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

S.K. Junnila *

Health Centre of The Town of Haapajärvi, 85800 Haapajärvi, Finland

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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

* Address: Siiponkoskentie 28, 85800 Haapajärvi, Finland. Tel.: +358 08834604.
E-mail address: seppo.junnila@pp.inet.fi

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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

can be identified 19 of the 24 known mammalian zinc transporters [12].

The physico-chemical reactions of Zn (speciation) in water and moist soil are very divergent. As a rule free ionic zinc is almost absent and most of zinc is ligand bound. Zinc binding ligands can be organic complexes, clay particles, mineral particles and metal oxides (including ASi particles). Adsorption of Zn to ASi has been studied much in laboratory, less in the field [11].

Hypothesis

T1D is an autoimmune disease that precipitates in genetically susceptible individuals by environmental trigger(s). In Finland the environmental trigger is colloidal ASi into whom Zn is adsorbed as tetrahedral coordination complex (ASiZn). Zn functions as an address label for ASiZn to gain access into the beta cell. It is known that the functions of transporter proteins, receptor proteins and various channels is based more on the coordination state of the transported material than the size of the molecule. Beta cells uses a lot of zinc and zinc is tetrahedrally coordinated on the surface of ASi nanoparticle. Only tetrahedrally coordinated zinc can enter the zinc transporter system. This ASiZn particle adheres the plasma membrane of the beta cell and is trapped in the zinc transporters and/or can entrance into the beta cell by endocytosis.

The ASi frame of the particle adheres for nearby proteins e.g. insulin, autoantigen ICA 512/IA-2 or zinc transporter ZnT8 and distorts the protein uncovering new epitopes in the protein. Immune effector cells keep these uncovered epitopes as non-self because the maturing T-cells in thymus and B-cells in bone marrow and fetal liver have not met these epitopes in the critical intrauterine time period because ASiZn particles are abundant in water only at two periods during the year. Both periods are about one month in duration. Besides through water these inexperienced immune cells can contact these ASiZn particles for first time when the are derived from root vegetables or milk.

As a summary; negative selection of T-cells in the thymus and/or B-cells in bone marrow and fetal liver has not been adequate following the periodic appearance of ASiZn nanoparticles in water and food.

Observations that support the hypothesis

1. Autoantibodies. Almost all T1D patients have autoantibodies against zinc transporter ZnT8 [1]. ZnT8 is zinc transporter specific to beta cells [15]. Another common autoantibody in T1D, ICA512/IA-2 is directed towards tyrosine phosphatase like intrinsic membrane protein of secretory granules in the beta cells [16]. This protein is homologous to the receptor type protein tyrosine phosphatase. Zinc regulates the function of this protein in picomolar concentrations [17]. This protein participates in the secretory function of the insulin containing granule i.e. insulin secretion [16]. Third common autoantigen in T1D is directed towards GAD65 that is GABA-synthesizing sulfhydryl enzyme. Zinc is the potent inhibitor of sulfhydryl enzymes [18]. GAD65 is localized to the membrane of the small synaptic vesicles in the beta cells. These vesicles do not contain insulin but they contains GABA [19]. It can be found that all the three autoantigens are membrane proteins and that the function of all are regulated by zinc. These proteins attract tetrahedrally coordinated zinc which can locate also in the surface of the ASiZn nanoparticle. At the same time ASi nanoparticle adheres to the membrane protein and distorts its tertiary structure exposing new epitopes in the protein.
2. Geographical variation. Although in Finland the incidence of T1D is highest in the world, there is at the same time a clear geographical variation in the country. It can be found the persistent high risk and low risk areas [20]. High risk areas are convergent to the areas to whom it is typical the low manganese and iron concentration in the stream waters [21]. As a rule the manganese concentrations in the stream waters are 2–3 times greater than the zinc concentrations and the iron concentrations are about 20 times the manganese concentrations. Manganese and iron are efficient scavengers for zinc ions. High manganese and iron concentrations in water prevent zinc adsorption to ASi particle and reduce ASiZn particles in drinking water. For the most time the greater part of zinc is adsorbed onto iron oxides than onto manganese oxide. However during the spring and fall rotation in the lake and river system (a period when manganese releases from sediments and precipitates as manganese oxide in the water) manganese functions as the principal zinc scavenger [22]. Variation of T1D incidence follows better the variation of manganese concentration than that of iron [20,21].
3. The quality of drinking water seems to influence the risk of T1D. Tap water pH has strong influence on the T1D risk. In the Norwegian study the highest risk was associated with tap water pH 6.2–6.9, OR 3.73 (if water pH > 7.7 then OR 1.00) [23]. Zn sorbed on silica has octahedral coordination with O atoms at pH below 6.12, coordination changes to tetrahedral at pH 6.56. However at pH 7.51 in the Zn-ASi system it was formed amorphous $Zn(OH)_2$ precipitate and the Zn loading on ASi began to decrease. In other words, the Zn loading on ASi increases when pH increases and Zn coordination changes from octahedral to tetrahedral at pH 6.56 but at pH 7.51 or higher the Zn loading on ASi begins to decrease when it begins to form amorphous $Zn(OH)_2$ precipitate [11]. This is so far the best explanation for the association of tap water pH and T1D risk. As it was mentioned before only tetrahedrally coordinated zinc or the particle coated with tetrahedrally coordinated Zn is incorporated into zinc proteins.
4. Sardinia. The incidence of T1D in Sardinia is almost as high as in Finland [24]. The risk of T1D in Sardinia is highest in the Southern part of the island. The high risk area is the river plain from Gagliari to Oristano. This plain is composed of thick riverine sediments, mainly flood sediments. Drinking water in these districts comes from deep sediment layers which contain mush ASi. Annual precipitation is divided very unevenly. Winter is rainy and summer is dry. In conditions like this, ground water ASi concentrations fluctuates. Perhaps there is only one peak after the rainy period. Until the World War II there were in Sardinia numerous swamps and flooded areas and much malaria. After World War II flooded and wet soils were dried in order to eradicate malaria [25]. Malaria was eradicated but T1D and multiple sclerosis began to increase as in Finland when settlements spread to these dried areas.
5. Root vegetables. It was found that early introduction of root vegetables (in Finland chiefly potatoes) before the age of four months is associated with increased risk of beta cell autoimmunity among Finnish children with HLA-conferred susceptibility to T1D [26]. ASi nanoparticles smaller than 200 nm efficiently penetrate walled plant root cells through endocytic pathways. Particles pass through pores in the root cell wall. Pore sizes varies with the plant. The uptake of ASi nanoparticles from the surrounding soil water is concentration dependant [27,28]. Water flows to the tubers of the potato directly from surrounding without circulating the other parts of the potato plant (root, stem, leaves), thus avoiding the filtration function of the longer flows within the plant xylem and phloem (types of plant vessels) [29].

