UDK :61

ISSN 1857-5587

PHYSIOACTA

Journal of Macedonian Association of Physiologists and Anthropologists

Vol 8 No 1
2014

58

UDK: 612.751.1.015.3:616-056.7

BONE TURNOVER MARKERS AND VITAMIN D STATUS IN PATIENTS WITH CYSTIC FIBROSIS

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Abstract

Imbalance between bone formation and degradation in cystic fibrosis (CF) has become an important issue for developing osteopenia. The aim of the study was to assess bone formation and resorption process with bone markers in prepubertal, pubertal and young adult CF patients. Materials and methods: The study included 80 clinically stable CF patients who regularly attended the Cystic Fibrosis Center at the University Pediatric Clinic in Skopje, R. Macedonia. Serum osteocalcin (OC), βcrosslaps (CTX), 25OHD and PTH were determine by ELISA assays in prepubertal CF group (mean age 8.25±SD1.9 years), pubertal CF group (mean age 14.3±SD 1.9 years) and young adults (mean age 24.1±SD 4.3 years) and in age-matched controls. Results: In prepubertal CF and control group, OC was 70.88±34.24ng/ml vs.100.02±47.98ng/ml, p=0.01. Serum levels of 25OHD in CF and control pubertal group were 21.15±8.77ng/ml vs.27.39±10.8ng/ml, p=0.05. There was a significant difference for 25OHD between CF and healthy controls. OC in prepubertal CF patients correlated significantly with the controls indicating a decreased formation rate whereas resorption rate was normal. Conclusion: Our results suggest that bone turnover in CF is impaired. Serum markers for bone formation can be used for predicting osteopenia in CF patients.
Key words: cystic fibrosis, osteoporosis, vitamin D deficiency, bone turnover

МАРКЕРИ НА КОСКЕН ТРНОВЕР И ВИТАМИН Д СТАТУС КАЈ ПАЦИЕНТИ СО ЦИСТИчНА ФИБРОЗА

Апстракт

Нерамнотежата помеѓу коскеното формирање и разградување кај цистична фиброза (ЦФ) стана многу важно прашање за развој на остеопенија. Целта на студијата беше да се оцени процесот на коскено формирање и ресорпција преку коскени маркери кај претпубертетски, пубертетски и млади адултни пациенти со ЦФ. Материјал и методи: Студијата вклучи 80 клинички стабилни ЦФ пациенти кои редовно го посетуваат Центарот за ЦФ при Универзитетската клиника за педијатрија во Скопје, Р. Македонија. Серумски остеокалцин (ОС), бетакрослапс (СТХ), 25ОХД и ПТХ беа утврдени со ELISA есеи кај претпубертетска ЦФ група (8,25±1,9 г.), пубертетска ЦФ група (14,3±1,9 г.) и млади адулти со ЦФ (24,1±4,3 г.), како и кај соодветни контролни возрасни групи. Резултати: Во претпубертетската ЦФ и контролна група, вредностите на остеокалцин беа 70,88±34,24нг/мл наспроти 100,02±47,98 нг/мл, p=0,01. Во пубертетската ЦФ и контролна група серумските нивоа на 25ОХД беа 21,15±8,77 нг/мл наспроти 27,39±10,8 нг/мл, p=0,05). Во нашата студија најдовме

Mean value of 25OHD in CF group was 22.53±10.09 ng/ml and mean value in control group was 26.44±11.1 ng/ml, which was statistically significant (p=0.02*) despite daily supplementation in CF patients with 800 IU (Figure 1).
DXA scans were performed in CF patients and we found decreased bone density (BMD) in prepubertal (-0.2±1.06SD), and pubertal (-.073±0.96SD) CF patients (Table 1.) In our study 30% of CF patients had osteopenia (Z or T score < -1SD) and 10% had osteoporosis (< -2SD).

We found a significant difference for serum values of 25OHD between CF and control pubertal group (0.05*) (Table 1). Serum levels of 25OHD, although not significant, were lower in adult CF patients. Their lower vitamin D levels may contribute to future bone problems.

