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Plasma zinc in adults with cystic fibrosis: Correlations with clinical outcomes

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ABSTRACT

Background: Zinc status has been previously documented in cystic fibrosis (CF) infants, children and adolescents. However, despite the increasing life expectancy observed in CF populations, data regarding zinc status of CF adults are surprisingly lacking. The objectives of this study were to (1) characterize zinc status and (2) explore associations between zinc status and clinical outcomes of CF adult patients.
Methods: A retrospective chart review was performed for patients who had their plasma zinc measured between 2009 and 2012. Data included demographics, clinical characteristics, biochemical parameters and co-morbid conditions.
Results: A total of 304 CF patients were included in the study. These patients displayed a good nutritional status (mean BMI ± SD: 22.7 ± 3.5) and moderate lung disease (mean FEV_1 ± SD: 66.3 ± 22.2). Low plasma zinc concentration (<9.2 μmol/L) was found in 68 out of 304 CF patients (22.4%). Compared to patients with normal zinc, those with low zinc had significantly lower forced vital capacity and forced expiratory volume in one second. 72% of CF adults with low zinc suffered from bone disease (vs 49% with normal zinc, $p = 0.037$) and 79% had impaired glycemic status (vs 58%, $p = 0.016$). Accordingly, negative correlations were found between plasma zinc and glucose ($r = -0.139$, $p = 0.0001$), HbA1c ($r = -0.237$, $p = 0.0001$) and fructosamine ($r = -0.134$, $p = 0.034$). In multiple linear regression, albumin and glycemic status were significant predictors of plasma zinc.
Conclusion: Our data indicated that nearly one quarter of CF adults with good nutritional status and moderate lung disease had low plasma zinc concentration and that low zinc status was associated with worse clinical outcomes.

Introduction

Zinc (Zn) is one of the most abundant essential trace elements within cells. It is required for general metabolic functions and its role is regrouped into three main categories: catalytic, structural and regulatory [36]. Zn acts as a catalyst for over 50 metalloenzymes that exert a wide range of biological actions [39]. As part of Zn finger motif, Zn plays a critical role in stabilizing the structure of a number of proteins including transcription factors, nuclear receptors and enzymes [36]. Its regulatory role lies in its capacity to regulate gene expression and function as a signal transducer comparable to the second messenger Ca^{2+} [36]. Increasing evidence demonstrates the importance of Zn in cystic fibrosis (CF)-affected tissues including the lungs and pancreas. In the airway epithelium, Zn is important for ciliary function, wound healing and suppression of oxidative stress and apoptosis, all of which have been shown to be impaired in CF [1,2]. Zn is particularly abundant in the pancreas where it is involved in the control of glucagon secretion, digestive enzyme activity and insulin packaging, release and signalling [3]. Zn deficiency is associated with decreased insulin secretion and sensitivity, features which are characteristic of CF-related diabetes (CFRD) [37]. Furthermore, Zn is known to play a regulatory role in the immune system where correlations have been found between plasma Zn and IL-2 levels, natural killer cell activity and active thymulin in CF children [4]. Zn status also affects the expression of proinflammatory cytokines such as TNFα, IL-1β and IL-8 [5].

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFRD, CF-related diabetes; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HbA1c, glycated haemoglobin; INR, international normalized ratio; Zn, zinc.

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CF patients suffer from maldigestion, malabsorption and steatorrhea which may interfere with Zn absorption and reabsorption from endogenous secretions. Accordingly, Easley et al. had shown a decrease in Zn fractional absorption in CF children in whom pancreatic enzyme supplementation had been withheld for 24 h [6]. Thus, CF populations may be at risk of low Zn status. Furthermore, there appears to be an interaction between Zn and vitamin A in patients suffering from CF where serum levels of both nutrients tend to be correlated [10]. For instance, a Zn therapy initiated in a CF patient had successfully reversed night blindness, a clinical sign generally associated with vitamin A deficiency [7].

Zn status has been almost exclusively investigated in young CF patients. Prevalence rates of low plasma Zn ranging from 0% to 40% in various populations of infants [8], children and adolescents [9–15,18] with CF and clinical manifestations of Zn deficiency, mostly cutaneous, have also been reported in a few cases [16,17]. Despite the increasing life expectancy observed in CF populations, data regarding Zn status of CF adults are surprisingly lacking. The primary aim of this study was to characterize Zn status in a cohort of adults with CF and identify clinical outcomes associated with Zn status in this population. The underlying hypotheses were that, like infants and children with CF, a proportion of CF adults would display Zn insufficiency and plasma Zn would be correlated to clinical outcomes of interest for this population.

