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Bone mineralization in children with inflammatory bowel disease: What is the role of zinc?

İnflamatuvar barsak hastalığı olan çocuklarda kemik mineralizasyonu: Çinkonun etkisi nedir?

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Background/aims: *Bone demineralization is a significant problem in pediatric inflammatory bowel disease. Contributing factors include inadequate nutrition, corticosteroid therapy and decreased physical activity. Although zinc is needed for osteoblastic activity and collagen synthesis, its role in bone development is uncertain. The aim of this study was to investigate the relation between the serum zinc level and bone mineral indexes of 28 children with inflammatory bowel disease.* ***Methods:*** *Bone mineral content and bone mineral density at lumbar 1-4 vertebrae were measured by dual energy X-ray absorptiometry in all patients and 56 controls. Serum zinc levels of patients and 31 controls were determined by spectrophotometric method.* ***Results:*** *The mean bone mineral density values of patients and controls were 0.661±0.201 g/cm^2 and 0.751±0.175 g/cm^2, the mean bone mineral content values were 33.357±17.104 g and 38.968±14.663 g, and the mean serum zinc levels were 101.2±28.8 µg/dl and 108.9±15.9 µg/dl, respectively. All controls had normal serum zinc level; however, 11 (39.3%) patients had low serum zinc level (p=0.000). The ratio of patients with Z-score below the -2SD was higher in patients with low zinc level than in patients with normal zinc level (70% vs. 42.8%).* ***Conclusions:*** *Although insignificant, some of the children with IBD had low levels of serum zinc and these patients had lower Z-scores than the others. Further studies including large numbers of patients may reveal a certain effect of zinc on bone development in patients with inflammatory bowel disease.*

Key words: Crohn's disease, ulcerative colitis, children, bone mineral density, zinc

Amaç: *Kemik mineralizasyonunda değişiklikler çocukluk çağı inflamatuvar barsak hastalığının önemli bir sorununu oluşturur. Yetersiz beslenme, steroid tedavisi ve aktivitenin azlığı kemik metabolizmasını etkileyen diğer faktörlerdir. Osteoblastik aktivite ve kollojen sentezi için gerekli olmasına rağmen çinkonun kemik gelişindeki rolü kesin bilinmemektedir. Bu çalışmada inflamatuvar barsak hastası olan 28 çocukta kemik mineralizasyon göstergeleri ile serum çinko düzeyi arasındaki ilişkiyi araştırmayı amaçladık.* ***Yöntem:*** *Hastalar ve 56 kontrolde kemik mineral içeriği ve kemik mineral dansitesi lumbar 1-4 vertebralardan "dual energy x-ray absorptiometry" kullanılarak ölçüldü. Serum çinko düzeyleri spektrofotometrik yöntemle hastalar ve 31 kontrolde çalışıldı.* ***Bulgular:*** *Sırasıyla hasta ve kontrollerin ortalama kemik mineral dansitesi değerleri 0.661±0.201 ve 0.751±0.175g/cm^2; ortalama kemik mineral içeriği değerleri ise 33.357±17.104 ve 38.968±14.663g idi. Hasta ve kontrollerin ortalama serum çinko düzeyleri 101.2±28.8µg/dL ve 108.9±15.9µg/dL bulundu. Tüm kontrollerin serum çinko düzeyleri normal iken, hastaların 11'inin (%39.3) çinko düzeyleri düşüktü (p=0.000). Düşük çinko düzeyi olan hastalarda Z-skorları 2 standart deviasyon altında olan hasta oranı normal çinko düzeyi olanlara göre daha fazla idi (sırasıyla %70 ve % 42.8).* ***Sonuç:*** *İnflamatuvar barsak hastalığı olan çocuklarda serum çinko düzeyinde düşüklük görülebilir ve bu çocuklarda Z-skorunun düşük olma oranı daha yüksektir. Çinkonun inflamatuvar barsak hastalığı olan çocuların kemik mineralizasyonuna etkisi ileri çalışmalar gerektirmektedir.*

Anahtar kelimeler: Crohn hastalığı, ülseratif kolit, çocuklar, kemik mineral dansitesi, çinko

INTRODUCTION

Inflammatory bowel disease (IBD) is an immune-mediated chronic intestinal inflammation that results from complex interactions between genes conferring susceptibility, exogenous or endogenous triggers, and modifying factors. IBD, which includes ulcerative colitis (UC) and Crohn's disease (CD), primarily affects young adults; however, in 25% of cases, the initial disease starts in childhood (1, 2). The most common symptoms associated with pediatric IBD are anorexia, abdominal pain, diarr-