In prepubertal CF patients the mean serum osteocalcin, a marker of bone formation, was significantly reduced (p=0.01*) compared to controls (Table 1). This finding may be an early indication of a problem with bone accretion in CF patients. Adult CF patients had higher levels of OC, probably a compensatory increase in bone formation (Figure 2.)

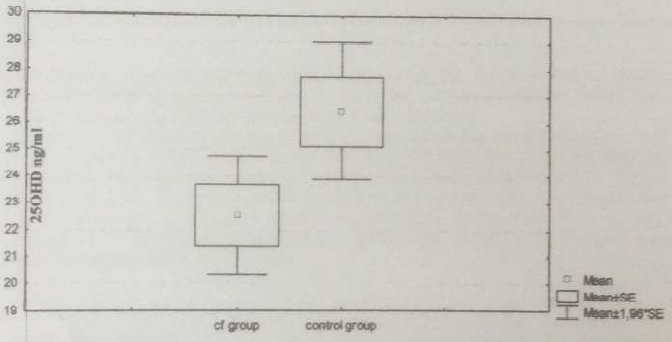
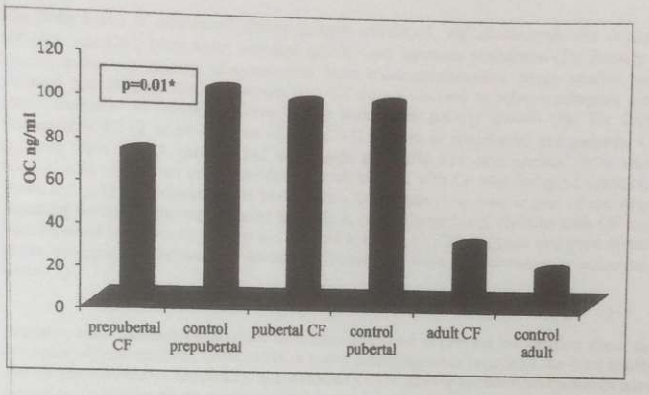


Figure 1 Serum concentrations of 25OHD in CF and control group



*statistically significant

Figure 2 Serum concentrations of osteocalcin in CF patients and controls

We found no statistically significant difference for serum CTX levels between CF patients and healthy controls (p=0.06), although the levels for CTX in pubertal CF patients were higher indicating that they may have accelerated bone resorption.
There was no statistical significance for PTH in CF groups beside impaired bone turnover in younger patients. Also, we found no significant difference for serum calcium and phosphorus. But there was a statistical difference for alkaline phosphatase (AF) between adult CF patients and controls (p=0.000*) (Table 1). Elevated AF levels in CF patients may have resulted from proliferating osteoblasts (accelerated osteoblastogenesis) who secret osteocalcin for accelerated bone accretion. Impaired bone turnover probably was a main cause in reducing BMD in our patients.

Discussion

Osteoporosis is highly prevalent in adults with cystic fibrosis (1) and this is caused by a variety of factors including malnutrition, chronic inflammation, vitamin D deficiency, hypogonadism, delayed puberty, physical inactivity and pharmacotherapy (2). As survival improves and the adult CF population continues to grow, osteoporosis becomes an increasingly important clinical problem. High prevalence of skeletal lesions, such as osteoporosis, kyphosis and increased fracture rate has been reported in patients with CF (3). There is a debate regarding the importance of "too little gain" versus "to much loss" in CF bone disease (4). Studies of bone metabolism may enhance our understanding of CF bone disease, but the results to date have been controversial.

The bone health is established during infancy, childhood, and adolescence and requires adequate nutrition, body mass, physical activity and hormone production (5). Puberty is crucial period for gaining adequate peak bone mass accumulation. Many studies have reported that children and adolescents with CF do not succeed to achieve adequate bone mass, compared to healthy children during their quick puberty growth (6). We found decreased BMD (Z score between -0.2 and – 0.7) even in prepubertal and pubertal CF children; 30% of CF patients had osteopenia and 10% had osteoporosis. In a study conducted in France, out of 114 children and adolescents with CF who had good nutritional status and mild lung disease, 34% had Z score lower than -1 in lumbar part of the spine, including 6-year-old patients. Similar findings in normal prepubertal children with CF have been reported in studies by Grey et al., Bianchi et al., (5, 6). This suggests that bone disease in the youngest CF patients can develop independently from the nutritional or pulmonary status (7).

