Hypothesis: Is the Omega-3 PUFA Content of Milk Related to Type 1 Diabetes?

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Introduction
The incidence of Type 1 Diabetes (T1D) has been increasing over the past 50 years.1 The geographical variation in the incidence of T1D varies 400 fold from a low rate in China to a very high incidence in Finland, Sardinia and Yemenite Jews in Israel.2,3 It is generally accepted that T1D should be viewed as a disease of autoimmunity that results in the destruction of beta cells of the pancreas of genetically susceptible individuals.4 Since less than 10% of those with this genetic predisposition progress to clinical disease, environmental factors and/or triggers are assumed to contribute to the manifestation of the clinical disease in genetically susceptible individuals.5 Identification of these environmental factors has great potential for reducing risk and the incidence of T1D. Various risk factors have been studied including: milk exposure, gluten, viruses, and toxins.6,7 Different protective factors have also been studied including: omega 3 fatty acids,8 early exposure to infections9 and vitamin D.10 Two frequently investigated environmental factors are the exposure to cow’s milk and breastfeeding. However, conflicting results have been found in different populations across different geographical locations. Even in populations with genetic similarities, such as Finland as compared with Iceland, or Yemenite Jews in Israel as compared with Yemenite Jews in Yemen, there are wide differences in incidence of T1D.11,12 The reason behind these epidemiologic findings is unclear at this time and further elucidating the factors related to this intriguing epidemiology of T1D can help us better understand certain risk factors, the pathogenesis of the disease, and help reduce the incidence of T1D.

We hypothesize that the variation of the omega-3 polyunsaturated fatty acid (PUFA) content of cow’s milk and human breast milk may play a very important role in the development of Type 1 Diabetes in genetically predisposed individuals and may also be an important confounder in many previously published and ongoing studies. Interestingly, the amount of omega 3 fatty acids in cow’s milk and human breast milk has been shown to vary widely depending on the diet of the cows13 and nursing mothers.14 This hypothesis could possibly help explain the conflicting results from various studies regarding cow’s milk exposure, breastfeeding and T1D and may also help explain some of the findings related to other environmental risk factors (e.g., viral infections, gluten) for the development of T1D through the beneficial effects of omega-3 fatty acids on this autoimmune disease.
Background

Many studies have shown that exposure to cow’s milk at an early age increases the risk of developing T1D in genetically predisposed individuals. However, not all studies have found an increased risk. Some researchers have postulated that these conflicting findings may be due to differences in the protein composition of the cow’s milk under study and numerous investigations have evaluated this possibility. In addition, longer exposure to breastfeeding has been shown to be protective.

Omega-3 PUFA deficient diets have been shown to heighten inflammatory reactions and thus may increase risk for autoimmune diseases. Various mechanisms have been proposed and different effects for the different omega-3 PUFAs have been investigated. One study of cod liver oil supplementation during the first year of life showed a reduced risk of developing T1D. The authors concluded that, though cod liver oil contains both omega-3 PUFAs and vitamin D, the beneficial effects of omega-3 PUFAs might explain their findings since there was no association found with the use of other vitamin D supplements in the study. Another study that specifically evaluated the role of dietary omega-3 PUFAs showed a significant reduction in the risk of development of islet autoimmunity in genetically predisposed children. One ecologic study did look at the fat content of cow’s milk consumed and T1D, but did not specifically evaluate the omega-3 PUFA component. There is also an ongoing feasibility study (Nutritional Intervention to Prevent Diabetes, ClinicalTrials.gov Identifier NCT00333554) to evaluate the use of omega-3 PUFA supplementation during pregnancy, breastfeeding and infancy to determine its effect on islet cell autoimmunity.

It is well documented that the omega-3 PUFA content of both cow’s milk and human breast milk can vary greatly depending on the diet consumed. For example, it has been shown that milk from cows feeding on grass in a pasture has significantly higher concentrations of omega-3 PUFAs as compared to milk from cows fed preserved grass. Feeding fresh alfalfa showed a significantly higher milk concentration of omega-3 PUFA as compared with the milk from cows fed alfalfa silage. Various studies have also demonstrated the effect of dietary factors on the omega-3 fatty acid composition of human breast milk, with some studies showing a 10-fold difference, depending on maternal intake. For example, in one study of lactating Icelandic women, it was found that high maternal intake of polyunsaturated fatty acids such as cod liver oil resulted in a much higher proportion of eicosapentaenoic acid, docosapentaenoic acid and docosahexaenoic acid in breast milk.

