

Many observational and experimental studies have been conducted to verify the culpability of cow milk protein in the pathogenesis of type 1 diabetes. In 1999, Finnish researchers monitored babies in diabetes-prone families and found that infants fed with cow milk are more likely later to develop the immune reactions associated with type 1 diabetes later [6]. The researchers tracked, until age 8 months, 173 newborns in Finland who had a close relative with type I diabetes. Half of these babies received cow milk formula and the rest got a formula in which the cow milk proteins had been broken into fragments called peptides (hydrolyzed formula). The two formulas taste and smell the same, so parents and researchers did not know which one a baby was drinking. At 2 years of age, 10 of 89 children administered cow milk formula had formed antibodies associated with type I diabetes. However, only 3 of 84 babies receiving the treated milk showed these antibodies. The immune system of the babies given the treated milk could have largely ignored cow milk proteins that have been chopped up in the hydrolyzed formula. However, contact with one intact protein in cow milk, might have set off a destructive process in the babies fed whole cow milk. The immune system of the babies given whole cow milk could have attacked insulin-producing beta cells in human, which resembles bovine insulin, and produced antibodies. A pilot study also from Finland found that compared to cow milk formula, a formula free of bovine insulin reduced the risk of type 1-related antibodies by age 3, in children at genetic risk of disease [17]. Another study found that children who later developed type 1 diabetes had higher levels of cow milk antibodies in infancy. The authors suggest that this finding may be due to increased gut permeability or delayed maturation of the gut immune system in the children who developed diabetes. It could also be that those children who developed type 1 diabetes had a dysfunctional gut immune system [16].

3.2 Gluten-containing Formulas

The seeds of some cereal grains such as wheat, rye and barley contain storage proteins otherwise known as prolamins. Some prolamins particularly gliadin (wheat), secalin (rye), and hordein (barley) contain high proline and have been shown to have toxic effects on intestinal cells of some sensitive people. The effects of these prolamins include the reduction of F-actin, inhibition of cellular growth, premature cell death, the rearrangement of the cytoskeleton, and increased small bowel permeability [18]. Gluten is another protein constituent found in wheat, rye, and barley. It is gluten that gives dough its elasticity, helps it rise and contributes to the texture of many food products such as bread, pasta, or imitation meats [19,20]. Gluten's involvement in the development of type 1 diabetes has been revealed by studies in humans and animals. A study has demonstrated that a diet without gluten reduces the level of NKG2D receptor and its ligand expression in mice. Thus, gluten may aid in diabetes pathogenesis by influencing proportional changes in immune cell populations or by modifying the cytokine/chemokine pattern towards an inflammatory profile. This suggests gluten intake plays an important role in the pathogenesis of type 1 diabetes [21].

Early introduction of gluten-containing foods (before 3 months of age) may contribute and even increase the risk of development of type 1-associated autoimmunity in genetically predisposed children [4,22]. Norris *et al* [23] found that exposure to any cereals before 3 months of age (and also after 7 months), led to a higher risk of developing auto antibodies in genetically susceptible U.S. children. The authors propose that perhaps the reason that the later introduction of cereals could increase the risk is that older babies are likely to be fed large amounts of food. Indeed, the study confirmed that babies given cereals at 7 months or older were more likely to be given more servings per day of cereals in the first month of exposure as compared to the others. This study also found that if cereals were introduced while the child was still breastfeeding, the risk of autoimmunity was lower. A paper published later on by the same authors confirmed that breastfeeding at the time of wheat or barley introduction was protective against later type 1 diabetes development [24]. Wahlberg *et al* [25] found that the combination of early cow milk formula and late introduction of gluten increased the risk of autoimmunity in children.

There are reported life experiences which have helped to confirm the involvement of gluten in the onset of type 1 diabetes. Among the life experiences was a story told of a 5 year old boy who developed type 1 diabetes with fairly normal HbA1c of 7.8%. He was not given insulin, but started eating a gluten-free diet instead and his HbA1c went down to 5.8-6%, which is essentially normal. For almost 2 years after diagnosis and on gluten-free diet, he still did not take insulin and his diabetes went into remission without insulin [26]. Another boy, 15 years old, with "silent" celiac disease, had signs of glucose abnormalities, and tested positive for the autoantibodies associated with type 1 diabetes. In other words, he was well on his way to developing type 1 diabetes. After 6 months on a gluten-free diet, his glucose went back to normal and the autoantibodies disappeared. Thirty six months later, he was still symptom-free [27]. In a long-term study, children with celiac disease

who had type 1 diabetes-related autoantibodies found that those antibodies gradually disappeared over two years after going on a gluten-free diet[28]. After a one-year trial of 15 children newly diagnosed with type 1 diabetes, HbA1c and insulin-dose adjusted A1c were lower in those who ate gluten-free. However, the number of people in remission was not different [29].

