Osteoporosis in Diabetic Children

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Abstract: Background: Osteoporosis is a disease characterized by low bone mass and deterioration of bone structure that causes bone fragility and increases the risk of fracture. . Children and adolescents with type 1 (insulin-dependent) diabetes mellitus (T1DM) show several impairment of bone metabolism and structure, resulting in a higher risk of decreased bone mass and its related complications later in life. Objective: to analyze whether bone mineral density (BMD) with bone status are influenced in children with T1DM and evaluate their relationships with clinical status, age and duration. Patients and Methods: Forty cases (age 7.5 $\pm$ 3.4 and duration of disease 3.7 $\pm$ 2.5 years) were studied. BMD expressed as Z-score was measured at neck of femur and Lumbar spines ($L_2 - L_4$) using dual energy x-ray absorptiometry (DEXA) for 15 cases. Urinary excretion of deoxypyridinoline (DPD) was measured by radio immunoassay and was corrected by creatinine (Cr). Serum levels of osteocalcin, osteoprotegrin, procollagen and rankle – markers of bone formation and resorption were measured. They were matched by age and sex for another 40 normal children as control. Results: there was a significant decrease in serum level of osteocalcin in 12 of our patients,all cases showed significant increase in serum rankle with significant difference $P < 0.05$ compared to control. Mean values of procollagen showed no significant difference compared to controls. As regard DPD mean values of cases showed a significant increase compared to control. BMD – expressed as Z-score-by DEXA revealed 10 cases with mild degree osteopenia, while the other 5 cases showed moderate degree. Conclusion: pediatric patients with T1DM appear to constitute a population at risk of developing osteopenia. Age-optimizing of metabolic control in growing diabetic children may prevent osteoporosis in later life.
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1. Introduction:

There are several different forms of idiopathic osteoporosis that can affect both children and adolescents (Sone,.2010). Juvenile osteoporosis affects previously healthy children between the ages of 8-14 (Heap et al., 2004).

The disease almost always goes into remission around the time of puberty with a resumption of normal bone growth at that time, (Ingberg et al., 2004). Patient with mild or moderate forms of the disease may be left with a curvature of the spine and short stature, but those with a more severe form may be incapacitated for life (Alonso et al,2010 and Gooch et al., 2000).

Diabetic osteoporosis is increasingly recognized as a significant comorbidity of type 1 diabetes mellitus (Saha et al, 2009 and Galluzzi et al,2005). . Alterations of the nuclear factor-kappa B ligand (RANKL)/osteoprotegerin (OPG) system have been implicated in several metabolic bone diseases characterized by increased osteoclast differentiation and activation and enhanced bone resorption (Carnevale et al,2004) Data uniformly support the concept that new bone formation as well as bone microarchitectural integrity are altered in the diabetic state, leading to an increased risk for fragility fracture and inadequate bone regeneration following injury, (Stagi et al,2010 and He et al., 2004).

The osteopenia associated with diabetes appears to be associated with a decreased bone turnover associated with impaired osteoclastic maturation and function (Brandao et al,2007) . This is reflected in a decrease in serum markers of bone formation, such as osteocalcin. Bone resorption and formation are usually tightly coupled, (Heilman et al,2009 and Gunczler et al., 2001).

Insulinopenia as occurs in type 1 diabetes is associated with several deleterious consequences for skeletal health. Skeletal defects that are observed in conjunction with T1DM include : 1) diminished linear bone growth during the pubertal growth spurt, 2) decreased adult bone density, 3) an increased risk for adult osteoporosis, 4) increased risk of fragility fracture, and 5) poor bone healing and regeneration characteristics,(Saha et al,2009 and Campos et al., 2000).

Aim of the study : To analyze whether bone mineral density (BMD) with bone status are

influenced in children with type 1 diabetes mellitus (T1DM) and evaluate their relationships with clinical status, age and duration.

2. Subjects and Methods:

Forty patients with type 1 Diabetes Mellitus – from endocrinology clinic, Children Hospital, Cairo University – were included in this study. Mean age was (7.5 ± 3.4 years) and mean duration of the disease (3.7 ± 2.5 years). They were matched by age and sex for another 40 normal children as control.

