ISSN 2475-5451

Short Communication

International Journal of Diabetes & Metabolic Disorders

Beyond Genetic Borders: Sardinian Exposure And Type 1 Diabetes

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Submitted: 24 May 2018; **Accepted**: 31 May 2018; **Published**: 06 June 2018

Type 1 diabetes mellitus (T1D), one of the most chronic childhood disease, results from an autoimmune destruction of pancreatic β cells producing insulin, with insulin deficiency. Recently significant technological advances have been achieved in treatment and quality of life in diabetic patients but the causes are still uncertain, so it is still very difficult to foresee the possible prevention of this disease. The genetic factors alone do not explain the high risk of T1D, sharply increased over the last 40 years in Sardinia, with the second highest risk in the world after Finland, even as many of the people genetically predisposed to T1D do not develop the disease [1]. It is still unknown why some people develop T1D although it is agreed that genetic, non-genetic and probably epigenetic environmental factors all together contribute to the disease. The environmental factors are probably very important for both the development and the increase of T1D. The epigenetic factor possible interrelationships are to be cleared at most.

All these factors make the Island an ideal region for investigation of T1D. Consequently, several studies have been carried out in the Island toward the aetiopathogenesis of T1D [1]. As the primary prevention trials, we have participated in the TRIGR study (Trial to Reduce IDDM in the Genetically at Risk,), the first T1D primary prevention study (double blind trials) in the world that started in 2002 [2].

The hypothesis of the study was that the early exposure to cow's milk could have accelerated the destruction of β cells in genetically predisposed individuals and that the weaning with an extensively hydrolysed formula could decrease the risk of T1D in young children. In Sardinia, the TRIGR study was conducted at the Diabetes Center of Brotzu Hospital in Cagliari, one of the 77 centres that had participated across Europe, Australia, Canada and the United States, with over 2,800 children recruited. It has been then proposed to Sardinian patients with T1D the genetic screening of their children. Newborn infants, with defined human leukocyte antigen (HLA) genotypes, were recruited between May 2002 and January 2007 and then followed up until the youngest participant reached 10 years of age. Enrolled infants received, in addition to breastfeeding (breastfeeding was always encouraged), the hydrolysed casein formula or cow's milk for the first 6-8 months of life. The final result of the TRIGR Study was published on 2 Jan 2018 in the Journal of the American Medical Association (JAMA): an extensively hydrolysed casein formula during infancy did not result in a reduction in the incidence of T1D compared to regular and the intact cow's milk-based formula [2]. As a result, the question is still open to debate: "What are the environmental factors that contribute to increasing the risk of diabetes?"

The T1D in Sardinia still remains an "enigma". Recent studies have linked the elevated presence of Mycobacterium Avium Paratubercolosis (MAP, a bacterium frequent present in cow's milk) to the onset of T1D in the Sardinian population [3]. The unique geochemistry of Sardinia with its particular concentration of heavy metals has suggested another triggering factor such as the exposure to heavy metals, already associated with the development of other autoimmune diseases in Sardinia [4]. In our search for any correlation between the incidence of T1D and heavy metals (performed in collaboration with the University Geology group led by Paolo Valera) a slight negative correlation ($r = -0.332$; $p = 0.0002$) between zinc and T1D was found [5].

These results would suggest a protective role of zinc towards the development of the disease, and its deficiency could be a possible triggering cofactor. A negative association between T1D risk and ultraviolet B (UV-B) solar irradiation has been also suggested [6, 7]. To verify this finding we conducted an ecological analysis to assess the possible relationships between UV-B radiation levels and T1D incidence in Sardinia (once again with the geology team of Paolo Valera). A standardized algorithm based upon the solar constant and the latitude of each municipality has been employed to calculate the amount of total solar irradiance. UV-B radiation during the winter solstice for each Sardinian municipality was then calculated. T1D incidence data were obtained through on going the Sardinian Diabetes Registry. The relationship between UV-B radiation and T1D incidence in Sardinia was assessed through a simple correlation analysis. A mild negative correlation ($r=-0.154$; $p= 0.002$) was obtained between UV-B radiation and T1D incidence [8].

A protective effect (even weak) of UV-B irradiance in T1D and/or a role of vitamin D deficiency on T1D risk was suggested by many authors and our results are consistent with this hypothesis (protective role of sun exposure?). From this, we hypothesize that the incidence of T1D could be influenced by exposure to multiple risk factors such as: MAP, common viruses, heavy metals, Zinc deficiency and solar irradiation which together would participate to increase the risk of T1D. Another environmental factor, possibly correlated with autoimmune diseases, emerged in recent years: the variation of the gut micro biome [9]. It would be interesting to unravel how

and how much of the risk to T1D could be ascribed to the gut micro biome alterations and how all this could be influenced by different environmental factors (air pollutants, heavy metals, MAP, etc.) in genetically predisposed subjects. The search for the "puzzle" is still open: what environmental factors actually are involved in the pathogenesis of the disease and its prevention?

Acknowledgments

Paolo Valera and Alessandro Sanna for their research work on Geomedicine and our collaboration.

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