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hea (with or without blood and mucus), and failure to thrive. Although its pathogenesis is not yet understood, bone demineralization is another significant problem affecting pediatric IBD patients. In IBD patients, contributing factors for bone demineralization include inadequate nutrition (vitamin D and calcium deficiency), chronic corticosteroid therapy and decreased physical activity. Nutrients and lifestyle are also related with bone health. As a nutrient, zinc may have some role in bone development. Zinc is needed for osteoblastic activity, collagen synthesis and alkaline phosphatase activity, and its effect on bone development is not certain (3). Some studies have shown a positive relation between zinc intake and bone mineral content (BMC) in children (4). A positive relation between the plasma zinc level and bone mineral density (BMD) in older men was reported (5). Decreased BMD, determined by dual energy X-ray absorptiometry (DEXA), has been observed in IBD patients, especially patients with CD (2). The aim of our study was to investigate the relation between serum zinc level and bone mineral indexes of patients with IBD and to compare them with controls.

MATERIALS AND METHODS

Twenty-eight patients with IBD (16 UC, 12 CD) were enrolled into the study. IBD was diagnosed on the basis of history and clinical, endoscopic and histological findings. Demographic features of the patients at diagnosis are shown in Table 1. The mean follow-up time of the patients was 29.1 ± 26.5 months (median: 22; range: 6-120).

After informed consent was obtained from the patients and/or parents, BMC (g) and BMD (g/cm^2) at lumbar 1-4 vertebrae were measured by DEXA (Hologic QDR 4500 with fan beam of X-ray) in 28 patients. The mean age of the patients during evaluation was 12.9 ± 3.3 years (median: 13.5 ± 3.3; range: 5-18). The coefficient of variation, obtained by daily measurements of a standard phantom on the instrument, was 1%. The results of the patients were compared with those of age- and gender-matched 56 healthy children (40 male, 71.4%). The mean age of the controls was 12.6 ± 3.4 years (range: 5-18 years).

Serum zinc levels in 28 IBD patients and in 31 controls (15 male; 48.4%) were determined by spectrophotometric method after deproteinization of samples, using Randox kits (Randox Laboratories LTD, United Kingdom). Normal zinc level was 70-114 µg/dl. The mean age of the zinc control group was 12.1 ± 2.9 years (median: 13.0; range: 5-16).

Statistics

Statistical Package for the Social Science (SPSS) software version 10.0 was used to evaluate the results. The results were expressed as mean ± SD. Comparisons of measurable data between two groups were done using Student's t-test and Mann-Whitney U test. Proportions were compared using chi-square test and Fisher's exact chi-square test wherever appropriate. Paired sample t-test was used to compare the measurable variables within groups. A two-tailed p value of <0.05 was accepted as significant.

Table 1. Initial demographic features and clinical and laboratory findings of the patients with inflammatory bowel disease

	Crohn's disease n = 12 (%)	Ulcerative colitis n = 16 (%)	Total n = 28 (%)
Mean age ± SD (year)	12.5 ± 2.8	11.3 ± 3.7	11.8 ± 3.4
(range)	(6-16)	(2-16)	(2-16)
Gender M/F	9 / 3	9 / 7	18 / 10
Clinical findings			
Diarrhea	9 (75.0)	12 (75.0)	21 (75.0)
Rectal bleeding	3 (25.0)	16 (100)	19 (67.8)
Abdominal pain	9 (75.0)	10 (62.5)	19 (67.8)
Growth retardation	8 (66.7)	4 (25.0)	12 (42.8)
Fever	-	4 (25.0)	4 (14.3)
Laboratory findings (mean ± SD, range)			
Hemoglobin (g/dl)	10.1 ± 1.8	10.9 ± 2.0	10.5 ± 1.9
	(6.6-13.5)	(6.9-13.4)	(6.6-13.5)
Sedimentation rate (mm/h)	58.1 ± 28.3	38.1 ± 24.7	46.6 ± 27.7
	(21-111)	(8-84)	(8-111)
CRP (mg/dl)	6.9 ± 3.7	3.3 ± 4.2	4.9 ± 4.4
	(2.2-14.9)	(0.1-15.2)	(0.1-15.2)
Albumin (g/dl)	3.5 ± 0.7	3.7 ± 0.8	3.6 ± 0.8
	(1.8-4.1)	(1.9-4.8)	(1.8-4.8)

CRP: C-reactive protein.

