Changes in bone mass in a child population with type 1 diabetes mellitus. Longitudinal study

Vázquez Gámez MA[1], Bocio Nuñez J[2], Bermudez de la Vega JA[3], Bernal Cerrato S[3], Giner García M[1], Miranda García MJ[4], Hernandez Cruz B[5], Olmo-Montes J[4], Barrera Barrera J[4], Montoya García MJ[1]
1 Department of Medicine. Seville University. Seville (Spain)
2 FISEVI. Virgin Macarena University Hospital. Seville (Spain)
3 Pediatric Service. Virgin Macarena University Hospital. Seville (Spain)
4 Internal Medicine Service. Virgin Macarena University Hospital. Seville (Spain)
5 Rheumatology Service. Virgin Macarena University Hospital. Seville (Spain)

Summary

Objetive: To evaluate, over a 79.2-month follow-up period, the behavior of bone mineral density (BMD) determined by Computerized Axial Densitometry (DXA), volumetric bone mineral density (BMDvol) and its relationship with anthropometric data, together with the parameters related to bone metabolism (calcium, phosphorus, alkaline phosphatase, parathormone (PTH) and vitamin D (25-OH-D3)) in a child population with Type 1 Diabetes Mellitus (DM1) without microvascular complications and a control group of reference with similar characteristics.

Material and methods: Initially, a cross-sectional study was carried out in 40 diabetic children (mean age 9.4±2.8 years) and 108 controls (9.3±1.5 years) to assess the possible differences between the two populations. 26 patients from the initial diabetic group were reassessed after 79.2 months of follow-up.

Results: It was observed that, at baseline, bone mass was similar in diabetics and controls. After follow-up, the BMD of the diabetic children was much lower than that expected in the non-diabetic child population.

Weight, height, and Body Mass Index (BMI) followed the same pattern as BMD. The values of calcium, phosphorus, alkaline phosphatase, PTH and vitamin D, although within the normal range, were lower than in the controls. Alkaline phosphatase did not increase in the pubertal period.

Conclusions: The present study demonstrates that children and adolescents with a recent diagnosis of DM1 have a normal BMD. However, over time, and especially during adolescence, they show less bone mass gain and changes in bone turnover parameters.

Key words: type 1 diabetes mellitus, childhood, bone mineral density, bone turnover, longitudinal study.

INTRODUCTION

Type 1 diabetes mellitus (DM1) has been associated with lower bone mass for more than 30 years[1,2], although existing data in children and adolescents are contradictory[3-8]. Published results on bone mass development in the adult diabetic population show a lower BMD in type 1 diabetics that persists over time and a higher risk of fractures[9-11]. However, in the pediatric population with DM1, longitudinal studies are very limited and with discrepant results. Some authors report a reduction in BMD during follow-up[6,12,13], while others do not observe long-term changes[14,15]. These discrepant results may be due to multiple variables such as the length of follow-up, which is almost always too short; the different ages and

anthropometric variables, or the different pubertal stages of the diabetic population included in the studies[11-14].

Few publications longitudinally evaluate BMD in children with long-term DM1, also relating it to the different parameters of bone metabolism and remodeling and to the degree of diabetes control[11,16].

Therefore, our study aim has been to compare the BMD of children and adolescents with type 1 diabetes, with a control group with similar anthropometric characteristics, and to carry out a long-term follow-up of this population, relating the changes in bone mineral density with data anthropometric, degree of metabolic control, analytical parameters related to calcium metabolism, serum levels of parathormone and vitamin D.

Correspondence: Jesus Bocio-Nuñez (jesus.bocio@gmail.com)

ORIGINALS   *Changes in bone mass in a child population with type 1 diabetes mellitus. Longitudinal study*   **83**

Rev Osteoporos Metab Miner. 2022;14(2):82-87

MATERIAL AND METHODS

Study design
This study includes 2 phases. The first consisted of a cross-sectional study in which bone mass was compared between control children and type 1 diabetic children, while in the second phase an observational longitudinal study of this population was carried out, reevaluating it after a long period of time (mean: 79.2 months).

