

## Original Article

# Can zinc deficiency be used as a marker for the diagnosis of celiac disease in Turkish children with short stature?

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### Abstract

**Background:** It is generally accepted that celiac disease (CD) must always be considered when dealing with growth failure in children. Therefore, it is important to develop screening tests for detecting patients that need an intestinal biopsy. The aim of the present study was to investigate the value of plasma zinc levels for the diagnosis of monosymptomatic CD in short-statured children.

**Methods:** Forty-nine children with a short stature and 34 healthy controls were investigated. Plasma zinc levels were assayed by atomic absorption spectrophotometry in short-statured children and controls. All patients with short stature underwent endoscopic small intestinal biopsy.

**Results:** Duodenal mucosal histopathology was normal in 25 children. Low plasma zinc values were observed in 54.2% of patients with CD, 32.0% of patients with idiopathic short stature and 14.8% of controls. The mean values of plasma zinc levels were not significantly different among the three groups. Sensitivity, specificity and the positive and negative predictive values for plasma zinc were 45.8, 76.0, 64.7 and 59.4%, respectively.

**Conclusions:** These results indicate that zinc deficiency is an important problem in CD children with short stature; however, plasma zinc levels are not useful as a screening test for selecting patients for jejunal biopsy.

### Key words

celiac disease, children, short stature, zinc.

Chronic diarrhea and failure to thrive are well-known symptoms of pediatric celiac disease (CD). A monosymptomatic presentation is becoming increasingly common in older children with short stature, constipation, pallor or recurrent abdominal pain.<sup>1</sup> In Italy, CD is considered to be a more common cause of short stature in otherwise healthy children than growth hormone deficiency.<sup>2</sup> Celiac disease may be identified by routine performance of duodenal biopsies in short children,<sup>3,4</sup> but this is an invasive and impractical diagnostic approach. The need for simple diagnostic tests for CD have forced many investigators to develop non-invasive screening tests.<sup>5</sup> However, no test has yet revealed better sensitivity and specificity than jejunal biopsy in the diagnosis of CD.

The aim of the present study was to investigate prospectively the value of measuring plasma zinc levels in the diagnosis of CD in short-statured children and to determine the sensitivity, specificity and positive and negative

predictive values (PPV and NPV, respectively) of zinc for the diagnosis of monosymptomatic CD. Although a review of the literature revealed some reports of zinc deficiency in children with CD as consequence of intestinal malabsorption,<sup>6–8</sup> this seems to be a unique study on the levels of zinc in children with monosymptomatic CD who present with short stature.

### Methods

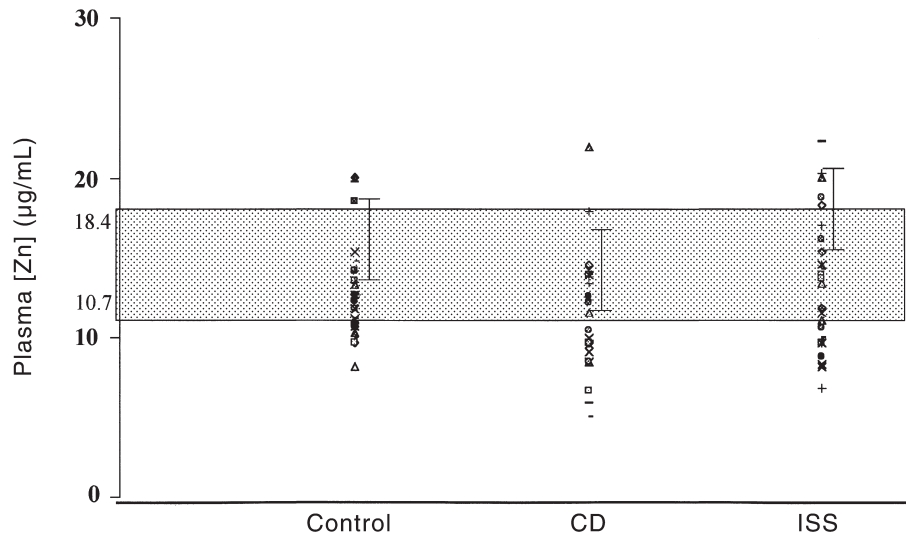
Eighty-three sick and healthy children were included in the study. Patients were admitted to the Pediatric Endocrinology Clinic and presented with a chief complaint of short stature. Forty-nine patients with short stature were studied. None of the patients had endocrinologic or chronic disease. The age ranged between 3 and 17 years and there were 22 girls and 27 boys. All were below the 3rd percentile for height according to the standards of Tanner *et al.*<sup>9</sup> The SD was calculated. Bone age was determined by the method of Greulich and Pyle.<sup>10</sup>

A group of 34 healthy students, 19 girls and 15 boys, aged 6–16 years, served as controls. All subjects and their

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**Fig. 1** Plasma zinc concentrations in controls and patients with either celiac disease (CD) or idiopathic short stature (ISS). Mean ( $\pm$  SD) values for plasma zinc in control, CD and ISS groups were  $12.5 \pm 2.8$ ,  $11.4 \pm 3.8$  and  $13.6 \pm 4.2$   $\mu\text{g/mL}$ . There were no significant differences between the ISS group and control and CD zinc plasma levels.  $P < 0.05$  for CD compared with control. (▢), normal range of plasma zinc.