Implications and Potential of the Hypothesis

This hypothesis has great potential to advance our understanding of the epidemiologic anomalies of T1D and certain risk factors for the development of T1D in genetically predisposed individuals. For example, it has been well documented that Iceland has approximately half the incidence rate of T1D as compared to the other four Nordic countries (Finland, Norway, Denmark and Sweden). These countries have similar genetic backgrounds, similar high dairy intakes, and are similar in breastfeeding habits. Some investigators have evaluated the protein content of the milk in each country in an attempt to help explain this difference in incidence. However, one additional factor that may help explain this difference in incidence is the variation of the omega-3 PUFA component of the cow’s milk consumed. Interestingly, studies have found that cow’s milk in Iceland has a much higher amount of omega-3 PUFAs as
compared with the other four Nordic countries evaluated.\textsuperscript{34,35} In view of the findings regarding the protective effect of omega-3 PUFAs in the development of T1D discussed above, it is reasonable to postulate that this difference in omega-3 fatty acid content of the cow’s milk among the countries studied may also help explain the differences in incidence in T1D found between Iceland and the other Nordic countries and thus requires further study.

Israeli Yemenite Jews have experienced a rapid increase in the frequency of T1D over the past few decades.\textsuperscript{36} They have a susceptible HLA diabetogenic genotype\textsuperscript{37} and currently have the highest incidence of T1D of any ethnic group in Israel\textsuperscript{3} and are approaching the incidence rate of Finland and Sardinia. However, Yemenite Jews did not have a high incidence rate of T1D when living in Yemen and this increase in incidence only occurred after they immigrated to Israel.\textsuperscript{72} One study explored the role of cow’s milk in Yemenite Jews and the development of T1D and found that early exposure to cow’s milk was common both in Yemen and in Israel for this population under study and concluded, “cow’s milk does not play a crucial role in triggering diabetes.”\textsuperscript{12} This ethnic group has gone through many changes since immigrating to Israel that could definitely be playing a role in the change in incidence.\textsuperscript{38} However, one possible reason for this “negative finding” regarding milk intake and T1D could be that the omega-3 PUFA content of the cow’s milk consumed in Yemen, where cows are mainly pastured, was much higher than currently in Israel, where cows use imported feed, thus leading to the different incidence rate of T1D. Therefore, it is very important to investigate the omega-3 PUFA content of both the cow’s milk and human breast milk as a possible confounder in any study evaluating the role of cow’s milk and duration of breastfeeding in the development of T1D. It could also be playing a role in the pregnant woman’s omega-3 PUFA status since many women are consuming cow’s milk during their pregnancy.

This hypothesized potential confounder also needs to be considered when assessing other risk factors in the development of T1D besides cow’s milk and breastfeeding. For example, it may help elucidate a better understanding of the findings regarding seasonality of birth and T1D. Some epidemiologic studies have shown that children born in the spring and summer have a higher risk of developing T1D.\textsuperscript{39-41} Some authors have attributed this to possible exposure to perinatal viral infections or other environmental factors.\textsuperscript{39} However, the documented seasonal variation of the omega-3 PUFA content of cow’s milk\textsuperscript{42-44} and human breast milk\textsuperscript{45} may also be playing a role in this association of seasonality of birth and T1D.

**Conclusion**

In conclusion, this hypothesis proposes that the variation of the levels of omega-3 PUFA concentration in both cow’s milk and human breast milk may play an etiologic role in the development of Type 1 Diabetes. In addition, the variation of the levels of omega-3 PUFAs may act as a confounder in different studies investigating various risk factors for the development of T1D. Thus, assessment of the omega-3 PUFA content of milk should also be incorporated into projects currently underway, if possible, and in any future studies to help better evaluate the various risk factors under study, e.g., viral factors, cow’s milk proteins, breastfeeding, vitamin D, and their relationship to the development of Type 1 Diabetes.
References

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