Materials and methods

A retrospective chart review was undergone on adult CF patients attending the Centre hospitalier de l'Université de Montréal (CHUM) CF Clinic who had their first plasma Zn assessed between 2009 and 2012 during one of their follow up visits. All patients were at least 18 years old and confirmed to have CF by sweat test and/or genotyping. Abstracted data included demographics (age and gender), clinical characteristics (genotype, body mass index (BMI), pancreatic insufficiency, pulmonary function), biochemical parameters (Zn, albumin, total proteins, glucose, glycated haemoglobin (HbA1c), fructosamine, C-reactive protein (CRP), retinol, transthyretin, 25-hydroxyvitamin D, alpha-tocopherol), and international normalized ratio (INR) and co-morbid conditions (diabetes, bone, kidney or liver disease, asthma and exacerbations). Liver disease was defined by the presence of at least one of the following features: cirrhosis, steatosis, cholestasis, oesophageal varices, portal hypertension or abnormal level of hepatic enzymes despite therapy with ursodiol. The diagnosis of osteopenia or osteoporosis was confirmed by bone mineral density (BMD) measurement made with dual-energy X-ray absorptiometry. Diagnosis was made based on the lowest *T*-score obtained from the lumbar spine (L1-4), femoral neck and hip. According to the World Health Organization criteria [40], osteopenia was defined by a BMD that was between −1 and −2.5 standard deviation (SD) below the young adult mean (*T* score −1 to −2.5) whereas a *T*-score below 2.5 indicated osteoporosis. To determine the glucose tolerance categories, patients underwent a 2 h-oral glucose tolerance test every 18 months and categories were defined according to the Canadian Diabetes Association Guidelines [38]. Data closest to the date of the plasma Zn measurement were collected. More specifically, all the demographics, clinical characteristics and biochemical parameters were collected on the same day (plus or minus a few days) plasma Zn was assessed. As for co-morbid conditions, data were collected within a 4-week period of plasma Zn assessment. Approval from the CHUM research ethics committee (project No. 11.198) was obtained to perform the chart reviews.

Plasma zinc

Plasma samples were collected at the CHUM CF Clinic and processed according to procedures to minimize risk of contamination. Hemolyzed specimens were discarded as they resulted in falsely elevated Zn concentration. Samples were kept at −20 °C until Zn assessment. Plasma Zn was analyzed at the CHUM Clinical Biochemistry Department by inductively coupled plasma mass spectrometry (ICP-MS; Model 7500 Agilent Technologies, Palo Alto, CA). The laboratory reference values for plasma Zn were 9.2–18.4 μmol/L.

Statistical analysis

Continuous data are presented as means ± SD and categorical data as percentages. The cut-off value for Zn deficiency was 9.2 μmol/L and individuals below and above or equal to this value were compared. Plasma Zn exhibited a normal distribution according to the Kolmogorov–Smirnov test. Group comparisons were determined by Student's *t* test, one-way ANOVA with Tukey's post hoc tests, Fisher's exact test or χ^2 as appropriate. Associations between plasma Zn and other continuous variables were determined using the Pearson correlation test. We used multivariate stepwise linear regression to determine independent predictors of plasma Zn. Each variable considered eligible for the regression had a $p \leq 0.1$ on bivariate analysis. The following variables were included in the model: age, forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), total proteins, transthyretin, glucose, albumin, HbA1c, fructosamine, retinol, kidney disease and glycemic status. The statistical analysis was performed using SPSS for Windows (Version 17.0, Chicago, IL). The statistical significance cut-off level was set at $p < 0.05$.

Results

A total of 304 out of 348 CF adults were included in the retrospective chart review. This number represented approximately 87% of all patients attending the CHUM CF Clinic. Patients with chronic kidney disease undergoing dialysis ($n = 1$), who received single Zn supplements ($n = 2$), did not have their plasma Zn measured ($n = 22$), and who were lung ($n = 16$) or liver ($n = 3$) transplanted before the assessment of plasma Zn were excluded. We compared excluded and included subjects and the excluded patients did not differ as regards to the parameters analyzed. Table 1 displayed the demographics and clinical characteristics of these subjects. Overall, patients were in their late twenties, exhibited a good nutritional status and had moderate lung disease. Despite the fact that mean plasma Zn was above the reference value for Zn deficiency, 68 out of 304 CF patients (22.4%) had Zn deficiency (Table 2). A comparison of patients who took multivitamins and minerals with Zn (mean of 14.5 mg of Zn) from those who did not revealed similar circulating Zn levels (10.94 ± 2.34 vs 11.47 ± 2.39 μmol/L, $p = 0.2$). Zn-deficient and Zn-sufficient patients had similar distributions of sex, genotype and BMI (Table 3). A trend towards an older age ($p = 0.077$) was present in the Zn-deficient group. On the other hand, %FVC and $\%FEV_1$ were significantly reduced in the Zn-deficient patients. Weak yet noticeable correlations were found between plasma Zn levels and %FVC ($r = 0.193$, $p = 0.001$) and $\%FEV_1$ ($r = 0.164$, $p = 0.005$).

In terms of comorbidities, bone status was remarkably different among the groups, with Zn-deficient subjects exhibiting 72% of impaired bone status compared to 49% in the Zn-sufficient group (Table 4). Similarly, 63% of Zn-deficient patients suffered from diabetes in comparison to 43% in Zn-sufficient subjects. Indeed, subjects with diabetes presented with a lower level of plasma Zn than those with normal (NGT) and impaired glucose tolerance (IGT)