

## Effect of Physical Exercise on Bone Density and Remodeling in Juvenile Diabetic Children and Pre-adolescence

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### ABSTRACT

*Osteoporosis had been considered to be a complication of long term type I diabetes (DM). Recently it was demonstrated that children several years after the diagnosis of clinical DM have decreased femoral neck mineral density compared to control group or healthy children matched for age, sex and pubertal status. The current study comprised 24 patients (14 boys & 10 girls) aged 14-18 years old, with type I diabetes compared to a control group of the same sex and age. The study aimed to assess the bone modeling status in children with type I diabetes mellitus, study the effect of physical exercises on bone metabolism in diabetic children with osteopenia and searching of correlation between indices of bone metabolism and age, sex, diabetes duration and glycemic control. Both groups were subjected to thorough clinical examination, bone densitometry (BDM) by DEXA at femur neck and laboratory investigation (serum and urinary calcium, inorganic phosphorus and alkaline Phosphatase, serum procollagen I propeptide (PIP) and glycated hemoglobin. The diabetic children group was subjected to planned physical exercise program for one hour, three times/week for three months. Pre-exercises program comparison between both groups (diabetic & control) revealed non significant difference in mean serum values or urinary bone mass parameters. Yet, osteopenic diabetic patients displayed higher mean serum procollagen I propeptide than the control group. A negative correlation was observed between (PIP) and degree of glycemic control reflected by serum glycated hemoglobin (Hb<sub>A1C</sub>), and bone densitometry was correlated with diabetes duration. Post-exercises comparison revealed a (PIP) level drop even to lower values than in control group, also the mean BDM was significantly improved and 5 patients out of the 24 (diabetic group) showed normal densitometry. In conclusion exercises as it plays an important role in glycemic control in diabetic children, it also plays an important role in minimizing the diabetes osteoporosis complications and can be considered an essential element in the treatment protocol of children with type I diabetes mellitus.*

### INTRODUCTION

**D** iabetes Mellitus is a syndrome of disturbed energy homeostasis caused by a relative or absolute deficiency in insulin or its action resulting in abnormal metabolism of carbohydrate, protein and fat<sup>2</sup>.

Osteopenia is not uncommon in children with insulin dependent diabetes mellitus. The mechanism by which bone loss occurs in diabetic patients could be explained by a reduction of insulin /insulin-Like growth

factor I action, sustained hyperglycemic state, generation of glycosylation end-products, and diabetic complications such as nephropathy and retinopathy. Osteoblast deficit is suggested to play a major role in the occurrence of diabetic osteopenia<sup>1,12</sup>.

Bone formation at onset of insulin dependent diabetes is not impaired. The introduction of insulin therapy together with achievement of a good metabolic control determine an increase of bone matrix formation coupled with decrease of bone

resorption, which determine a positive balance of bone modeling<sup>4</sup>.

Physical exercise is beneficial for skeletal health of children and adults. It induces a positive effect on bone density in children with cerebral palsy. It is becoming increasingly clear that exercises may be a therapeutic tool in a variety of patients with or at risk for diabetes<sup>6,23</sup>.

### **Aim of the study**

1. Assessment of bone modeling status in children with type I diabetes mellitus.
2. Study the effect of physical exercise on bone metabolism in diabetic children with osteopenia.
3. Searching for any correlation between indices of bone metabolism and age, sex, diabetes duration, and glycemic control.

### **Patients**

The study was conducted on twenty-four children patients with type I diabetes mellitus recruited from Diabetes Outpatient Clinic, Children Hospital, Ain Shams University, ten females (41.7%) and fourteen males (58.3%) with ages ranged between 14 and 18 years served as study group.

### **Controls**

Thirty eight, age and sex- matched, healthy subjects, twenty females (52%) and eighteen males (48%), were chosen from patient's relatives attending the Outpatient Pediatric Clinic Ain Shams University. Their ages ranged between 14 and 18 years served as control groups.

### **Both groups were be subjected to**

1. History taking including: Age, age of onset the disease to calculate diabetes duration, history suggestive of microvascular complications, history

suggestive of any musculoskeletal disease and history of any regular exercise or medications other than insulin is being taken.