Study subjects
There were 40 diabetic children (17♂/23♀) included in the study ranged in age from 3.3 to 16.7 years at the outset of the study, with a disease duration of 4.04±2.8 years (9.4±2.8 years) and with no obvious microvascular complications. 70% of the diabetic population studied was in Tanner stage I, 10% in stage II, another 10% in stage III, 7.5% in stage IV and 2.5% in stage V of pubertal development. All of them came from the Pediatric Endocrinology clinic of the "Virgen de Macarena" University Hospital in Seville. The 109 controls (55♂/54♀) (mean age: 9.32±1.6 years) with an age range of 6.1 to 16.9 years, were included by age, sex and pubertal stage, similar to the study group.

In the second phase of the investigation, 26 of the 40 diabetic patients (13♂/13♀) initially studied (65%) were reassessed after a mean follow-up of 79.2 months, when their mean age was 15.88± 2.9 years and the mean evolution of the disease of 10.61±3.0 years (range 5-18). After this follow-up period, these patients did not show complications secondary to their underlying disease. At this point in the study, 73.1% of the patients were in Tanner stage V, 11.5% in stage IV, 3.8% in stages II and III, respectively, and 7% were in stage I of pubertal development.

The remaining 14 patients included in the initial study could not be located due to changes in their address and/or assigned health area.

The longitudinal study results were compared with a reference control population of 234 children, matched by age, sex and pubertal stage with the cases, in whom BMD was assessed in the same period of time as the diabetic population.

Bone mass
In all study participants, both those included in phase 1 and 2, areal BMD, volumetric density (vol BMD), anthropometric parameters (age, weight and height), pubertal stage, menarcheal age of girls, serum levels of calcium, phosphorus, alkaline phosphatase, PTH and 25-OH-D3 were assessed. In the diabetic population, the mean values of glycosylated hemoglobin (HbA1c) were collected (obtained based on all HbA1c determinations since the initial diagnosis), number of years of the disease, existence of complications and regimen of administered insulin, expressed in IU/Kg/day.

Weight and height were obtained using a platform scale and an Atlántida S-11 stadiometer (Año Sayol S.A. Barcelona). Body mass index was calculated as weight/height^2 (Kg/m^2).

BMD was measured by DXA (Hologic-QDR-1000) in the lumbar spine (L2-L4). BMD measurement was performed with the same densitometer in both phases of the study. The Z-score of the control population was used as a reference for bone mineral density. The coefficient of variation (CV) of DXA was 0.5% in vitro (phantom) and the CV in vivo was 1.4%.

To avoid the variable size of the vertebrae in a growing population as a confounding factor, volBMD was determined, following the formula described by Kroger et al.[17].

Analytical parameters and bone remodeling
Blood samples for the different serum determinations were taken under fasting conditions, using the same measurement techniques in both phases of the study. Biochemical parameters (calcium, phosphorus, and alkaline phosphatase levels) were determined by autoanalyzer.

The degree of metabolic control was evaluated by determining the HbA1c levels by HPLC (high performance liquid chromatography), where the mean level was obtained based on all the determinations made from diagnosis to inclusion in the study (minimum 3 determinations per patient not anymore). Good metabolic control was considered when the mean HbA1c values were less than 7%; moderate control when they ranged between 7 and 8.5% and poor metabolic control when HbA1c figures were greater than 8.5%.

Parathormone (PTH) was measured by chemiluminescence immunometry. The determination was made by photometric analysis with a 2nd generation IMMU-LIITE DEP (Dipresa) autoanalyzer. Its normal range was considered between 15-80 pgr/ml.

Serum 25-OH-D3 was quantified by R.I.A. (Nichols Institute Diagnostics USA), after separation of the vitamin D metabolites. All the samples were collected in the same summer period to avoid bias.

All the patients' parents were informed of the purpose of the study and their consent was previously obtained. Likewise, the approval of the Ethics Committee of the Center was obtained.

Statistic analysis
Results are presented as mean ± standard deviation (SD). Statistical treatment was carried out using the statistical package "(SPSS) 22.0". To compare the means between the groups studied, Student's t test was applied to paired data and independent data when they followed a normal distribution. The Mann-Whitney U test was used with variables that did not show a normal distribution. Bone mineral density, weight, height, and BMI are expressed in absolute values. In the longitudinal study, the reference values of weight, height and BMI have been expressed as Z-score (value of BMD, weight, height and BMI of the patients-mean values of the control group/SD), to evaluate the changes that produce in time. The relationship between BMD (expressed in Z-score) and the rest of the parameters studied was calculated using the Pearson correlation coefficient in the case of those variables that followed a normal distribution; otherwise, the correlation coefficient used was Spearman's. Confounding factors were identified by multivariate analysis and, in the second part of the study, by a repeated measures test. Values of $p<0.05$ were considered levels of statistical significance.

