Insulin resistance in children and adolescents after bone marrow transplantation for malignancies

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We read with interest the letter by Mohn *et al.*[1] regarding the long-term follow-up of β-cell function in 32 children and adolescents previously treated with chemotherapy, but not cranial radiotherapy, for acute lymphoblastic leukaemia. Oral glucose tolerance test performed during 3 follow-up visits showed a progressive reduction of impaired glucose tolerance, as well as an improvement of insulinogenic index and HOMA β-cell function. The authors concluded that alterations of glucose metabolism persist after stop therapy, but are reversible with time. We would like to report our results regarding fasting plasma glucose (FPG), fasting plasma insulin (FPI), HbA1c levels and immunologic markers of β-cell damage (anti-islet cell antibodies, ICA and anti-insulin autoantibodies, IAA) in 21 patients (14 males and 7 females, aged 6.1-17.6 years) with acute or chronic leukaemia, 9 months to 10.2 years after autologous or allogenic bone marrow transplantation (BMT). All patients underwent chemotherapy combined with total body irradiation or thoraco-abdominal irradiation before BMT. In all cases BMI (kg/m^2) and BMI-SDS were computed for each subject. Family history was negative for both type 1 and type 2 diabetes mellitus. Since FPI levels were elevated, we assessed insulin resistance and secretion indexes through the homeostasis model assessment of insulin resistance index (HOMA-IR), the HOMA β-cell function (HOMA β-cell) and the QUICKI. HOMA-IR was measured as FPI in μU/ml x FPG in mmol/l divided for 22.5 (2); HOMA β-cell function was measured as (20 x FPI in μU/mL)/(FPG in mmol/l –3.5);[2] QUICKI was measured as 1/(log$_{10}$ FPI in μU/ml + log10 FPG in mmol/l).[3] As controls, 98 Italian healthy children and adolescents, with normal fasting plasma glucose, absence of obesity and positive family history for both type 1 and type 2 diabetes mellitus were considered.

Normal values of FPG and HbA1c levels, absence of ICA and IAA were observed in all patients. As regards insulin resistance and secretion indexes, HOMA-IR was significantly higher in patients (2.07; 1.51-3.33, median; 1st-3rd quartile) than in controls (1.41; 0.89-2.24) (p=0.007; Mann-Whitney U test) (Figure 1a). HOMA β-cell function was higher in patients (206.6; 133.7-556.5) than in controls (123.1; 72.2-197.9) (p=0.0009; Mann-Whitney U test) (Figure 1b). The QUICKI index was significantly lower in patients (0.60; 0.53-0.65) than in controls (0.67; 0.59-0.77) (p=0.007; Mann-Whitney U test) (Figure 1c). BMI was higher than 95th percentile in 3 cases (21%), all with increased indexes of insulin resistance. BMI-SDS was positively related with HOMA-IR (p=0.0012). No significant correlation was found between indexes of insulin resistance and secretion and chronological age or time since BMT. Our results showed absence of autoimmunity against β-cells but impaired indexes of insulin resistance and insulin secretion in children and adolescents after BMT. Taskinen[4] reported a high risk of insulin resistance, impaired glucose tolerance and type 2 diabetes mellitus even at young age in patients who underwent BMT in childhood. The hyperinsulinemia observed in our patients may be interpreted as direct or indirect action of irradiation, as reported in personnel cleaning up after the Chernobyl nuclear plant accident.[5] Moreover, the pancreatic gland might be more sensitive to the long-lasting effect of ionising radiations in childhood and adolescence than in adulthood.[6] In our patients, no transient reduced β-cell secretory damage, otherwise reported in children with acute or chronic leukaemia treated only with chemotherapy was found.[1] At present, the effect of ionising radiations on β-cell autoimmune damage is controversial. In the Gomel Region, highly exposed to radiation arising from Chernobyl nuclear accident, an increase of type 1 diabetes mellitus in pediatric age has been reported,[7] while in the Warmia and Mazury Regions in the North of Poland, similarly reached by the nuclear material released by the reactor explosion from Chernobyl, the incidence of type 1 diabetes mellitus was not raised after the event.[8] Based on these data, in long-term survivors after BMT a careful follow-up of insulin resistance indexes and glucose metabolism is strongly recommended, since a high prevalence of metabolic syndrome[9] and diabetes mellitus,[10] whose symptoms range from isolated polyuria to severe ketoacidosis, has been recently observed.

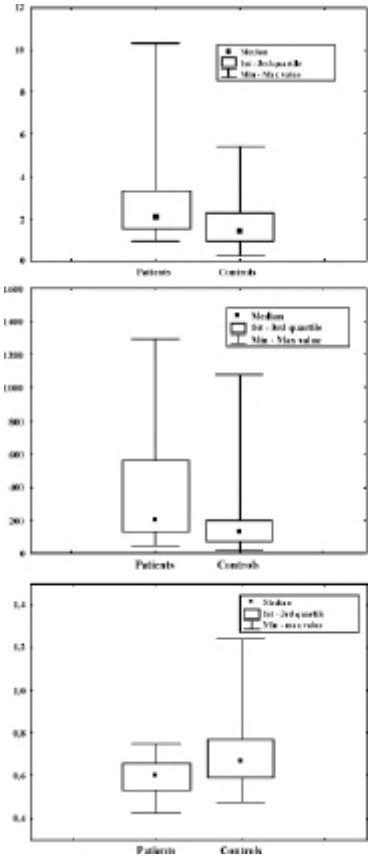

Figure 1. Values of HOMA-IR (a), HOMA ?-cell (b) and QUICKI (c) in patients after BMT and controls.

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