2. Full clinical examination with special stress on growth parameters (weight and height, blood pressure assessment, fundus examination and full neurological assessment).
3. Laboratory investigation including:
  - a. Glycosylated hemoglobin (HbA1c) routinely done every 3 months.
  - b. Creatinine clearance was determined by synchron CX5 clinical systems.
  - c. Estimation of biochemical parameters of bone turnover; alkaline phosphates, calcium and inorganic phosphorus; in serum and urine by standard techniques on the Hitachi 747.
4. Estimation of serum procollagen I propeptide n-terminal (PIP) by radioimmunoassay (Ruby Martinis et al., 2001).
5. Bone densitometry: all diabetic were osteopenic as determined by bone mineral density of femoral neck by dual Energy X-ray absorptiometry (DEXA, Hologic QDR 1000).
6. Exercise program for the diabetic patients for three months, 3 times per week in the form of:
  - a. Fifteen minutes warming up for abdominal and back muscles.
  - b. Five minutes rest, then 20 minutes on ergometer.
  - c. Ten minutes rest, then 20 minutes on ergometer with constant speed and resistance.

Precautions were taken to avoid hypoglycemia during and for 24 hours post-exercise.

## RESULTS

The study was conducted on 24 diabetic patients matched to 38 healthy children and adolescents as regard age and sex.

**Table (1): Age & sex distribution in both diabetic & control groups.**

	Control		Patients		P
	Male	Female	Male	Female	
Sex	18	20	14	10	0.4 (NS)
Age	16.97±3.54		17.17±2.01		0.7 (NS)

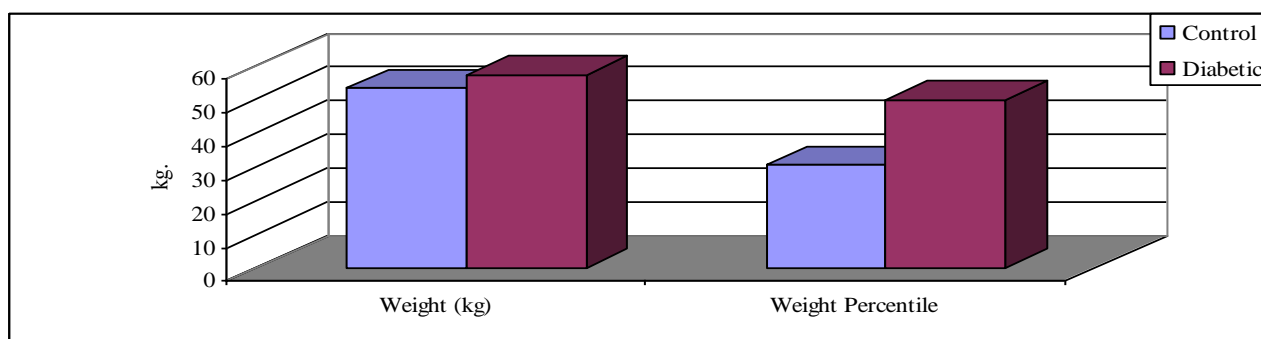
NS: Non significant

**Table (2): Comparison of growth parameters in both diabetic & control groups.**

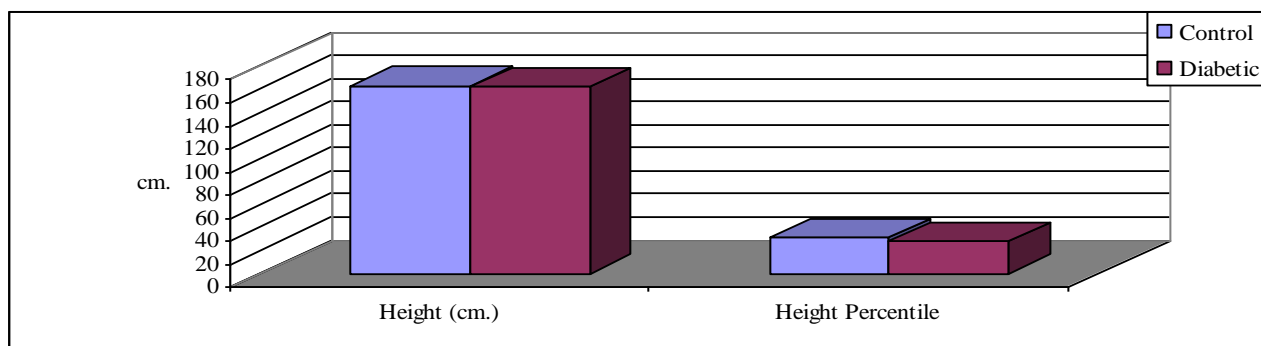
	Control	Patients	P
Weight (Kg)	53.43±8	57.25±8.81	>0.05 (NS)
Weight Percentile	30.43±26.59	50.00±28.17	
Height (cm.)	162.43±9.07	161.96±5.34	>0.05 (NS)
Height Percentile	31.43±26.59	27.46±26.51	

Comparison of growth parameters (mean weight (Kg.) and height (Cm.) of both groups

(diabetic & control) showed non significant differences (table 2, figure 1 & 2).