RESULTS
The anthropometric data and baseline biochemical parameters of the groups studied are included in table 1.

We have not observed significant differences in bone mass between DM1 and controls, neither globally, nor when comparing them by sex. There were also no significant differences in weight and height between patients

84 Vázquez Gámez MA, Bocio Nuñez J, Bermudez de la Vega JA, Bernal Cerrato S, Giner García M, Miranda García MJ, et al. ORIGINALS

Rev Osteoporos Metab Miner. 2022;14(2):82-87

and controls, although the BMI was lower in diabetic children. 70% of the children included in this first part of the study were in Tanner stage I.

Serum calcium was significantly higher in the diabetic population. Phosphorus did not show differences between both populations. Circulating levels of 25-OH-D3, PTH, and alkaline phosphatase (AP), although within the normal range, were significantly lower in the diabetic population than in the control group (table 1).

The positive correlation between BMD and alkaline phosphatase present in the control group (r=0.198 p=0.04), is not observed in the diabetic group.

In children with DM1, serum HbA1c levels were 8.5±1.4% and the mean duration of the disease was 4.04±2.8 years. We did not find any relationship between BMD, the degree of metabolic control (HbA1c) and the time of evolution of the disease.

The anthropometric, biochemical and BMD data of the patients included in the longitudinal study (baseline and after 79.2 months) are shown in table 2.

At the end of the study, in diabetics, bone mass had increased significantly in absolute values from 0.715±0.13 gHA/cm² to 0.940±0.12 HA/cm²; p=0.000), as expected in a stage of full growth. However, the BMD values (expressed in Z-score) were significantly lower than those found in the first phase of the study (0.537±1.12 Z-score vs. -0.116±1.03 Z-score; p=0.001). This implies that the bone mass gain was much lower than expected for their age and gender (figure 1).

Vol BMD showed the same behavior as areal BMD, clearly correlating with it at the L2-L4 level (r=0.835) p=0.001.

At the beginning of the follow-up, 6 of the 26 patients presented negative BMD values (expressed in Z-score), even in three of them, the values were lower than -1SD. At the end of the study, there were 14 patients who presented a BMD below the expected values for their age and gender, doubling the number of them with -1SD. Only 4 diabetics showed an increase in bone mass consistent with the period of bone mass apposition expected for a growing adolescent population.

We did not explore the influence of pubertal stages on BMD, since most of the cases (19 of the 26) were in the last Tanner stage, and the rest of the patients were distributed in the remaining stages, being fairly homogeneous group.

The analysis by gender showed comparable results, with a non-significant lower BMD gain in adolescents.

Table 1. Anthropometric data and biochemical and bone mineral density parameters of patients with diabetes mellitus-1 and controls

	Diabetics N=40 X±SD*	Controls N=10 X±SD*	P#
Age (years)	9.3±1.5	9.4±2.8	NS
Weight (kg))	33.7±11.0	35.6±10.7	NS
Size (cm)	133.7±16.3	133.6±10.0	NS
BMI** (Kg/m²)	18.3±3.0	19.5±3.8	P=0.05
BMD** (gHA/cm²)	0.761±0.1	0.756±0.9	NS
Z-score (SD)	0.059±0.15	0.0±0.0	NS
Calcium (mg/dl)	9.6±1.6	9.0±0.35	P=0.000
Phosphorus (mg/dl)	4.8±1.0	4.6±0.42	NS
Alkaline phosphatase (U/L)	288.0±97.3	492.5±159.4	P=0.000
PTH** (pg/ml)	24.4±12.7	30.7±13.6	P=0.01
25-OH-D** (ng/ml)	27.5±16.5	40.2±9.9	P=0.000

*X±SD: mean ± standard deviation; #: statistical significance p<0.05; **BMI: Body Mass Index; BMD: Bone Mineral Density; PTH: parathormone; 25-OH-D: vitamin D.

