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Type 1 diabetes epidemic in Finland is triggered by zinc-containing amorphous silica nanoparticles

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ABSTRACT

Type 1 diabetes (T1D), an autoimmune disease, breaks out in some of the children who has genetic susceptibility to T1D. Besides genetic susceptibility some environmental factor(s) are required to trigger the disease. The incidence of T1D in Finland is highest in the world, so we must seek an environmental factor, that is typical for Finland and can declare many aspects of T1D epidemiology and biology. In the literature most popular trigger has been enterovirus infections. It is difficult however to find why enteroviruses would be in this role in Finland in contrary to neighbouring countries e.g. Sweden.

Colloidal amorphous silica (ASi) is typical for Finnish environment in consequency of the geohistory of Finland, great part of Finland is an ancient lake and sea bottom. ASi concentrations in natural waters are high in April–June and in November, only traces can be found in the rest of months. Pure colloidal ASi is not a strong trigger for T1D, but ASi particle which has surface adsorbed tetrahedrally coordinated zinc (ASiZn) is probably the trigger which has kept it's secret up to date. Zn functions as address label which conducts the ASiZn particle to the beta cell, whose content of zinc is highest in the body. ASi particle adheres to membrane proteins distorting their tertiary structure revealing new epitopes. If the fetus has not met these epitopes at proper time during intrauterine development, the consequence is that the negative selection of lymphocytes in the thymus and bone marrow and fetal liver is not perfect. When a child later in postnatal life becomes predisposed to ASiZn particles the immune system reacts to these as to nonself proteins. As a consequence the insulin producing beta cells are destroyed.

Many observations from diabetes research support the hypothesis, some to mentioned. 1. Three common autoantigens (ZnT8, ICA512/IA-2, GAD65) are membrane proteins whose function zinc regulates. 2. Geographical variation in Finland is convergent with surface water manganese concentrations. Manganese is the principal Zn scavenger and high manganese in water reduces ASiZn particle formation and the incidence of T1D. 3. The incidence of T1D depends of drinking water pH. The highest incidence can be found within water pH 6.2–6.9. Zn coordination changes from octahedral (unphysiologic) to tetrahedral (physiologic) at pH 6.56. In the text are presented five more supporting observations e.g. the similarity between the soils in Sardinia and Finland in respect to ASi.

Introduction

Type 1 diabetes (T1D) is a disease in which the beta cells in the islets of pancreas are destroyed and there is total lack of insulin in the patients system. T1D is an autoimmune disease. Patients own immunologic system destroys the beta cells. As a rule the disease is diagnosed before the age of 15 years. Large epidemiological data concerning T1D has been collected in Europe longer time than in USA. At global level the incidence and prevalence of T1D varies greatly. It can be found about 350-fold variation in T1D incidence among different countries [1].

The incidence of T1D has been increasing throughout the world for decades. In Finland the incidence of T1D is highest in the world and it has increased 4.5-fold from the early 1950s [2]. In Sardinia the incidence of T1D is almost as high as in Finland (in Finland about 60 cases per 100,000 per year, in Sardinia about 40 cases per 100,000 per year). In the neighboring countries of Finland the incidence is about one-third that of Finland [1].

T1D breaks out in some of the children who has a genetic susceptibility to T1D [3]. However only 1 of 15–20 with HLA conferred susceptibility progresses to the clinical disease [2]. It is obvious that besides the genetic susceptibility some environmental factor(s) are needed for disease to develop. In spite of tremendous research, the progress in the field of environmental factor(s) or trigger(s) has been limited. More success has been achieved in

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the field of genetics and in the knowledge of the function of immune system [1].

I think that we have enough knowledge to resolve the T1D enigma in Finland. A good guideline in resolving the enigma is what Milton Terris wrote: "Epidemiology must draw upon and synthesize knowledge from the biological sciences of man and of his parasites, from the numerous sciences of the physical environment and from the sciences concerned with human society".

Characteristic features of Finnish environment (soil and water environment)

Up to now T1D research has not analyzed the special features of Finnish environment. The last glaciation came to an end in Finland about 10,000 years ago. Earth's crust had been sank under the ice sheet especially around the Gulf of Bothnia (the northern long gulf of the Baltic Sea). When ice smelted the land began to uplift and the uplift continues still. Most of Finland is therefore the ancient sea and lake bottom (there is also in the post-glacial development of the Baltic Sea the 1800 year long flood lake period, the Ancylus lake). Land uplift takes place nowadays slowly (max 8 mm/year in Oulu region) but immediately after the ice lost much faster. The earth revealed is flat and susceptible to flooding, especially to spring flood after the smelting of snow.