**Fig. (1): Comparison of growth parameters (weight & weight percentile) in both the diabetic and control groups.**



**Fig. (2): Comparison of growth parameters (height & height percentile) in both the diabetic and control groups.**

**Table (3): Serum biochemical parameters of bone mass in diabetic in comparison to control group.**

	Control	Patients	P
Serum Ca (mg/dL)	9±0.22	9.12±0.19	>0.05 (NS)
Serum Ph (mg/dL)	3.7±0.19	3.75±0.28	>0.05 (NS)
Serum ALP (U/L)	190.86±44.72	245.9±137.23	>0.05 (NS)

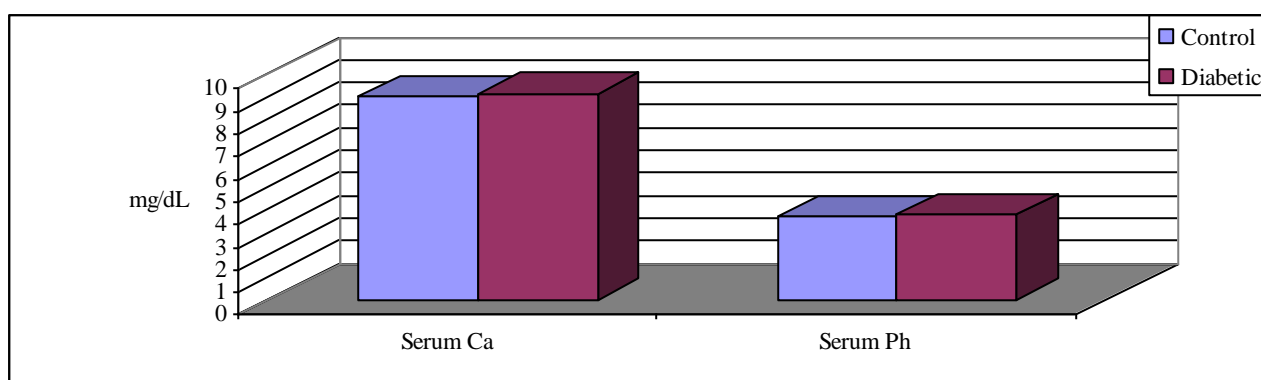
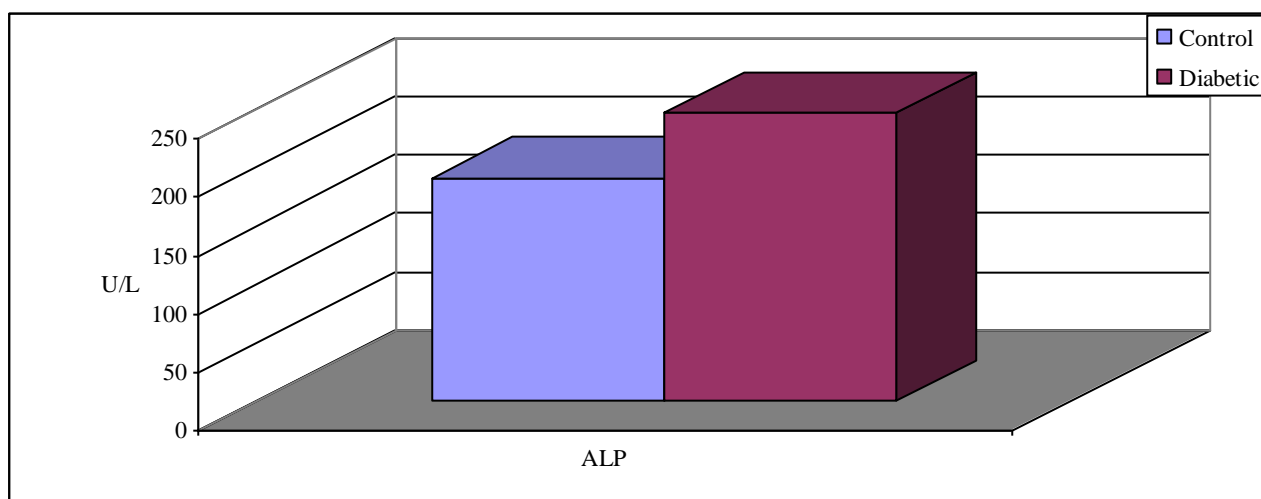
Ca: Calcium

Ph: Phosphorus

ALP: Alkaline Phosphatase

Comparison of the serum biochemical parameters showed a non significant

difference between the diabetic and control groups (table 3, figure 3 & 4).