Table 2. Anthropometric and biochemical data of the diabetic population, baseline and after almost 7 years of follow-up

| N=26	Basal X±SD*	After 79.2 months X±SD*	P#
Age (years)	9.23±3.3	15.88±2.9	0.000
Weight (Kg) (Z-score)	0.836±0.89	0.187±0.90	0.002
Size (cm) (Z-score)	0.629±0.87	-1.092±1.40	0.000
BMI** (%) (Z-score)	0.63±1.3	0.47±1.0	0.000
BMD** (gHA/cm²)	0.715±0.13	0.940±0.12	0.000
Z-score (SD)	0.537±1.1	-0.116±1.0	0.001
HbA1c (%)	8.8±1.3	9.3±1.9	NS
DMOA** (gr/cm³)	0.138±0.15	0.149±0.14	0.000
Calcium (mg/dl)	9.9±0.3	9.6±0.1	0.01
Alkaline phosphatase (U/L)	299.5±99.3	269.8±151.9	NS
PTH** (pg/ml)	27.3±12.4	19.8±7.7	NS
25-OH-D** (ng/ml)	27.9±18.1	40.4±17.4	0.02

*X±SD: mean ± standard deviation; #: statistical significance p<0.05; **BMI: Body Mass Index; BMD: Bone Mineral Density; DMOA: Areal Bone Mineral Density; PTH: parathormone; 25-OH-D: vitamin D.

Mean HbA1c levels after follow-up were 9.31±1.98% with a range of 6.4-14.4%. None of our patients had good metabolic control; 12 of them had moderate control and 14 were poorly controlled. We have not observed any relationship between changes in bone mass and the degree of metabolic control or the duration of the disease.

The same behavior that bone mass showed was observed when evaluating weight, height and BMI. Although these parameters increased significantly in absolute values, the diabetic patients had BMI values expressed in Z-score that were significantly lower than those found at the beginning of the study (table 2).

In phase 2 of the investigation, calcium levels decreased and vitamin D levels were significantly higher than baseline levels in the diabetic population (table 2).

ORIGINALS *Changes in bone mass in a child population with type 1 diabetes mellitus. Longitudinal study*
Rev Osteoporos Metab Miner. 2022;14(2):82-87

85

Figure 1. Changes in bone mineral density after 79.2 months of follow-up expressed in absolute values (A) and in Z-score (B)
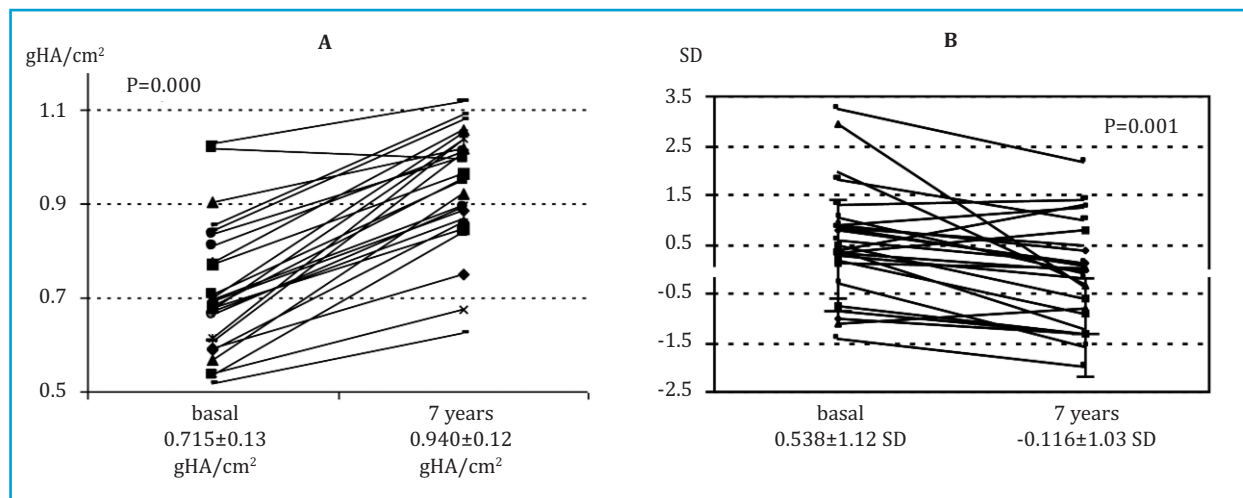
The changes produced in BMD at the end of the study were not influenced by pubertal stage. We observed that, although the older group (>15 years) reached more negative Z values from lower values in the initial study, the lower BMD gain is similar in both groups (figure 2).