All the above cases were subjected to:

Full history taking for the clinical status, all investigations were done for diagnosis and full details about scheme of treatment.

Special clinical files were done for all the studied cases with all their clinical data.*Blood samples were collected. Separated sea was froozen at –20.

Serum levels of osteocalcin were measured by host-ELISA kit prepared by Bio Source Europe S.A. Serum procollagen Type 1 was detected by Enzyme Immunoassay. Osteoprotegrin was measured by Biovendor Human Osteoprotegrin, while serum level of RANKL was detected by Biomedica Gruppe

Enzyme Immunoassay.

BMD was done by DEXA manifested on the femur bone and Lumbar spines (L_2- L_4) expressed as Z-score.

Statistical methods:

All the above data were collected and statistically tested by analysis of variance or students t-test. Correlations were studied by simple pearsons coefficient. Significance was defined as $P < 0.05$.

3. Results

Our study revealed significant decrease in osteocalcin level (range 2.1 – 5 ng/ml) in 28 of our T1DM cases compared to 12 cases showed normal range of (5-25), with mean values of osteocalcion 5.7 ± 6 for cases against 9.5 ± 7 ng/ml for control with statistical significant difference $P < 0.05$ (Table 1 and Fig. 1).

Positive correlation ($r = 0.6$) was recorded between osteocalcin level and age of the patients in years (Table 2 and Fig. 2).

Forty cases of the study, showed increase in procollagen type 1 level (mean 352.4 ±18.3) compared to control (mean 339.2 ± 19.2) but without significant differene $P > 0.05$. Table (1).

Levels of osteoprotegnin were markedly decreased in all the cases (3.1 ± 6.9) against (7.9 ± 5.4) for controls with $P < 0.05$ (Table 1 and Fig.1). A positive correlation ($r = 0.5$) was detected between osteoprotegrin level and duration of the disease (Table 3 and Fig. 3).

As regard Rankl levels, the cases record significant increase in all the cases (mean 78420.9 ± 16.2) compared to control (15977.2 ± 25.1) with $P < 0.05$ Table (1).

Urinary levels of DPD, revealed marked increase in all the cases (mean 68.65 ± 8.2) compared to control (36.11 ± 1.2) with statistical significant difference $P < 0.05$ Table (1).

The BMD- expressed as Z score – was measured in 15 cases only at the femur and lumbar spines (L_2 – L_4). Our results showed 10 cases with mild form of osteopenia (-1: -1.5) and the other 5 cases with moderate form of osteopenia (-1.5: -2).

Table (1) : Mean Values of some Laboratory Finding of Patients Versus control:

	Osteocalcin ng/ml	Procollagen ng/ml	Rankl Pmol/L	Osteoprotegrin Pmol/L	Deoxypyridin (DPD) n mol DPD/ n mol Cr
Patient (n=40) mean ± SD	5.7 ± 6	352.4 ± 18.3	78420.9 ± 16.2	3.1 ± 6.9	68.65 ± 8.2
Control (n=40) mean ± SD	9.5 ± 7	339.2 ± 19.2	15977.2 ± 25.1	7.9 ± 5.4	36.11 ± 1.2
P-value	P < 0.05	P > 0.05	P < 0.05	P < 0.05	P < 0.05

Statistical sig. difference p<0.0

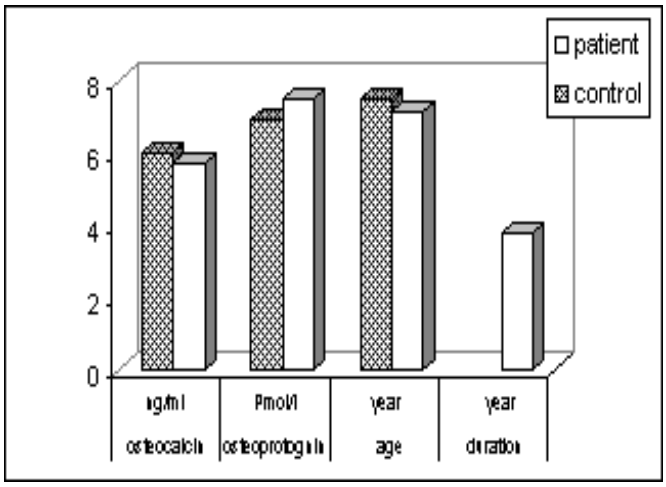
Table 2 : Relation between Osteocalcin and age of the patients.