6. Different speed of seroconversion in the two towns. It has been done very large epidemiological studies in Finland concerning T1D. One of these is "The diabetes Prediction and Prevention Study (DIPP)" [3]. In cited study Kukko et al. found that among children with increased HLA-DQB1-conferred genetic susceptibility towards T1D seroconversion to ICA positivity was faster in the Turku region than in the Tampere region. The same was true also for seroconversion at least to one additional antibody (IAA, GAD65 or IA-2A). Not a single high risk child seroconverted to ICA positivity during the first year of life in the Tampere region whereas in the Turku region 15 children seroconverted (the series comprised 1203 children in the Tampere region and 1793 children in the Turku region). However at the end of follow-up time (36 months) the proportion of seroconverted to ICA was the same in the Tampere region and in the Turku region. Seroconversion occurred only slower in the Tampere region than in the Turku region. The Turku region belongs to a clay plain which is the ancient sea bottom. The town of Turku takes it's raw water from the small river which flows through the clay plain. Into river water is released plenty of ASi from the ancient sea bottom clays twice a year (in April–June and November) [7]. The town of Tampere takes it's raw water from the lake Roine. The lake Roine is large and very deep in Finlands scale and water is very clear. ASi (diatomaceous earth) does not accumulate at the bottom of such a lake. The landscape is more hilly in the Tampere region than in the Turku region. High sandy eskers are typical in the Tampere region contrasted clay plains in the Turku region. In the light of this study the quality of drinking water is the crucial originator for seroconversion. The babies in the Turku region have a greater probability to become predisposed to great dose of ASiZn nanoparticles earlier than the babies in the Tampere region.
7. Enteroviruses. The results of many cohort and case control studies indicate that enteroviral RNA can be found in the sera and/or peripheral blood of prediabetic and newly diagnosed T1D patients more frequently than in control cases with the same HLA-conferred susceptibility to T1D [30] However in fecal samples it could not be found any difference between the groups [31]. Enterovirus serology seems also to be positive (IgG and IgM immunoglobulins specific to enteroviruses) more frequently in the seroconverted (prediabetic) case subjects than control subjects with the same HLA-conferred susceptibility. In accordance with my hypotheses ASiZn nanoparticles when occurring in a great amount in the body trigger T1D. It is known that ASi particles adsorb strongly viral RNA and enteroviral particles [32] and preserve RNA for a long time. Silica bound RNA and virus particles also retain their infectivity and antigenicity for some time [33]. ASi function also as an adjuvant eliciting the stronger immunoglobulin response. The subject material in the cited studies comprises mainly of young children with whom subclinical enteroviral infections are common, viruses homing the gut. In this light enteroviral RNA in blood only represents a significant biomarker of early stage of T1D. Enteroviral RNA in serum and/or blood is the proof that the patient has been exposed to the great amount of ASi particles in the near past and enteroviral RNA has shifted along with ASi nanoparticles from the gut to the circulation without verified acute infection.
8. Changes in the significance of genotype. The incidence of T1D has increased 2.5 times from 1960's to 2000's in Finland and the same trend can be find in almost all developed countries [34]. However there is a subgroup of T1D in which the incidence has not rised, the patients which have highest genetic risk profile. The rise in incidence has occurred among the patients with lower genetic risk. In the same time period the age at the diagnosis of T1D has declined. This means that the impact of environment on the children has increased and more and more the lower risk children get T1D [35]. This is in the line of the before mentioned changes in Finnish environment e.g. in the water and milk distribution. The result of these changes is the stronger predisposition to ASiZN nanoparticles.

Discussion

Nanotechnology has developed rapidly in recent years. Titanium dioxide and silica dioxide nanoparticles (Si in the form of either crystalline or amorphous one) are used as food additives and in cosmetics. Asi nanoparticles are also used in drug delivery devices and in gene therapy. Therefore it is surprising how little attention naturally occurring nanoparticles in the surrounding has received. ASi is typical for many soils and waters in the northern hemisphere. Many autoimmune diseases are also typical for the northern hemisphere e.g. T1D, multiple sclerosis and rheumatoid arthritis. I have now pointed out two autoimmune diseases that in Finland are associated with colloidal ASi, namely autoimmune thyroiditis and T1D [9].

Earlier no one has done a comprehensive synthesis of the etiology of T1D comprising all the aspects of the good epidemiological study, namely biological sciences of man, numerous sciences of physical environment and sciences concerning with human society. I am conscious that the hypothesis demands much verifying studies. I hope that it is in future possible to reduce the incidence of T1D in Finland and in other high incidence areas.

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Conflict of interest

None declared.

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