In the multivariate analysis to determine the possible influence on bone mass of different variables (weight, height, BMI, serum calcium and 25-OH-D3), we found that only BMI was independently associated with the value of the score. Z (95% CI: 0.150-0.890; p=0.009) beta coefficient: 0.535.

Discussion

In our study, the child population with DM1 and with a short duration of the disease, showed a bone mass similar to that of the healthy population. These data corroborate the findings obtained in a previous study of our group, with a type 1[18] diabetic population. After a follow-up period of almost 7 years, BMD and volBMD increased in absolute values, but bone mass gain did not reach the desirable levels for a non-diabetic population with similar characteristics (figure 3).

Although there are numerous cross-sectional publications to evaluate bone mass in children with DM1, longitudinal studies carried out in this population are very limited, and with a follow-up period that is too short. We have only found one publication, which covers a broader period[6].

**Figure 2. Evolution of bone mass in type 1 diabetics, grouped by age (Z-score)**
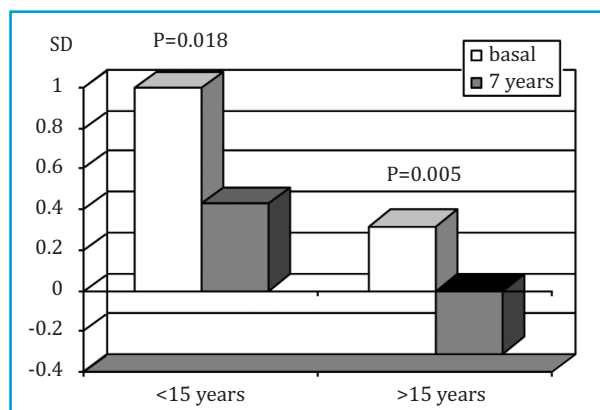
Those publications found that show no changes or these are minimal in the BMD of children with DM1, are carried out in a very short period of time (12 months)[12,14] and some start from a lower initial bone mass12. Hui et al.[15], with a somewhat longer follow-up (3 years), did not find changes in bone mass in a large population with type 1 diabetes either, but based their results on the measurement only of cortical bone in different locations of the radius, and the mean age of the patients is much higher than that of our diabetic population.

We have only found one study6 with characteristics similar to ours in temporality and study population. These authors observe a lower bone mass gain in the diabetic population than in controls. Unlike our study, they include patients with microvascular complications (5%) and the duration of DM1 was not homogeneous, with considerable variability between subjects, both at baseline and during follow-up. Despite this, their results are very similar to ours.

The discrepancy in bone mass results in the child population with DM1 could be explained by multiple factors: different bone mass measurement methods, type of bone measured (trabecular or cortical), age and number of patients included, or different stages puberty of the children studied[3,7,15,19]. To save the influence of changes in BMD induced by sex hormones, we selected a fairly homogeneous initial group, with 70% of cases in Tanner stage I. Like most authors, we have not found any relationship between bone mineral density and the degree of metabolic control or the time of evolution of the disease[4,13,14,15]. In our case, none of our diabetics had good metabolic control, which prevented us from making a comparison in this regard.

Our type 1 diabetic child population gains less weight, less height and their BMI is lower than expected for a healthy population of similar age and gender. BMI correlated with BMD. Studies that find a lower height and lower weight in prepubertal type 1 diabetic children with poor metabolic control relate it to a lower secretion of IGF-1 secondary to insulin deficiency[20-22]. In our case, almost all the patients had poor metabolic control and the onset of the disease had manifested before puberty except in one case, which could explain these metabolic alterations, and the lower bone mass gain.