3.3 Soy

Soy has been heavily promoted by the soybean industry as being "the perfect food." The truth is, it is more like "the perfect storm" for anyone with diabetes [30]. Soy contains isoflavones- a thyrotoxic substance that blocks receptors for thyroid hormones and causes people to become hypothyroid. Since lowered thyroid function raises blood sugar and leads to weight gain, lowering thyroid by eating too much soy is the last thing anyone with diabetes needs to do to themselves. For people who are already taking thyroid hormones, soy makes it necessary to take a higher dosage to get to a healthy hormone level than when one does not eat soy [30]. Soy is proven to mimic or antagonize estradiol, a most potent and dangerous endogenous estrogen. Soy phyto-estrogens also abnormally manipulate ER-alpha and ER-beta hormone systems, further disrupting extensive endocrine systems throughout the entire body and brain [31]. Mostly during developmental exposures, soy endocrine disruptors disrupt the reproductive system and are toxic to multiple hormone systems. Along with all estrogenic chemicals, soy is established as extensively damaging to the reproductive system of both females and males. Generally, soy is reported as an accumulative endocrine disruptor capable of multiplying endocrine disruptor adverse effects. These effects are transgenerational, passing damaging endocrine disruptor effects from generation to generation. In fact, the FDA Poisonous Plant Database includes soy bean genistein and daidzein (soy estrogens) on its list of poisonous plants. Developmental exposures to soy estrogenic endocrine disruptors fail to meet several FDA codes and regulations [31].

The National Institute of Environmental Health Sciences (NIEHS) reports that soy phyto-estrogens demonstrate estrogenic effects equal to or lower than doses of DES estrogen. In 2002, NIEHS researcher, Retha Newbold expressed concern when her colleagues demonstrated that soy genistein triggers reproductive abnormalities, including uterine adenocarcinoma, a rare form of cancer. She fears that what is toxic to the reproductive tract is toxic to multiple hormone systems throughout the body and brain. Also like DES estrogen, the maternal consumption of soy products transfers estrogenic hormone disruptors to her fetus and again to her child while breastfeeding. Soy-based formula as 100 percent of an infant's dietary intake contains active estrogenic and anti-nutrient endocrine disruptors [31]. The amount of estrogen contained in 100 grams of soy protein is equivalent to that of one high-dose birth control pill. In women, this can be responsible for the onset of early menopause, hot flushes, PMS and many other hormone-related issues. A study estimated that babies who are being fed a soy-based formula are being fed the equivalent of around five birth control pills worth of estrogen every day. This amount of estrogen is thought to be responsible for the increased amount of learning disabilities and cases of ADD/ADHD. It is also thought to be responsible for the fact that girls are now going through puberty from as young as eight or nine years old [32].

Several human and animal studies have shown that early infant exposure to soy-based formulas may aid in the pathogenesis of type 1 diabetes. One human study from China found that infants given soy-based infant formula had double the risk of type 1 diabetes. It also found that more children with type 1 had been introduced to solid food before 3 months of age than children without diabetes [33]. In experimental animals, lifetime exposure to a soy-based formula caused high blood glucose levels in adult rats [34].

3.4 Fruits, Berries and Roots

The mechanisms by which early introduction of fruit, berries and roots aid in the emergence of β cell autoimmunity in children are not defined. However, one may speculate that such food items contain toxic contaminants [35]. Fruits, berries, roots, and vegetables may be infected by *Actinobacteria* called *Streptomyces* species which produces bafilomycins and concanamycins. These two are toxic plecomacrolide antibiotics characterized by a 16 or 18 member macrolactone ring. In potatoes, for example, *Streptomyces* infection causes common scab disease, which presents as crusted lesions or pits on the surface of the tuber and occurs wherever potatoes are grown. The ability of *Streptomyces* species to infect vegetables and to produce bafilomycins provides an avenue for these toxins to enter the human diet, either directly or indirectly, because of toxin accumulation through the food chain. Australian investigators have shown that bafilomycins can accelerate the onset of autoimmune diabetes in the offspring of exposed non-obese diabetic mice [36]. Cereulide toxin extracted from potatoes and milk has been shown to cause β cell destruction in fetal porcine islets [37].

It can also be argued that fruits, roots and vegetables are solid foods which can elicit an immune response in children genetically predisposed to type 1 diabetes. This has been supported by a study which investigated the diabetogenic effects of early exposure to solid foods among 1, 835 children who are genetically

predisposed to type 1 diabetes. All the participants included in the study were monitored from birth with complete information about solid food exposure. During the study, 53 of the children were diagnosed with type 1 diabetes and introduction of solid foods too soon or too late was observed to be a risk factor. Specifically, early exposure to fruits, excluding fruit juice, was observed to be associated with a greater risk, although the relationship became non-significant after accounting for other food exposures [38]. The researchers suggest that the risk posed by early exposure to solid foods might involves an abnormal immune response to solid food antigens in an immature gut immune system in susceptible individuals. On the other hand, the relationship between late exposure to solid foods and risk of type 1 diabetes may be related to the larger amounts given at initial exposure to older children. Also, if solid foods are introduced too late, when breast milk alone no longer meets the infant's energy and nutrient needs, nutrient deficiencies may occur, which may play a role in increasing risk. Additionally, the increased risk predicted by late exposure to solid foods may be related to the cessation of breastfeeding before solid foods are introduced, resulting in a loss of the protective effects of breast milk at the introduction of foreign food antigens [38].

4. Conclusion

Many studies have established an association exists between early exposures to infant-feeding formulas and type 1 diabetes pathogenesis, however the mechanism of their actions depend on the diet. Early introduction of feeding formulas, particularly before 3 months of age is problematic, perhaps because the intestine is still immature and unable to handle these foods. The proteins in the feeding formulas could also be too strong for a baby's immune system to handle. Some solid foods such as roots and berries could also be infected with toxic antibiotic bacteria in the soil and can start off an immune response if ingested. Mothers are therefore advised to adopt a total or partial breastfeeding for a long time before placing their children on pure infant feeding.

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