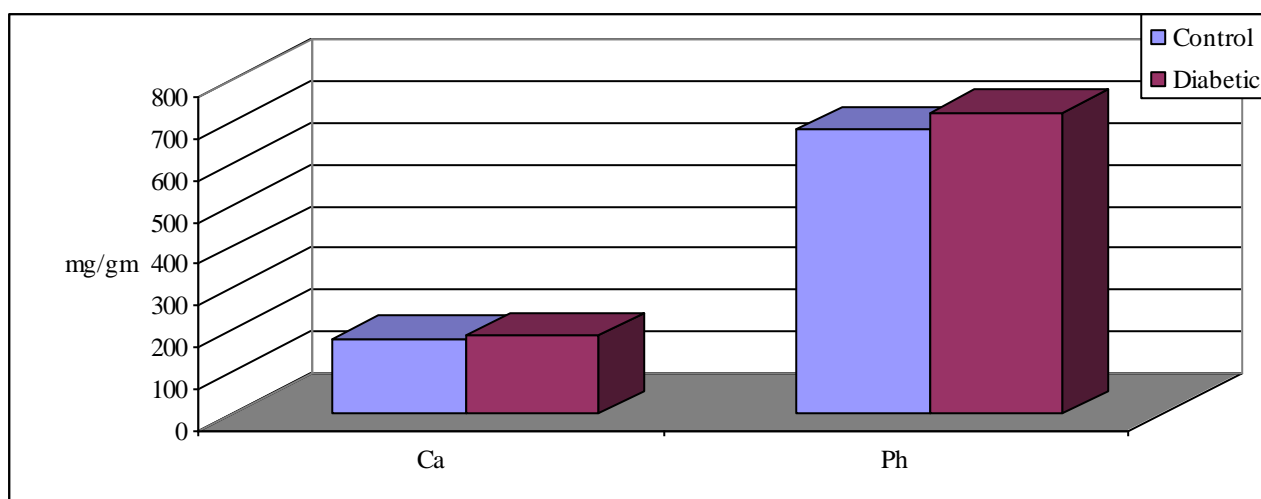
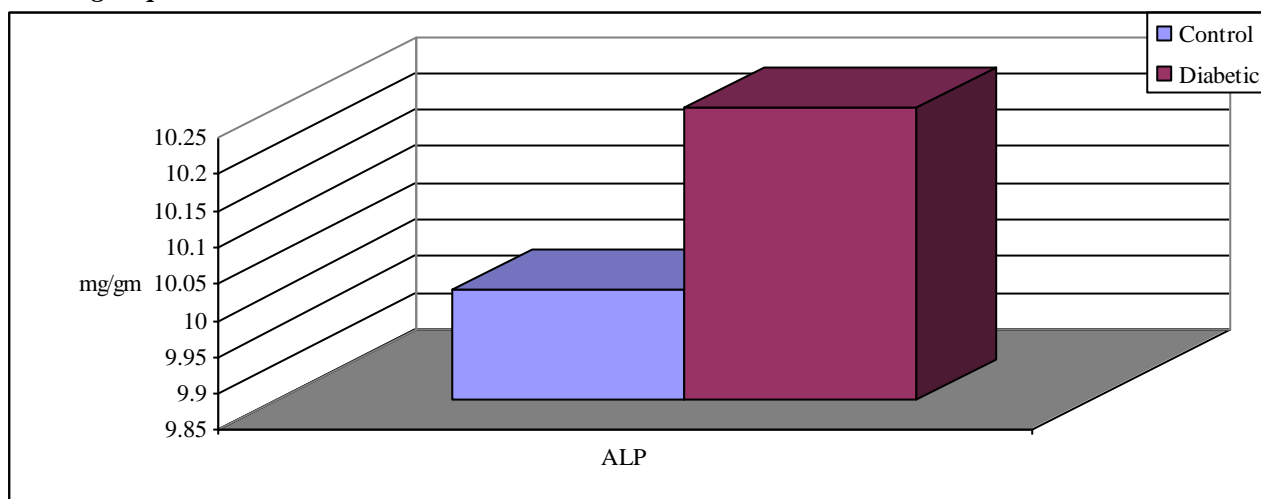
**Fig. (3): Comparison of serum biochemical parameters of bone mass (Ca & Ph) in both the diabetic and control groups.****Fig. (4): Comparison of serum biochemical parameters of bone mass (ALP) in both the diabetic & control groups.**

**Table (4): Urinary biochemical parameters of bone mass in diabetic in comparison to control group.**

	Control	Patients	P
Urinary Ca (mg/gm creatinine)	181±31.9	187.75±38.9	>0.05 (NS)
Urinary Ph (mg/creatinine)	680±216.1	721.4±179	>0.05 (NS)
Urinary ALP (mg/gm creatinine)	10±1.02	10.2±1.17	>0.05 (NS)

Comparison of the urinary biochemical parameters showed a non significant

difference between the diabetic and control groups (table 4, figure 5 & 6).