86 *Vázquez Gámez MA, Bocio Nuñez J, Bermudez de la Vega JA, Bernal Cerrato S, Giner García M, Miranda García MJ, et al.* ORIGINALS

Rev Osteoporos Metab Miner. 2022;14(2):82-87

Figure 3. Number of patients with values less than -1 SD (expressed in Z-score) in the initial study and after a 7-year follow-up (the position of the bars correspond to the same patient)
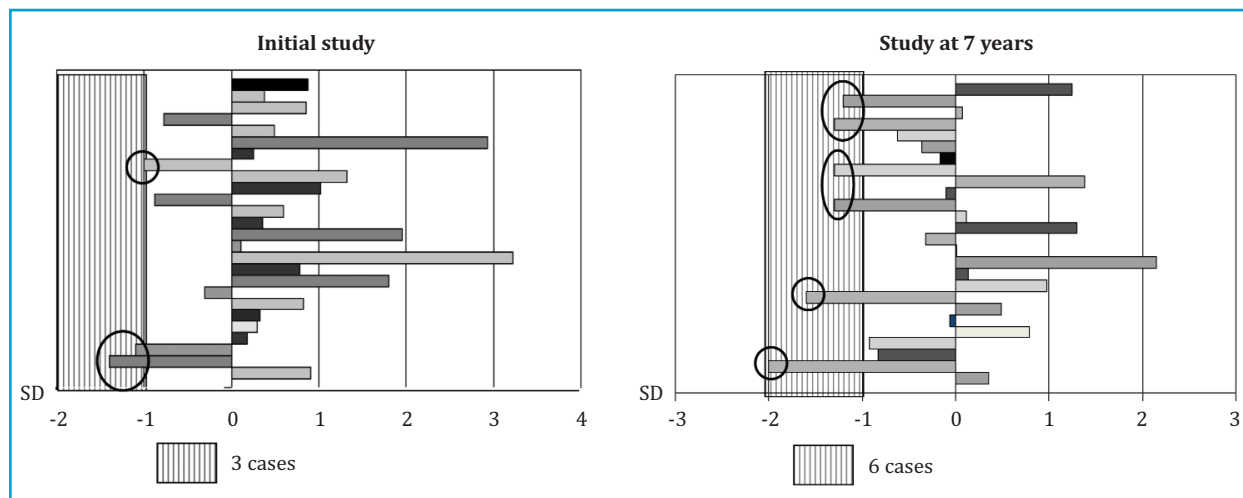
There are few works that relate the biochemical parameters with the changes experienced in the BMD of children with DM1. Most studies are cross-sectional and show disparate results. Of the few follow-up studies that measure bone mass in diabetic children, few include biochemical parameters[12,14]. Although our patients had serum levels of calcium, phosphorus, alkaline phosphatase, PTH, and vitamin D within the normal range, these were lower than in the control population. In cross-sectional studies of adolescent or adult populations, the results have been similar[4,23-25]. It is suggested that, possibly, this altered metabolic control is conditioned by low insulin levels, giving rise to abnormalities in calcium metabolism and, therefore, to low bone formation[23,24,26-28]. The hypotheses about decreased PTH levels are based on the insulinopenia present in type 1 diabetics or on a decrease in the activity of the enzyme 1-alpha-hydroxylase-renal, and could be related to the lower weight gain they present type 1 diabetics[28,29]. As with other authors' observations, we did not find any relationship between these biochemical parameters and bone mass[4,24,25,30,31].

In our results, the serum alkaline phosphatase values stand out, which, although within the normal range, were significantly lower than those of the controls in phase 1 of the study. After almost 7 years, these values did not increase as occurs in the non-diabetic adolescent population and were negatively and significantly related to bone mass in phase 2. This could be explained by the lower growth and acquisition of bone mass that we detected in patients with DM1. This aspect has not been evaluated in longitudinal studies of children with DM1. Cross-sectional studies do not find these differences[4,32].

Although our study is of great interest due to the homogeneity of the samples and the long follow-up, it has limitations. First, the number of cases studied may be insufficient to draw definitive conclusions. Furthermore, serum levels of Insulin-like Growth Factor-1 (IG-F1), sex hormones and insulin have not been determined, which would undoubtedly help us improve our understanding of the pathophysiology of the disorder.

Although it would have been desirable to longitudinally evaluate the control subjects' BMD, we have compared the data of the diabetic population studied almost seven years later, with a second healthy control group, with adequate bone apposition and similar anthropometric characteristics, obtained from a cross-sectional analysis. We believe this does not detract from the validity of our study, since the results clearly show the lower bone mass gain in type 1 diabetic children even without the presence of microvascular complications, as in other publications carried out with the same methodology.

In *conclusion*, the present study shows that children and adolescents recently diagnosed with DM1 have normal BMD. However, with the passage of time and, above all, in the period of adolescence, they show less bone mass gain.