RESULTS

The mean age of the 28 IBD patients was 11.8 ± 3.4 years (median: 13.0; range: 2-16) at the time of diagnosis. No patient had a family history of IBD. The most prominent initial complaints of the CD patients were growth retardation and diarrhea and of the UC patients were rectal bleeding and diarrhea (Table 1). Disease locations were colon in 6 CD and ileocolon in the other CD patients. Upper gastrointestinal tract involvement was defined in 3 (25%) out of 12 CD patients. All UC patients had pancolonic diseases. Iron deficiency anemia was observed in 11 CD patients (91.7%) and in 10 UC patients (62.5%). All CD patients had high sedimentation rate (ESR) and C-reactive protein (CRP), but ESR was high in 12 (75%) and CRP in 10 (62.5%) patients with UC. Low levels of albumin were measured in 3 (25%) CD and 3 (18.8%) UC patients. At the time of the study, all IBD patients except 2 were taking aminosalicylates. Seven CD and 8 UC patients were taking corticosteroid and azathioprine together. One CD and 3 UC patients were taking only corticosteroid. Only 9 patients were taking corticosteroids before the determination of BMD and BMC values. The mean time of corticosteroid usage was 6.8 ± 12.5 months (range: 2-48) in these 9 patients.

The mean lumbar spine BMD values of 28 IBD patients and controls were 0.661 ± 0.201 and 0.751 ± 0.175 g/cm^2 (p=0.034) and the mean lumbar spine BMC values were 33.357 ± 17.104 and 38.968 ± 14.663 g (p=0.091), respectively (Table 2). The mean Z-score of the patients with CD was significantly low compared with the controls (p=0.001). The difference between the mean BMD and BMC values of CD and UC patients was insignificant (p=0.029). We did not find any difference in mean BMD and BMC values between the 9 patients who were on steroid treatment before the investigation and the 19 patients who were not. The mean BMD values were 0.617 ± 0.152 g/cm^2 in patients with steroid treatment and 0.681 ± 0.221g/cm^2 in the others (p=0.53).

The mean serum zinc levels of IBD patients and controls were 101.2 ± 28.8 µg/dl (median: 97.8; range: 58.0-178.1) and 108.9 ± 15.9 µg/dl (median: 107.4; range: 84.6-142.9), respectively (p=0.114). All controls had normal serum zinc level; however, 11 (39.3%) out of 28 IBD patients had low serum zinc level (p=0.000). The difference between the mean serum zinc level of UC and CD patients was not significant (105.2 ± 30.9 vs. 95.8 ± 26.2 µg/dl; p=0.478); however, the mean serum zinc level of CD patients was lower than that of the UC patients. The difference between the bone mineral in-

Table 2. Bone mineral indexes and serum zinc levels of the inflammatory bowel disease patients and controls (mean ± SD)

	Crohn's disease n = 12	Ulcerative colitis n = 16	Total n = 28	Control n = 56
Z-score	-2.68 ± 1.36*	-1.49 ± 1.70	-2.00 ± 1.65$^{£}$	-0.87 ± 1.05$^{*,£}$
(range)	(-4.69 – +0.48)	(-3.71 – +1.92)	(-4.69 – +1.92)	(-3.18 – +1.18)
BMC g	31.010 ± 15.889	35.118 ± 18.267	33.357 ± 17.104	38.968 ± 14.663
(range)	(7.8 – 55.3)	(13.13 – 71.67)	(7.8 – 71.67)	(12.87 – 71.37)
BMD g/cm^2	0.617 ± 0.176$^{&}$	0.693 ± 0.218	0.661 ± 0.201**	0.751 ± 0.175&,**
(range)	(0.304 – 0.936)	(0.441 – 1.089)	(0.304 -1.089)	(0.441 – 1.101)
				Control n = 31
Serum zinc µg/dl	95.8 ± 26.2	105.2 ± 30.9	101.2 ± 28.8	108.9 ± 15.9
(range)	(58-139)	(71-178.1)	(58.0-178.1)	(84.6-142.9)

* p=0.001, £ p=0.0001, & p=0.029, ** p=0.034
BMC: Bone mineral content. BMD: Bone mineral density.

Table 3. Bone mineral indexes of the inflammatory bowel disease patients with normal serum zinc level and with low zinc level (mean ± SD)

	Patients with normal zinc level n = 17	Patients with low zinc level n = 11	p
Z-score	-1.7 ± 1.8	-2.4 ± 1.3	0.285
(range)	(-4.7 – +1.9)	(-3.8 – +0.37)	
BMC g	33.720 ± 19.866	32.797 ± 12.562	0.89
(range)	(7.800 – 71.670)	(13.130 – 49.110)	
BMD g/cm^2	0.661 ± 0.226	0.659 ± 0.165	0.817
(range)	(0.304 – 1.089)	(0.441 – 0.924)	

BMC: Bone mineral content. BMD: Bone mineral density.

dexes (Z-score, BMD and BMC) of the patients with low serum zinc level and with normal zinc level was insignificant (Table 3). However, it was noted that the ratio of patients with Z-score below the -2 SD was higher in the patients with low zinc level than in the patients with normal zinc level (70% vs. 42.8%, p=0.195). Although female IBD patients had lower mean serum zinc level (97.3 ± 16.5 µg/dl, median: 102.7) than the male patients (103.3 ± 34.1 µg/dl, median: 95.9), the difference was insignificant (p=0.981).