Finland has been the land of spring flood and flood lakes and flood meadows. When we now look at the Finnish landscape, we cannot imagine in our mind what was the landscape like five hundreds years ago. Man has dried thousands of shallow lakes and altogether about one million hectares of peatland has been taken into cultivation since 1600s. Environment like this has been favorable for diatom growth and preservation (as various size particles) at the sediments and in the soil. A cell wall of diatom is formed from amorphous silica (ASi) and after diatom death the cell wall begin to dissolve in water. In shallow waters the cell wall reaches the bottom before it is solubilized. The lakes in Finland are as a rule very shallow. It is not known why ASi in sediment does not solubilize, on the contrary it becomes more resistant with time. The cell wall is composed of nanosized silica spheres, which release when the cell wall partially solubilizes [4].

Phytoliths from dead plants bring a part of environmental ASi. ASi content of the plants that grow in the wet soils is especially high (e.g. sedges). Weathering of clays by organic humus acids and carboxylic acid generate ASi into the environment [5].

Freezing of natural waters generate microporous ASi because soluble orthosilicic acid precipitates [6]. In Finland all the lakes and the rivers freeze at winter time.

In natural waters ASi appears as particles of different size in the suspended particulate matter and the concentrations of ASi vary much seasonally in Finnish natural waters. The monthly concentrations of ASi in the Vantaa river (a small river in southern Finland, drains to the Gulf of Finland) varied from 0.3 mg/L to5.4 mg/L. ASi concentration was high in the spring (April–June) 2.3 mg/L and the second peak was in November 5.4 mg/L. Only traces were found in the rest of months [7].

In the Finnish lakes the entire water column is rotated or mixed two times a year in the spring and in the fall. The water rotation can release fine particles from the surface of the sediments. Interestingly in the before mentioned river, zinc concentrations in the suspended particulate matter (fractionated as >25 μm, 2–25 μm and 0.2–2 μm) were highest in the finest fraction in April (128 μg/L) and in November (126 μg/L), in other months the concentrations were 0–21 μg/in the finest fraction. In the coarser fractions zinc concentrations varied between 0–43 μg/L. Zinc concentrations varied along the concentrations of ASi and zinc was mainly in the finest fraction of ASi (unpublished personal communication M. Lehtimäki).

There is no research about the amount of ASi in the Finnish soils. Nearest research findings are from Southern Sweden, where the total amount of ASi exceeds 20 metric tons per hectare [8].

Changes in the social environment after World War II in Finland

Significant changes in the water distribution has been taken place after the 1940's. Before that time in the countryside the drinking water was taken from the own wells. The wells had been dug as a rule into moraine or clayed ground. After the 1940's the municipal water distribution has become prevalent. Raw water is taken from the sandy aquifers which however often get water from near located lake or pond (synclinal aquifers). These sandy aquifers are often so called concealed eskers, sandy layers are underneath a clay or peat layers. Many big towns take raw water from lakes or rivers. Water purification has not been planned for colloid particle removal. In the countryside raw water is not in a every case purified at all.

Before the 1940's there were a dairy in nearly every parish and the people used milk produced in the near distance. Nowadays there are only few big dairies and milk is carried for long distances to the users. Milk production is concentrated in the western part of the Central-Finland.

The T1D incidence has grown coincident with these trends. Milk and raw water mirrors the environment in which they are produced. The same is true for root vegetables. The production of potatoes is concentrated to the same areas as the milk production. I have earlier represented the connection between the quality of drinking water and autoimmune thyroiditis in Finland. Autoimmunity is triggered by nanocolloidal amorphous silica particles coated with humus and iodine (the ternary system ASi-humus-iodine particle) [9].

Unique zinc

Zinc (Zn) participates in many biological reactions. Zinc has many unique properties that make it suitable for many functions that are essential part of the life [10]. Because Zn is spectroscopically silent the significance of Zn in metabolic processes was understood much later than e.g. iron. Zn does not undergo easily oxidation or reduction reactions. The most significant feature of Zn is it's flexible coordination geometry. Zn coordinates both tetrahedrally (coordination number 4) and octahedrally (coordination number 6) and can switch coordination geometry without energy change. A little change in pH switches the coordination [11]. Zn can expand its coordination sphere at one step of the enzyme reaction and contract coordination sphere at another step.

The highest Zn content in the body has been found in the pancreatic islets. In the islets most zinc is stored in the secretory vesicles of the beta cells. The concentration of Zn in these vesicles is very high, approximately 20 mM. Within the beta-cell secretory vesicles insulin and zinc form hexameric insulin crystal that contains two Zn atoms and six insulin molecules [12]. Although Zn is an essential trace metal, the intracellular Zn concentration is tightly regulated. Free Zn ion concentration in the cytoplasm is estimated to be in the picomolar range [13]. Therefore Zn homeostasis inside the cell is controlled by fine mechanism, which contains 24 various zinc transporters, 14 transporters that conduct zinc into the cytoplasm (ZIP-family) and 10 transporters which draw zinc away from the cytoplasm into cell organelles or out of the cell (ZnT-family). Inside the cell numerous metallothioneins buffer the Zn concentration [14]. In the human pancreatic islet