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### The environment and the type 1 diabetes in Sardinia

ype 1 diabetes mellitus (T1D) results from an autoimmune destruction of insulin-producing  $\beta$  cells, with lack of insulin. Newly significant advances in technology have been achieved in the treatment and quality of life in diabetic patients but the causes are still uncertain, so its prevention is still far away. Genetic factors are relatively well known, even most people genetically predisposed to T1D do not develop it. The genetic factors alone do not explain the increased risk for T1D, sharply increased over the last 40 years in Sardinia, reaching the second highest risk in the world after Finland. The environmental factors are probably very important for the development and the increase of T1D risk. The epigenetic interrelationships are to be cleared at most. All these factors make the Island an ideal region for prevention of T1D. Consequently, several studies have been carried out in the Island toward the aetiopathogenesis of T1D. As the primary prevention trials, we have participated to the TRIGR study (Trial to Reduce IDDM in the Genetically at Risk), the first T1D prevention study (primary, double blind) across the world that started in 2002. The hypothesis of the study was that the early exposure to cow's milk could have accelerated the destruction of  $\beta$  cells in genetically predisposed individuals and that the weaning with an extensively hydrolysed formula could decrease the risk of T1D in young children with a family history for T1D. 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 the entire world (Europe,

Australia, Canada and the United States) with over 2,800 children recruited. The final result of the TRIGR Study was recently published (2 Jan 2018 in the Journal of the American Medical Association JAMA): no correlation was found between the risk of T1D and early exposure to cow's milk. As a result, the question is still open: "What are the environmental factors that contribute to increasing the risk for T1D?". The T1D in Sardinia still remains an "enigma". Recent studies have linked the elevated presence of Micobacterium avium paratubercolosis (MAP, a bacterium presents frequently in cow's milk) to the onset of T1D in the Sardinian population. The unique geochemistry of Sardinia with its particular concentration of heavy metals has been hypothesised another triggering factor such as the exposure to heavy metals, already associated, in Sardinia, with the development of other autoimmune diseases. In our search for the correlation between the incidence of T1D and heavy metals distribution across Sardinia, a slight negative correlation (r = -0.332; p = 0.0002) between zinc and T1D was described. These results would suggest a protective role of zinc in the development of the disease, and its deficiency could be a plausible triggering cofactor. A negative association between T1D risk and ultraviolet B (UV-B) solar irradiation has been suggested. We conducted an ecological analysis to verify the possible relationships between UV-B radiation levels and T1D risk in Sardinia. A standardized algorithm based upon the solar constant and the latitude of each Sardinian municipality has been used to calculate the amount of total solar irradiance. UV-B radiation during the winter solstice for each Sardinian municipality



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was then calculated. This value was adjusted to the annual average of cloudiness and to the percentage of direct solar irradiation of the territory. T1D incidence data were obtained through 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. 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 in raising the risk of incidence of diabetes. The search for the "puzzle" is still open: what environmental factors actually are involved in the disease and its prevention?

#### Biography

Marco Songini is the Director Center for the Treatment of Complications of Diabetes, San Michele Hospital Cagliari, Sardinia, Italy. He has published over 161 papers on the subject of atherosclerosis and epidemiology of Diabetes. He is a recognized expert in the etiopathology and epidemiology of type 1 diabetes and diabetes in general. After obtaining a degree in Medicine from the University of Cagliari in 1977, he obtained his specialization in Diabetology from University of Turin (1980), his specialization in Endocrinology from University of Rome (1984) and specialization in Dietology from University of Cagliari (1988).

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