DISCUSSION

Inflammatory bowel disease primarily affecting young adults has also been increasingly diagnosed in the pediatric age group. Although the etiology of IBD is uncertain, a triggering factor or factors causing stimulation of cell-mediated immune response in genetically susceptible patients result in the clinical symptoms (2). Reduction in BMD has been reported in children with IBD (6-8). The use of corticosteroids has been implicated as a major factor in the pathogenesis of reduced bone mass. Other contributing factors include inadequate nutrition and decreased physical activity (2). However, Harpavat et al. (8) reported that decreased bone mass was also common in steroid naive children with newly diagnosed CD. As other factors for bone development, zinc intake and serum zinc level have been investigated in men with osteoporosis (5), adolescent girls (9), and also in patients with IBD, especially CD patients (10). A positive relation between the serum zinc and BMD in adolescent girls and men with osteoporosis was reported (5, 9).

One of the main problems in children and adolescent patients is growth failure. Decreased growth velocity, short stature and delayed bone age have been reported especially in CD patients. The cause is multifactorial, including inadequate intake, malabsorption, and fecal loss of protein and essential trace elements such as zinc, and corticosteroid therapy (2). Griffin et al. (11) reported that the reduced zinc absorption with normal fecal and urinary excretion of zinc caused negative zinc balance in adolescents with CD. Ojuawo et al. (12) reported that children with CD had low serum zinc levels. It was also shown that up to 15% of adult IBD patients had subnormal levels of zinc (13). Zinc is a dietary essential trace mineral necessary for normal collagen synthesis and mineralization of bone, and it is also required for normal growth (3). The aim of our study was to assess the relationship between the serum zinc level and the bone mineral indexes. As we expected, our IBD patients had significantly lower BMD values than the controls. Although the mean BMC and BMD values were not different between the CD and UC patients, CD patients had significantly lower BMD values than the controls. CD patients had lower mean serum zinc level than UC patients, but the difference was insignificant. The serum zinc level was low in 39.3% of IBD patients, but we did not find any difference between the bone mineral indexes of patients with low zinc level and with normal zinc level. Our results could not indicate a positive relation between serum zinc level and the bone mineral indexes of IBD patients. The small number of our patients may be a contributing factor for these results. Studies with large numbers of patients may reveal a positive relationship between serum zinc level and bone development, so zinc supplementation can be given to children with IBD and development of growth failure and osteoporosis may be prevented.

REFERENCES

1. Griffiths AM. Specificities of inflammatory bowel disease in childhood. Best Pract Res Clin Gastroenterol 2004;18: 509-23.
2. Kim SC, Ferry GD. Inflammatory bowel diseases in pediatric and adolescent patients: clinical, therapeutic, and psychosocial considerations. Gastroenterology 2004;126:1550-60.
3. Palacios C. The role of nutrients in bone health, from A to Z. Crit Rev Food Sci Nutr 2006;46:621-8.
4. Bounds W, Skinner J, Carruth BR, Ziegler P. The relationship of dietary and lifestyle factors to bone mineral indexes in children. J Am Diet Assoc 2005;105:735-41.
5. Hyun TH, Barrett-Connor E, Milne DB. Zinc intakes and plasma concentrations in men with osteoporosis: the Rancho Bernardo Study. Am J Clin Nutr 2004;80:715-21.
6. Boot AM, Bouquet J, Krenning EP, de Muinck Keizer-Schrama SM. Bone mineral density and nutritional status in children with chronic inflammatory bowel disease. Gut 1998;42:188-94.
7. Gokhale R, Favus MJ, Karrison T, et al. Bone mineral density assessment in children with inflammatory bowel disease. Gastroenterology 1998;114:902-11.
8. Harpavat M, Greenspan SL, O'Brien C, et al. Altered bone mass in children at diagnosis of Crohn disease: a pilot study. J Pediatr Gastroenterol Hepatol Nutr 2005;40:295-300.
9. Bougle DL, Sabatier JP, Guaydier-Souquieres G, et al. Zinc status and bone mineralization in adolescent girls. J Trace Elem Med Biol 2004;18:17-21.

10. Reed CA, Nichols DL, Bonnick SL, DiMarco NM. Bone mineral density and dietary intake in patients with Crohn's disease. J Clin Densitom 1998;1:33-40.
11. Griffin IJ, Kim SC, Hicks PD, et al. Zinc metabolism in adolescents with Crohn's disease. Pediatr Res 2004;56: 235-9.
12. Ojuawo A, Keith L. The serum concentrations of zinc, copper and selenium in children with inflammatory bowel disease. Cent Afr J Med 2002;48:116-9.
13. Vagianos K, Bectro S, McConnell J, Bernstein CN. Nutrition assessment of patients with inflammatory bowel disease. J Parenter Enteral Nutr 2007;31:311-9.