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Association of trace elements with lipid profiles and glycaemic control in patients with type 1 diabetes mellitus in northern Sardinia, Italy: An observational study

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HIGHLIGHTS

- The blood Zn level influences the distribution of TG, TC, and LDL.
- Cu and Cr are more strongly associated with glycaemic control.
- Se was significantly and positively correlated with triglycerides.
- Zn, Fe, and Se are more strongly associated with lipid metabolism.

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ABSTRACT

Sardinia is an Italian region with a high incidence of type 1 diabetes mellitus. This study aimed to determine the associations of trace elements with lipid profiles and glycaemic control in patients with T1DM. A total of 192 patients with T1DM who attended the Unit of Diabetology and Metabolic Diseases in Sassari, Italy, were enrolled. Trace elements zinc, copper, selenium, chromium, and iron were measured in whole blood by sector field inductively coupled plasma mass spectrometry. The correlations between metabolic variables and the levels of trace elements were determined. Zinc was positively correlated with total cholesterol ($P = 0.023$), low-density lipoprotein ($P = 0.0015$), and triglycerides ($P = 0.027$). Iron as significantly correlated with TC ($P = 0.0189$), LDL ($P = 0.0121$), and high-density lipoprotein (HDL) ($P = 0.0466$). In males, Cr was positively correlated with HDL ($P = 0.0079$) and Se, in females was correlated with TG ($P = 0.0113$). The mean fasting plasma glucose was166.2 mg dL^{-1}. Chromium was correlated with fasting plasma glucose ($P = 0.0149$), particularly in males ($P = 0.0038$). Overall, 63.5% of the patients had moderate HbA1c (7–9%). Copper was significantly correlated with HbA1c% in males ($P = 0.0155$). In conclusion, the results of this study indicate that trace elements show different associations with lipid levels and glycaemic control in T1DM. Zinc, Fe, and Se were associated with lipid levels whereas Cu and Cr were associated with HbA1c%.

1. Introduction

After Finland, Sardinia in Italy has the highest incidence of type 1 diabetes mellitus (T1DM) in Europe. The Sardinian population has several peculiar features resulting from Sardinia's historical and geographical isolation. The socioeconomic context is based on the patriarchal structure of the family, there is mainly agricultural and farming economy, there is high endogamy, low immigration rates and high longevity and, moreover, the

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Sardinian population has a genetic background different from Italian mainland (Cavalli-Sforza et al., 1994; Caselli et al., 2006; Forte et al., 2014).

Type 1 diabetes incidence has been rising over the last decade by an yearly average of 3.2% in Europe with a higher rate of increase among children 5 years of age (Green and Patterson, 2001). Island of Sardinia in Italy had the second highest type 1 diabetes incidence in the world among children aged 15 years and previous data have demonstrated an increased prevalence of type 1 diabetes among young men aged 18 years (Songini et al., 1998). The incidence of type 1 diabetes in this island was quite high at the age of 3 years (41.0/100 000) and this characteristics make Sardinia an interesting place to investigate the epidemiology of the disease (Casu et al., 2004).

T1DM, also known as insulin-dependent diabetes, is characterised by autoimmune destruction of pancreatic β-cells. Diabetes can lead to serious complications, such as ketoacidosis, retinopathy, nephropathy, stroke, myocardial infarction, neuropathy, and diabetic foot ulcers (Deshpande et al., 2008).

Imbalances of some metals are known to affect glucose metabolism and insulin production and signalling (Pasula and Sameera, 2013). Zinc (Zn) is involved in glucose metabolism and plays a key role in the synthesis, storage, and secretion of insulin (Viktorínová et al., 2009).

Zinc deficiency is also accompanied by excess copper (Cu). Several studies have documented elevated plasma Cu levels in patients with diabetes, especially in those with diabetes-related complications such as retinopathy, microvascular disease, and hypertension (Walter et al., 1991). Chromium (Cr) affects the metabolism of carbohydrates, lipids, and proteins. Studies have also demonstrated that Cr is involved in the regulation of blood glucose levels in patients with diabetes (Bahijiri et al., 2000; Ali et al., 2011).

Selenium (Se) has antioxidant properties, and helps protect against oxygen free radicals and lipid peroxidation. Some studies have also shown that Se can affect lipid profiles (Gebre-Medhin et al., 1988; Laclaustra et al., 2010). At high levels, iron (Fe) may promote the development of free radicals, whereas anaemia in patients with T1DM is associated with elevated glycated haemoglobin (HbA1c%) levels (Tarim et al., 1999; Liu et al., 2009).