	Osteocalcin (ng/ml)	Age of patients (year)
Patients (n = 40) Mean ± SD	5.7 ± 6.2	7.50 ± 3.4
r	+ 0.6	

Table 3 : Correlation between Osteoprotegrin and duration of disease.

	Osteoprotegrin (Pmol /L)	Duration of Disease (year)
Patients (n = 40) Mean ± SD	7.9 ± 5.4	3.7 ± 2.5
r	+ 0.f	

Statistical sig. difference p<0.0



Fig, 1: Mean values of some laboratory finding of patients versus controls.

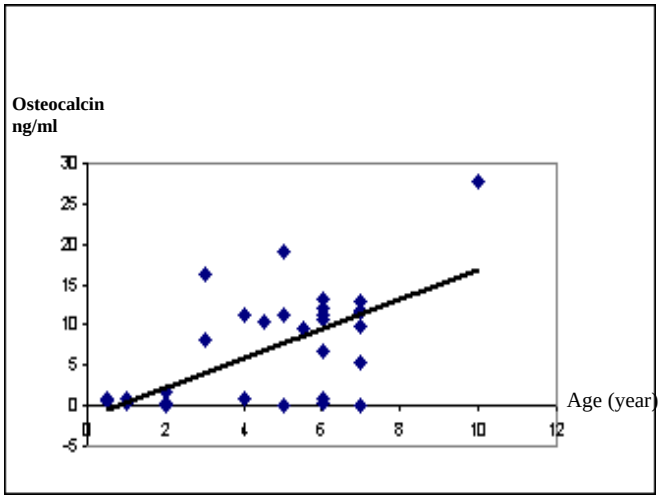


Fig. 2 :Relation between Osteocalcin and age of the patients

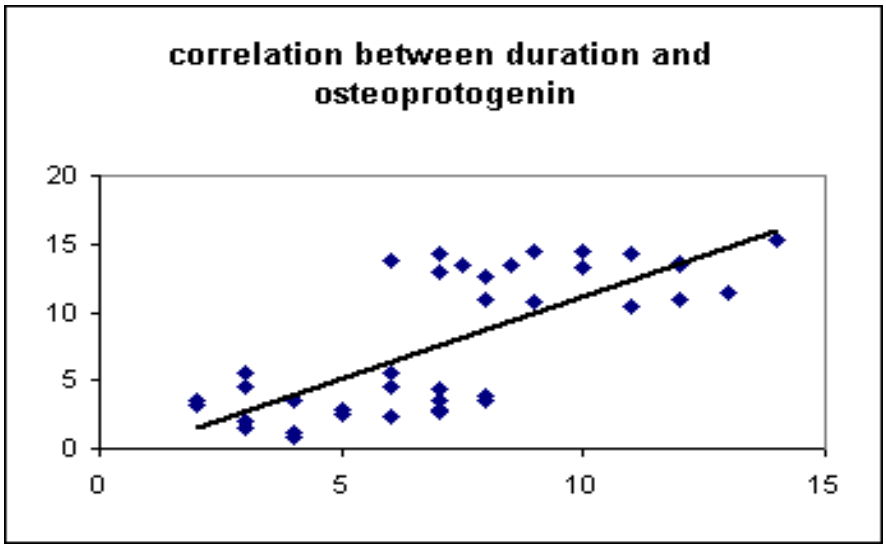


Fig.3 Correlation between osteoprotegrin and duration of disease.

4. Discussion:

Osteoporosis can vary broadly and may involve more than one disorder. Some young patients with osteoporosis may have a primary defect in the regulation of bone cell function, resulting in depressed bone formation, increased bone resorption or both,(Alonso et al,2010 and Heap et al., 2004).