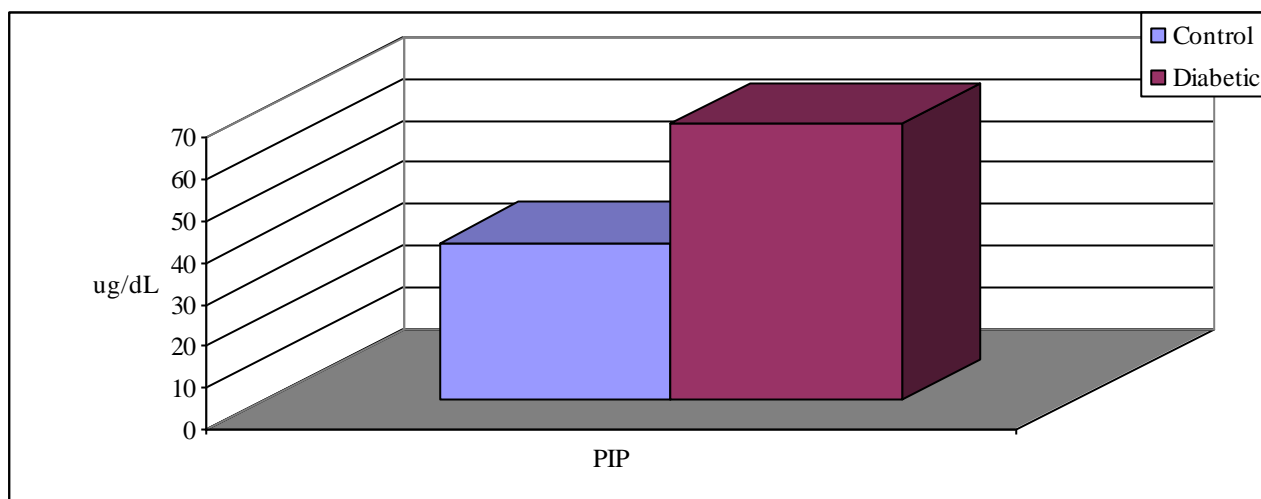
**Fig. (5): Comparison of urinary biochemical parameters of bone mass (Ca & Ph) in both the diabetic and control groups.****Fig. (6): Comparison of urinary biochemical parameters of bone mass (ALP) in both the diabetic and control groups.**

**Table (5): Comparison between both groups (Diabetic &Control) with respect to serum procollagen I peptide.**

	Control	Patients	P
PIP (ug/dL)	37.65±17.21	66.16±41.04	<0.05 (S)

PIP: Procollagen peptide I.

Comparison of the serum procollagen I peptide showed a significant difference between the diabetic and control groups (table 5, figure 7).



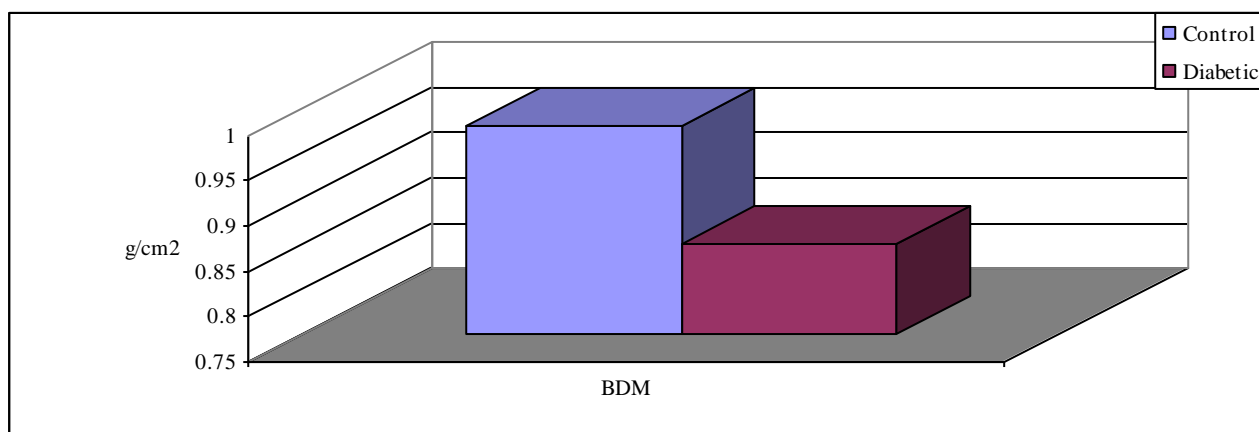
**Fig. (7): Comparison of serum procollagen I peptide in both the diabetic and control groups.**