The changes observed in the parameters of bone turnover after a long follow-up period could be interpreted as a consequence of insulin deficiency that causes poor metabolic control. The lower weight and height obtained at the end of the study could justify, together with these bone metabolic alterations, the lower bone mass gain acquired by diabetic patients. All these findings will lead to a lower peak bone mass and, surely, to a higher risk of developing osteoporosis and fragility fractures in adulthood.

Bibliography

1. Levin ME, Boisseau VC, Avioli LV. Effects of diabetes mellitus on bone mass in juvenile and adult-onset diabetes. N Engl J Med. 1976;294(5):241-5.
2. Maddaloni E, D'Eon S, Hastings S, Tinsley LJ, Napoli N, Khamaisi M, Bouxsein ML, Fouda SMR, Keenan HA. Bone health in subjects with type 1 diabetes for more than 50 years. Acta Diabetol. 2017 May;54(5):479-488.
3. Liu EY, Wactawski-Wende J, Donahue RP, Dmochowski J, Hovey KM, Quattrin T. Does low bone mineral density start in post-teenage years in women with type 1 diabetes? Diabetes Care. 2003; 26(8):2365-9.
4. De Schepper J, Smitz J, Rosseneu S, Bollen P, Louis O. Lumbar spine bone mineral density in diabetic children with recent onset. Horm Res Paediatr. 1998;50(4):193-6.
5. Pascual J, Argente J, Lopez MB, Muñoz M, Martinez G, Vazquez MA, et al. Bone mineral density in children and adolescents with diabetes mellitus type 1 of recent onset. Calcif Tissue Int. 1998;62(1):31-5.
6. Salvatoni A, Mancassola G, Biasoli R, Cardani R, Salvatore S, Broggini M, Nespoli L. Bone mineral density in diabetic children and adolescents: a follow-up study. Bone. 2004 May;34(5):900-4.
7. Viña Simón E, Bueno Lozano G, Armadá Maresca MI, Ruibal Francisco JL, Fernández Pérez C, Lozano Tonkin C, et al. Bone mineral density in juvenile onset diabetes mellitus. An Esp Pediatr. 2000;52(6):507-15.
8. Gunczler P, Lanes R, Paoli M, Martinis R, Villaroel O, Weisinger JR. Decreased bone mineral density and bone formation markers shortly after diagnosis of clinical type 1 diabetes mellitus. J Pediatr Endocrinol Metab. 2001;14(5):525-8.
9. Weber DR, Haynes K, Leonard MB, Willi SM, Denburg MR. Response to comment on Weber et al. Type 1 diabetes is associated with an increased risk of fracture across the life span: A population-based cohort study using the health improvement network (THIN). Diabetes care 2015;38:1913-1920. Diabetes Care. 2015;38(12):e205-6.
10. Devaraja J, Jacques R, Paggiosi M, Clark C, Dimitri P. Impact of type 1 diabetes mellitus on skeletal integrity and strength in adolescents as assessed by HRpQCT. JBMR Plus. 2020;4 (11):e10422
11. Léger J, Marinovic D, Alberti C, Dorgeret S, Chevenne D, Marchal CL, et al. Lower bone mineral content in children with type 1 diabetes mellitus is linked to female sex, low insulin-like growth factor type I levels, and high insulin requirement. J Clin Endocrinol Metab. 2006;91(10):3947-53.
12. Moyer-Mileur LJ, Dixon SB, Quick JL, Askew EW, Murray MA. Bone mineral acquisition in adolescents with type 1 diabetes. J Pediatr. 2004;145(5):662-9.
13. Leão AAP, Fritz CK, Dias MRMG, Carvalho JAR, Mascarenhas LPG, Cat MNL, et al. Bone mass and dietary intake in children and adolescents with type 1 diabetes mellitus. J Diabetes Complications. 2020;34(6):107573.
14. Gunczler P, Lanes R, Paz-Martinez V, Martins R, Esaa S, Colmenares V, et al. Decreased lumbar spine bone mass and low bone turnover in children and adolescents with insulin dependent diabetes mellitus followed longitudinally. J Pediatr Endocrinol Metab. 1998;11(3):413-9.