Recently, some biochemical markers have been proposed to provide information about the dynamics of bone turnover. Osteocalcin, a major noncollagenous protein of the bone matrix specifically secreted by osteoblasts, is considered a valid marker for the examination of bone formation, in that its serum levels are higher at ages when the bone mineralization rate is increased (8). Serum βcrosslaps (CTX) seems to reflect the bone resorption rate (9). During childhood, serum levels of OC and CTX are much higher than in adulthood. Levels of bone turnover markers increase during puberty and reach their peak soon after sexual maturity. Studies have shown that CF patients have pathological bone turnover. For the first time this was presented in a study by Grey who had found high levels of hydroxyprolin, βcrosslaps (CTX) and deoxypirolin in urine (10). Bone turnover markers in CF patients indicate that they suffer from hyperresorption and an inadequate compensation in bone formation even when they are clinically stable (11, 12, 13). In our study, prepubertal CF patients had significantly decreased levels of osteocalcin than controls, implicating a reduced number of osteoblasts and a reduced formation rate in the early period of life. We found significantly higher alkaline phosphatase values in adult CF patients. Mortensen et al. (14) in their study found no significantly different levels for osteocalcin, but they found lower alkaline phosphatase values in prepubertal CF patients, suggesting that there was an early problem with bone accretion. Baroncelli et al. performed a study of bone metabolism in a mixed group of CF children and adults (15). They demonstrated augmented NTX urine levels that reflected increased bone resorption rates in prepubertal CF patients. Furthermore, they found evidence of reduced bone formation, as measured by serum OC and AF in pubertal and young adults. Haworth et al. (16) reported that OC and AF levels were higher in their patients suggesting a high bone turnover physiology. Mischler et al. (17) found that CF patients at the greatest risk for bone demineralization were adolescent girls and Bachrach et al. (18, 22) did not find reduced bone mineralization in CF patients.

There is evidence from more than 20 reports that vitamin D insufficiency (low 25OHD levels) is common among individuals with CF (23%-75%), irrespective of season and despite supplementation with 800-1000 IE/day (19, 20, 21). In our study we found that 30% of CF patients had vitamin D deficiency, despite supplementation with 800 IE/day. CF patients included in our study had significantly lower levels of vitamin D than healthy subjects. We found significant difference for serum values of 25OHD between CF and control pubertal group. Serum levels of 25OHD, although not significant, were lower in adult CF patients. Their lower vitamin D levels may contribute to future bone problems.

Bhudhikanok, Salamoni et al. in different studies reported (22, 23) low serum 25 OHD concentrations that were associated with lower BMD, suggesting that vitamin D deficiency may play a significant role in the pathogenesis of demineralization in cystic fibrosis (21).

Conclusion

- Childhood growth in CF patients represents a critical period for acquisition of bone mass.
- Levels of serum markers for bone formation were lower in prepubertal children with CF and this may contribute to impaired bone turnover.
- Vitamin D deficiency and osteopenia were present in 30% of CF patients in our study.
- Bone turnover in CF patients is impaired.
- Promoting a healthy life style including physical activity and optimal intake of calcium and vitamin D may be the best way to achieve maximal peak bone mass.