**Table (6): Comparison between both groups (Diabetic &Control) as regards bone densitometry**

	Control	Patients	P
BDM (g/cm <sup>2</sup> )	0.98±0.12	0.85±0.17	<0.05 (S)

BDM: Bone densitometry.

Comparison of the bone densitometry showed a significant difference between the diabetic and control groups (table 6, figure 8).



**Fig. (8): Comparison of bone densitometry (BDM) in both the diabetic & control groups.**

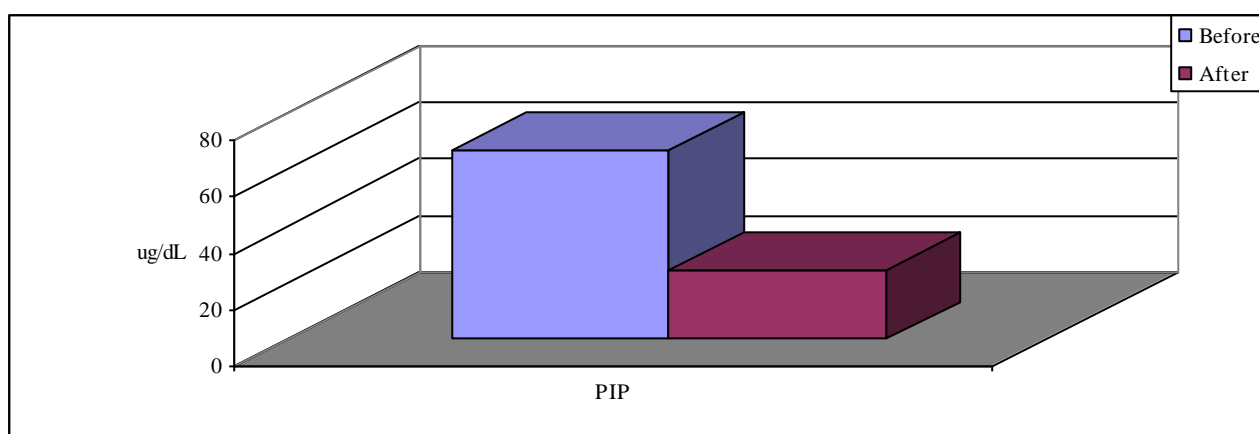
**Table (7): Comparison of serum procollagen I propeptide before & after exercises in the diabetic group.**

	Before	Patients	P
PIP (ug/dL)	66.16±41.04	24.25±7.29	<0.05 (S)

PIP: Procollagen peptide I.

Comparison of the serum procollagen I propeptide in the diabetic group before and

after exercises showed a significant difference (table 7, figure 9).



**Fig. (9): Comparison of serum procollagen I peptide in the diabetic group before & after exercises.**

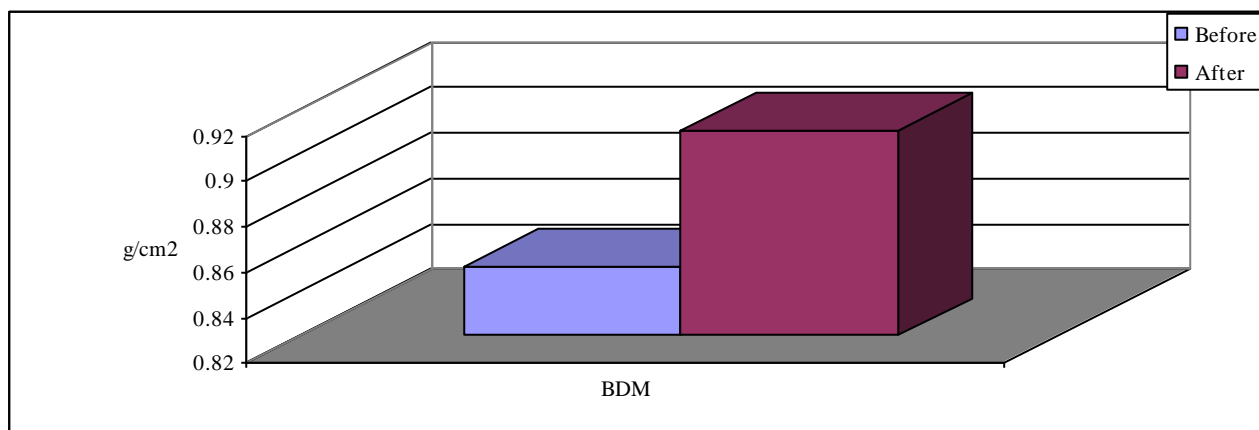
**Table (8): Comparison of bone densitometry in the diabetic group before & after exercises.**