15. Hui SL, Epstein S, Johnston CC Jr. A prospective study of bone mass in patients with type I diabetes. J Clin Endocrinol Metab. 1985;60(1):74-80.
16. Slavcheva-Prodanova O, Konstantinova M, Tsakova A, Savova R, Archinkova M. Bone Health Index and bone turnover in pediatric patients with type 1 diabetes mellitus and poor metabolic control. Pediatr Diabetes. 2020;21(1):88-97.
17. Kröger H, Vainio P, Nieminen J, Kotaniemi A. Comparison of different models for interpreting bone mineral density measurements using DXA and MRI technology. Bone. 1995;17(2): 157-9.
18. Vázquez Gámez MA, Marín Pérez JM, Montoya García MJ, Moruno García RM, Argüelles Martín F, Pérez Cano R. Evolución de la masa ósea durante la infancia y adolescencia en niños con diabetes mellitus tipo 1 [Evolution of bone mass in children and adolescents with type 1 diabetes mellitus]. Med Clin (Barc). 2008 Apr 19;130(14):526-30.
19. Heap J, Murray MA, Miller SC, Jalili T, Moyer-Mileur LJ. Alterations in bone characteristics associated with glycemic control in adolescents with type 1 diabetes mellitus. J Pediatr. 2004;144 (1):56-62.
20 Kelly SD, Howe CJ, Hendler JP, Lipman TH. Disordered eating behaviors in youth with type 1 diabetes. Diabetes Educ. 2005;31(4):572-83.
21. Quinn M, Ficociello LH, Rosner B. Change in glycemic control predicts change in weight in adolescent boys with type 1 diabetes. Pediatr Diabetes. 2003;4(4):162-7.
22. Raisingani M, Preneet B, Kohn B, Yakar S. Skeletal growth and bone mineral acquisition in type 1 diabetic children; abnormalities of the GH/IGF-1 axis. Growth Horm IGF Res. 2017;34:13-21.
23. Vargas DM, Rigotti T, Gütz CNRM, Lobe MCS, Fernades J de A. Bone mineralization in children and adolescents with type 1 diabetes. J Pediatr (Rio J). 2003;79(3):253-8.
24. Kemink SA, Hermus AR, Swinkels LM, Lutterman JA, Smals AG. Osteopenia in insulin-dependent diabetes mellitus; prevalence and aspects of pathophysiology. J Endocrinol Invest. 2000;23 (5):295-303.
25. Weber DR, Gordon RJ, Kelley JC, Leonard MB, Willi SM, Hatch-Stein J, Kelly A, Kosacci O, Kucheruk O, Kaafarani M, Zemel BS. Poor Glycemic Control Is Associated With Impaired Bone Accrual in the Year Following a Diagnosis of Type 1 Diabetes. J Clin Endocrinol Metab. 2019 Oct 1;104(10):4511-4520.
26. Ponder SW, McCormick DP, Fawcett HD, Tran AD, Ogelsby GW, Brouhard BH, et al. Bone mineral density of the lumbar vertebrae in children and adolescents with insulin-dependent diabetes mellitus. J Pediatr. 1992;120(4 Pt 1):541-5.
27. Ersoy B, Gökşen D, Darcan S, Mavi E, Oztürk C. Evaluation of bone mineral density in children with diabetes mellitus. Indian J Pediatr. 1999;66(3):375-9.
28. Pedrazzoni M, Ciotti G, Pioli G, Girasole G, Davoli L, Palummeri E, et al. Osteocalcin levels in diabetic subjects. Calcif Tissue Int. 1989;45(6):331-6.
29. Kamycheva E, Sundsfjord J, Jorde R. Serum parathyroid hormone level is associated with body mass index. The 5th Tromsø study. Eur J Endocrinol. 2004;151(2):167-72.
30. Thalassinos NC, Hadjiyanni P, Tzanela M, Alevizaki C, Philokiprou D. Calcium metabolism in diabetes mellitus: effect of improved blood glucose control. Diabet Med. 1993;10(4):341-4.
31. Kayath MJ, Dib SA, Vieira JG. Prevalence and magnitude of osteopenia associated with insulin-dependent diabetes mellitus. J Diabetes Complications. 1994;8(2):97-104.
32. Chen SC, Shepherd S, McMillan M, McNeilly J, Foster J, Wong SC, Robertson KJ, Ahmed SF. Skeletal Fragility and Its Clinical Determinants in Children With Type 1 Diabetes. J Clin Endocrinol Metab. 2019 Aug 1;104(8): 3585-3594.