References

1. Buzzetti R, Salvatore D, Baldo E, et al. An overview of international literature from cystic fibrosis registries: 1. Mortality and survival studies in cystic fibrosis. J Cyst Fibros 2009;8:229–37.
2. Kanis JA. Osteoprosis. 4th revised ed. London: Blackwell Healthcare; 1997.
3. Cashman KD, Seamans K. Bone health, genetics, and personalized nutrition. Genes Nutr 2007;2:47-51.
4. Davies JH, Evans AJ, Gregory JW. Bone mass acquisition in healthy children. Arch Dis Child 2005;90:373-378.
5. Sermet-Gaudelus I, Souberbielle JC, Ruiz JC, et al. Low bone mineral density in young children with cystic fibrosis. Am J Respir Crit Car Med 2007;175:951–957.
6. Grey V, Atkinson S, Drury D, et al. Prevalence of low bone mass and deficiencies of vitamins D and K in pediatric patients with cystic fibrosis from 3 Canadian centers. Pediatrics 2008;122:1014–1020.
7. Bianchi ML, Romano G, Saraifoger S, et al. BMD and body composition in children and young patients affected by cystic fibrosis. J Bone Miner Res 2006;21:388–396.
8. Paccou J, Zeboulon N, Combescure C, et al. The prevalence of osteoporosis, osteopenia, and fractures among adults with cystic fibrosis: a systematic literature review with meta-analysis. Calcif Tissue Int 2010;86:1–7.
9. Mortensen LA, Chan GM, Alder SC, Marshall BC. Bone mineral status in prepubertal children with cystic fibrosis. J Pediatr 2000; 136:648-652.
10. Aris RM, Merkel PA, Bachrach LK, et al. Guide to bone health and disease in cystic fibrosis. J Clin Endocrinol Metab 2005;90:1888–96.
11. Baroncelli GI, Luca F, Magazzu G et al. Bone demineralization in cystic fibrosis: evidence of imbalance between bone formation and degradation. Pediatr Res 1997;41:397-403.
12. Bhudhikanok GS, Wang MC, Marcus R, Harkins A, Moss RB, Bachrach LK. Bone acquisition and loss in children and adults with cystic fibrosis: a longitudinal study. J Pediatr 1998;133:18–27.

13. Shead EF, Haworth CS, Gunn E et al. Osteoclastogenesis during infective exacerbations in patients with cystic fibrosis. Am J Respir Crit Care Med 2006;174:306-11.
14. Mora S, Pitukcheewanont P, Kaufman FR et al. Biochemical markers of bone turnover and the volume and the density of bone in children at different stages of sexual development. J Bone Miner Res 1999;14:1664-71.
15. Schulze KJ, O'Brien K, Baer D et al. Efficiency of calcium absorption is not compromised in clinically stable prepubertal and pubertal girls with cystic fibrosis. Am J Clin Nutr 2003;78:110-6.
16. Stephenson A, Jamal S, Dowdell T et al. Prevalence of vertebral fractures in adults with cystic fibrosis and their relationship to bone mineral density. Chest 2006;130:539–44.
17. Elkin SL, Fairney A, Burnetti et al. Vertebral deformities and low bone mineral density in adults with cystic fibrosis: a cross-sectional study. Osteoporos Int 2001;12:366–72.
18. Aris RM, Renner JB, Winders AD et al. Increased rate of fractures and severe kyphosis: sequelae of living into adulthood with cystic fibrosis. Ann Int Med 1998;128:186–93.
19. Hahn TJ, Squires AE, Halstead LR, Strominger DB. Reduced serum 25-hydroxyvitamin D concentration and disordered mineral metabolism in patients with cystic fibrosis. J Pediatr 1979; 94:38-43.
20. Hall WB, Sparks AA, Aris RM. Vitamin D deficiency in cystic fibrosis. Int J Endocrinol 2010;201:2186-91.
21. Rovner AJ, Stallings VA, Schall JI et al. Vitamin D insufficiency in children, adolescents, and young adults with cystic fibrosis despite routine oral supplementation. Am J Clin Nutr 2007;86:1694–719.
22. Buntain HM, Greer RM, Schluter PJ et al. Bone mineral density in Australian children, adolescents and adults with cystic fibrosis: a controlled cross sectional study. Thorax 2004;59:149–55.
23. Mischler EH, Chesney PJ, Chesney RW, Mazess RB. Demineralization in cystic fibrosis. Am J Dis Child 1979;133:632-5.
24. Salamoni F, Roulet M, Gudinchet F, Pilet M et al. Bone mineral content in cystic fibrosis patients: correlation with fat-free mass. Arch Dis Child 1996;74:314-7.