**Table 1** Clinical characteristics of patients

	Celiac disease	ISS	P
Sex (M/F)	14/10	13/12	NS
Age (years)	10.79 $\pm$ 3.01	11.92 $\pm$ 3.07	NS
HSD score	-2.76 $\pm$ 0.85	-2.95 $\pm$ 0.97	NS
Bone age (years)	8.05 $\pm$ 2.85	9.76 $\pm$ 3.77	NS

Results are expressed as the mean  $\pm$  SEM. ISS, idiopathic short stature; HSD, height standard deviation.

**Table 2** Plasma zinc concentrations in the study group

	No. subjects (%)	
	Normal	Low
CD	11 (45.8)*	13 (54.2)*
ISS	17 (68.0)	8 (32.0)
Control	29 (85.2)	5 (14.8)

There were no significant differences between the celiac disease (CD) and idiopathic short stature (ISS) groups. \* $P \leq 0.05$  compared with control.

parents agreed to participate in the study after a full explanation of the nature and purpose of the investigation.

For zinc analysis, blood samples were taken after at least 10 h fasting from all patients and controls. Venous blood was drawn into plastic syringes and placed into trace metal-free tubes. Plasma zinc levels were assayed by atomic absorption spectrophotometry (model varian Techtron 1200) by using standard procedures.<sup>11</sup> Reference values for plasma zinc levels are accepted as normal between 10.7 and 18.4  $\mu\text{mol/L}$  according to the same method.

**Table 3** Calculations of sensitivity, specificity and predictive values of plasma zinc levels

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Plasma zinc	45.8	76.0	64.7	59.4

Sensitivity, the probability of a positive test (low plasma zinc level) among patients with celiac disease (CD); specificity, the probability of a negative (normal plasma zinc level) test among patients without CD; PPV, positive predictive value, the probability of the presence of CD when the test is positive; NPV, negative predictive value, the probability of the absence of CD when the test is negative.

Statistical analysis was performed with the Student's *t*-test and Fisher's exact test.  $P < 0.05$  was regarded as statistically significant.

## Results

Small intestinal biopsies were performed in 49 children with short stature. Pathologic biopsy results (subtotal villous atrophy, dense inflammatory infiltrate in the lamina propria, elongated crypts and intra-epithelial lymphocytic infiltration) were found in 24 children (CD). Duodenal mucosal histopathology was normal in 25 children (idiopathic short stature; ISS). The clinical features are summarized in Table 1.

In the CD patient group, plasma zinc levels were below the cut-off point of the assay in 13 children. There was no correlation between the severity of zinc deficiency and the SD score in CD patients. Eight children in the ISS group and

five children in the control group had low plasma zinc values (Table 2; Fig. 1).

The mean ( $\pm$ SD) values of plasma zinc levels in the control, CD and ISS groups were  $12.5 \pm 2.8$ ,  $11.4 \pm 3.8$ ,  $13.6 \pm 4.2$   $\mu\text{mol/L}$ , respectively. Plasma zinc levels were not significantly different between the three groups. Sensitivity, specificity and PPV and NPV for plasma zinc were 45.8, 76.0, 64.7 and 59.4%, respectively (Table 3).

## Discussion

Zinc is an important trace element for the growing organism. Retardation of physical growth, poor appetite, impairment of sexual maturation and impaired taste acuity have been described in zinc-deficient children.<sup>12,13</sup> Currently, different methods are being used in the assessment of zinc nutritional status. Unfortunately, none of these techniques is completely efficient. For clinical purposes, the measurement of plasma zinc levels has been the most widely used method. It is generally assumed that a low plasma zinc concentration is indicative, in the majority of cases, of zinc deficiency.<sup>7</sup> In 1972, Hambidge *et al.*<sup>12</sup> observed an association between poor growth and unsatisfactory zinc status assessed by low hair zinc levels. The same relationship was reported by Halsted *et al.* in Iranian boys.<sup>14</sup> In 1976, Walravens and Hambidge<sup>15</sup> found that a zinc-supplemented formula had a positive effect on growth in male infants. In the present study, eight patients with ISS had low plasma zinc levels (32%).

Zinc deficiency has been documented in many chronic diarrheal syndromes (i.e. CD, inflammatory bowel disease, cystic fibrosis) as a consequence of intestinal malabsorption and increased fecal zinc loss.<sup>16</sup> Celiac disease predominantly affects the proximal small intestine.<sup>1</sup> The small intestine has the central role in maintaining zinc homeostasis.<sup>16</sup> In this study, 13 children in the CD group and five children in the control group had low plasma zinc levels ( $P = 0.001$ ). Although there was no significant difference between the mean plasma zinc concentration in the three groups, mean plasma zinc concentrations were lower in patients with CD than in patients with ISS and the control group. In these CD patients, zinc deficiency may result from a cumulative loss of insoluble zinc complexes with fat and phosphate, exudation of zinc protein complexes into the intestinal lumen and massive loss of intestinal secretions or impaired zinc absorption because of injured intestinal epithelial cell membrane.<sup>6</sup>

Our data also suggest that a decrease in the plasma zinc level can be found in children with CD. Some of the symptoms of CD (e.g. anorexia and reduced growth rate) may be related, in part, to zinc deficiency.<sup>17</sup> These data could

indicate the importance of an adequate supplementation of zinc in children with CD.

In contrast with other screening tests, such as endomysial antibodies, gliadin antibodies and absorptive tests,<sup>18</sup> plasma zinc level measurements have a much lower sensitivity, specificity, PPV and NPV. Therefore plasma zinc determination is not useful as a screening test for mono-symptomatic CD in children with short stature.

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