	Before	After	P
BDM (g/cm <sup>2</sup> )	0.85±0.17	0.91±0.07	<0.05 (S)

BDM: Bone densitometry.

Comparison of the bone densitometry in the diabetic group before and after exercises

showed a significant difference (table 8, figure 10).



*Fig. (10): Comparison of bone densitometry (BDM) in the diabetic group before & after exercises.*

## DISCUSSION

Osteopenia has been considered to be a complication of long-term type I DM and was associated with poor metabolic control. It was proposed that osteopenia may already present if we recruit patients with long diabetes duration. Hence all the subjects selected were having diabetes duration for 4 or more years. The choice was somewhat difficult because the presence of diabetic microvascular complications had to be excluded. All included patients were normoalbuminuric and their fundi were normal by direct ophthalmoscope. Thorough neurological assessment was performed to exclude presence of neuropathy<sup>24</sup>.

Osteopenia was confirmed in the current study by subjecting diabetic patients to bone densitometry (BDM) determination by dual energy X-ray absorptiometry (DEXA) using pencil beam X-ray source directed at neck of femur. The finding of low BDM (osteopenia) in type I DM was approved in many previous studies<sup>1,11,13,14,18,21,24</sup>.

The pathogenesis of diabetes related osteopenia remains uncertain, but bone microangiopathy insulinopenia and abnormalities in vitamin D metabolism and

mineral metabolism have been proposed, as well as other hormonal and nutritional changes. Some of the foregoing mechanisms may operate at very early stages of disease, even before diagnosis of DM. In some studies, however investigators have shown that bone mineral loss is higher during the first few years of DM and subsequently stabilizes<sup>5,14,17,19,20</sup>.

In the present cohort, biochemical markers of bone mass reflected by serum calcium, phosphorus and alkaline phosphatase were comparable in diabetic osteopenic patients and healthy subjects. Also urinary excretion of the same indicators was not significantly different in both groups. However the serum concentration of procollagen I propeptide was significantly higher in diabetic osteopenic patients when compared to controls. This increment in peptide levels reflects excessive bone resorption in those patients.

It is reported that a decrease in osteoblast function as characterized by a reduction in osteocalcin levels, while a decrease in procollagen I propeptide carboxy-terminal (PICP) concentration, was observed both in diabetic children very early in the disease and in children with more than four years duration. PICP splits off from procollagen in a 1:1 molar



ratio during the formation of type I collagen and is released into the extra cellular fluids so that its concentration correlates with the role of bone formation as measured histomorphometrically. These results may indicate a defect in osteoblast maturation which possibly correspond to the decreased growth velocity observed in children with DM, the increased incidence of low bone mass, and increased healing time of fractures reported in human DM<sup>9</sup>.

It has been postulated that chronic hyperglycemia may increase bone fragility by an increment of non-enzymatic glycosylation of bone collagen. Infants of diabetic mothers who have been exposed in utero to hyperglycemia, have been found to have decreased bone mineral content and biochemical evidence of increased bone resorption. Several follow up studies support the concept that osteopenia in patients with type I DM is not influenced by the duration of the disease or the degree of metabolic control. Other studies showed that the bone disease was already clearly present at the time of the clinical diagnosis of type I DM and both cortical and trabecular bone were involved<sup>7,10,16</sup>.

Certain studies done on patients with type I DM (having similar age, maturation and body size and composition with control groups) showed lower tibia trabecular and femoral neck density and whole body mineral content and density in patients with type I DM. In contrast other studies done on patients with long standing type I diabetes with onset in childhood and adolescence seem to show only minor differences in body composition and no difference in BMD compared with closely matched healthy controls<sup>8,18</sup>.

All levels of exercise including leisure activities, recreational sports, and competitive professional performance, can be performed

by individuals with type I DM who do not have complications and are in good blood glucose control. Before beginning an exercise program, patients with DM should undergo a detailed medical evaluation with appropriate diagnostic studies to screen for macro- and micro-vascular complications that may be worsened by exercise program<sup>3</sup>.