The result of this study on T1DM patients revealed significant decrease in serum values of osteocalcin and osteoprotegrin, (2.1 – 5 ng/mL, 62 ng/ml, 3.1 – 6.9 pmol/L respectively). These findings indicate active depression of bone formation during diabetic illness.

Mean while, our data showed increase mean values of serum Rankl (0.3 – 0.4 pmol/L) and urine values of DPD (600-852 pmol/L). Both indicate increase bone resorption.

These finding indicate that, early onset of diabetes, in particular, is associated with reduced bone density, and patients with type 1 diabetes show evidence of low bone mass following adolescence. Our data fit the same founded by, Geurs, et al., in (2003)and Heilman et al., (2009) who stated that, osteopenia with diabetes appears to be associated with a decrease bone turnover and impaired osteoblastic maturation and function. This is reflected in a decrease in serum markers of bone formation. Bone resorption and formation are usually tightly coupled, (Melhus et al., 2003).

Positive correlation between osteoprotegrin and duration of the disease (r = 0.5), could be explained by the fact that, all bone metabolic changes which occure in early childhood of type 1 diabetic patients will be gradually corrected with long duration of the disease, these results fit the same of Ingberg et al., (2004) and Gilluzzi et al., (2oo5) who suggested that the impact of T1DM on skeletal health may by especially pertinent during adolescence.

The patients in the study were all between age of 5 and 16 and had been receiving treatment for diabetes for at least five years in the endocrinology clinic at Abu-reach hospital. Bone mineral density and bone mineral content measurements were taken for neck of femur and lumbar spine (L_2-L_4) by dual energy X-ray absorptiometry (DEXA). Our result revealed ten cases with mild form of osteopenia (Z-score - 1: -1.5) while only 5 cases were of moderate osteopenia (Z score - 1.5: -2). Careful clinical history taking revealed that, those 15 cases of T1DM were with uncontrolled diabetes with in adequate doses of insulin. This can be explained by findings of, Hou et al.,(1993) vankuijk,(2010)and Kemink et al.(2000), who stated that insulin is an anabolic agent in bone. It can preserve and increase bone density and bone strength, presumably through direct and /or indirect effects on bone formation.

The results of this work demonstrated that osteopenia and osteoporosis are frequent complications of T1DM. This fit the results of Heilman et al, (2009) and Heap et al., (2004). It is relevant therefore, that many studies confirm that T1DM is associated with decreased bone density, (Lopez et al., 2001 and Rozadilla et al., 2003) and a state of low bone turnover, (Thrailkill, 2004).

The osteopenia founded in some of our T1DM population, can be explained by numerous factors which may contribute to the development of osteoporosis over the life time of those diabetic children, 1) insufficient skeletal mineralization during critical periods of bone mass accrual; 2) increased urinary calcium excretion coupled with diminished calcium absorption, leading to chronic clacium deficiency, 3) life long effects of chronic hyperglycemia on osteoblast function; 4) detrimental effects of accumulated glycated end products on bone formation; 5) insulinopenia.

Kemink et al. (2000), suggested that, although insulin as an anabolic agent can preserve and increase bone strength through its effects on bone formation, the persistence of fracture risk in certain hyperinsulinemic states, however, under scores the multifactorial nature of the effects of diabetes on bone and may suggest a threshold for insulin in promoting healthy bone. Multiple confounding variables may have independent negative impacts upon bone mineral acquisition in T1DM and ultimately, on peak bone mass, (Rozadilla et al., 2003).

5. Conclusion:

Pediatric patients with type 1 Diabetes Mellitus appear to constitute a population at risk of osteoporosis in adulthood. Poor metabolic control may expose those patients at adolescents to the risk of osteopenia. So, optimization of metabolic control in growing diabetic children may prevent osteoporosis in later life.

5. Recommendations:

Type 1 diabetes does appear to be a significant risk factor for osteoporosis. Currently we recommend that patients with type 1 diabetes be monitored more carefully than persons without diabetes. Those patients should be encouraged to consume a diet high in both calcium (at least 1200 mg/day) and vitamin D (400-600 Iu/day). It appears that intensive insulin therapy and a stable body weight in patients with type 1 diabetes are important in preventing bone loss.

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