Imbalances of trace elements can adversely affect metabolism. The aim of this study was to assess the associations of trace elements with lipid profiles and glycaemic control in patients with T1DM.

2. Materials and methods

2.1. Study subjects

A total of 192 outpatients with T1DM who were treated at the Unit of Diabetology and Metabolic Diseases, University Hospital, Sassari, Italy, were included in this study. Most of the patients (60.9%) lived in urban areas with more than 15 000 inhabitants. All participants provided written informed consent forms for the use of their data. Blood samples were collected with approval from the university's ethics committee.

All of the patients completed a questionnaire about their place of residence, anthropometric variables, age, sex, height, weight, and duration of diabetes. Data were also retrieved from their medical records regarding diabetes-related complications and the presence of other comorbidities.

Patients who smoked, who did not follow a diet, who took vitamins, mineral supplements, thyroid hormone, diuretic drugs, or antihypertensive drugs, and patients with a current acute infection were excluded from the study. None of the patients were reported to be addicted to alcohol and none were occupationally exposed to metals.

All of the patients were prescribed controlled diets. Patients with dyslipidemia were prescribed a diet with daily intake of 50% carbohydrates and 20–23% lipids to manage their blood cholesterol levels; the protein content was 0.8–1.2 g kg^{-1} body weight. Patients with a normal body mass index (18.5–25 kg m^{-2}) were prescribed a normo-caloric diet with respect to nutritional intake according to the guide lines for patients with diabetes. Patients with a body mass index of >25 kg m^{-2} or <18.5 kg m^{-2} were prescribed diets intended to provide healthy nutrition levels.

The duration of diabetes varied considerably among the patients, with a duration of <10 years in 32.3% of patients, 11–20 years in 26.5% of patients, 21–39 years in 32.8% of patients, and ⩾40 years in 8.4% of patients. All of the patients attended the outpatient clinic for regular follow-ups and were on insulin therapy. Glucose and HbA1c levels were also measured regularly. Good glycaemic control was defined as HbA1c <7%.

2.2. Measurement of clinical parameters

Blood samples were collected in potassium-EDTA vacutainer BD tubes (Becton Dickinson Labware, Franklin Lakes, USA) from the clinic staff of Unit of Diabetology. Analysis of biological parameters were performed in the laboratory of analysis of Unit of Diabetology and Metabolic Diseases of the University Hospital, Sassari.

2.3. Measurement of trace elements

Blood samples were collected in potassium-EDTA vacutainer BD tubes (Becton Dickinson Labware, Franklin Lakes, USA) and stored at −20 °C until required for processing. The procedure entails a microwave digestion (ETHOS-Mega II oven, FKV, Bergamo, Italy) in 15-mL plastic tubes (Falcon, Becton, Franklin Lakes, USA) with the addition of superpure concentrated HNO_3 (Romil Ltd, Cambridge, UK).

For accuracy of the analytical procedure, blood Seronorm lyophilized human whole blood (level 1) certified reference material was used (Sero AS, Billingstad, Norway). Metals were measured by sector field inductively coupled plasma mass spectrometry (SF-ICP-MS, ThermoFischer, Bremen, Germany). Details of the microwave digestion and the SF-ICP-MS method were previously reported (Alimonti et al., 2005; Bocca et al., 2011). The limits of quantification (LOQ), calculated on the blank values were: Cr 0.005 μg L^{-1}, Cu 0.5 μg L^{-1}, Fe 6 μg L^{-1}, Se 0.6 μg L^{-1}, and Zn 0.8 μg L^{-1}. The reproducibility in the three days of analysis ranged from 2.4% for Cu to 6.3% for Cr. Mean recovery of all elements were found in the range 94–100% of the certified values.

2.4. Statistical analysis

Data are presented as the mean ± standard deviation. For trace elements, results of the Shapiro–Wilk test confirmed that the data were normally distributed. Spearman's rank correlation coefficients were calculated to determine the correlations among variables in all patients, both together and after dividing the patients by gender. Student's *t* test for independent samples was used to detect differences between groups of patients. The *Z* test was used to detect significant differences in proportions between groups of patients. All statistical analyses were performed using Stata software version 12 (Stata Corp, College Station, TX, USA). Statistical significance was set at $P < 0.05$.