In the current study BMD was improved in patients after 3 months exercise program with a variable degree and 5 out of 24 (20.8 %) resumed normal BMD for age, sex and height. This might be explained in part by reduced bone resorption in such patients as manifested by significant drop in serum PIP to levels even lower than control subjects.

Mechanical loading provides an anabolic stimulus for bone. More importantly, the mechanosensing apparatus in bone directs osteogenesis to where it is most needed for improving bone strength<sup>22</sup>.

The most easily demonstrable interaction between physical activity and bone mass is the substantial bone loss that follows complete immobilization such that attending spinal cord injury. Immobilized patients may lose 40% of their original bone mass in 1 year where as standing upright for as little as 30 minutes each day prevents bone loss. Several goals must be addressed when designing an exercise program for patients with osteoporosis. Most importantly the program should not be harmful. It should increase a patient's ability to carry out routine daily activities while minimizing the risk for subsequent fractures, and it should lead to a reduction in the risk for falls<sup>15</sup>.

BMD assessment should be one of the routine work up of type I DM patients that has to be performed at diagnosis and on regular intervals later especially for known osteopenic diabetics or those on regular exercise. Diabetic patients should adhere to a regular exercise regimen since diagnosis, aiming at not only

improving glycemic control and hence delaying microvascular complication; also resuming bone mass and density back to normal.

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### الملخص العربي

#### تأثير التمرينات الرياضية على التمثيل البنائي وكثافة العظام في الأطفال المصريين المصابين بمرض السكر

تعتبر هشاشة العظام من المضاعفات الشائعة على المدى الطويل لمرض السكر (النوع الأول) ولوجز حديثا أن الأطفال يعانون من نقص في كثافة عظام مفصل الحوض بعد فترة من الإصابة بمرض السكر مقارنة بالأطفال الأصحاء في نفس العمر والجنس. ركزت هذه الدراسة على 24 مريض بمرض لبول السكرى ومصابين بهشاشة العظام من عيادة السكر بجامعة عين شمس ومقارنتهم بعدد 38 طفل أصحاء كمجموعة ضابطة بأعمار تتراوح بين 14 الى 18 سنة وهدفت الدراسة الى دراسة التمثيل البنائي في الأطفال المصابين بالسكر ودراسة تأثير التمرينات الرياضية على التمثيل البنائي للعظام في الأطفال المصابين بمرض السكر والتحرى عن وجود علاقة بين السن والجنس وطول فترة الإصابة بالمرض ومستوى السكر في الدم ووجود الهشاشة. وتم عمل لكلا المجموعتين كشف طبي مفصل (الطول - الوزن - الضغط - فحص قاع العين - وفحص الأعصاب) ، التحاليل المعملية (السكر و الهيموجلوبين و نسبة الكالسيوم الكلى والفوسفور والفوسفات القاعدى فى كل من المصل والبول) وايضا قياس نسبة البروكولاجين 1 بروبييتيد فى المصل وايضا قياس نسبة كثافة العظام بعنق عظمة الفخذ بواسطة جهاز قياس هشاشة العظام و قد خضع المرضى لبرنامج رياضى محدد على مدى ثلاثة أشهر تم بعدها اعادة قياس الهشاشة وكذا بروكولاجين 1 بروبييتيد . وقد تبين عدم وجود اختلاف ذو دلالة احصائية فى مستوى الأملاح المعدنية (الكالسيوم والفوسفور فى المصل وكذا انزيم الفوسفات القاعدى) بين كلا المجموعتين قبل بدء برنامج التمرينات. أما بالنسبة لمستوى بروكولاجين 1 بروبييتيد وجد ان مستواه اعلى فى الأطفال المرضى ويعانون من هشاشة العظام مع وجود علاقة عكسية بين مستواه ودرجة مستوى السيطرة على نسبة السكر فى هؤلاء المرضى كما تبين وجود علاقة بين درجة الهشاشة ومدة مرض السكر. وعند اعادة تقسيم المرضى بعد البرنامج تبين تحسن ملحوظ فى كل المرضى مع استعادة 5 منهم للمستوى الطبيعى لكثافة العظام وكان ملحوظا ايضا انخفاض فى مستوى البروكولاجين 1 بروبييتيد لمستوى المجموعة المقارنة. وقد خلص البحث الى أهمية الرياضة فى علاج مرض السكر ليس فقط بغرض التحكم فى مستوى السكر فى الدم ولكن أيضا فى تحسين درجة كثافة العظام فى هؤلاء المرضى المصابين بالهشاشة مبكرا مع بدايه المرض .