Turkish Journal of Endocrinology and Metabolism, (1999) 4 : 177-180 **CASE REPORT**

Hypercalciuria and Hyperphosphaturia in Insulin Dependent Diabetes Mellitus

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Thirty child ren with insulin dependent diabetes mellitus age ranging from 7-19 years, were evaluated for hypercalciuria and hyperphosphaturia. The relationship of hypercalciuria metabolic control and duration of diabetes were shown in IDDM. In our patients the age of onset of diabetes varied from 6 to 14 years and duration of diabetes varied from 2 to 10 years. In this study, there were 15 male and 15 female patients with a mean age of 13.5±3.1. All children were receiving insulin therapy. None had diabetic nephropathy, proteinuria, albuminuria or any other renal disease and all serum creatinine levels were normal. Each patient's diabetic control was performed by fasting taking a blood sample of serum glucose and HbA 1c. Metabolic control was evaluated with parathormone (PTH), osteocalcine, serum calcium, phosphorus, 24 hour urinary calcium, phosphorus and tubular phosphate reabsorption (TPR). Hypercalciuria was defined as 24 hr urine calcium excretion of more than 4 mg/kg/day. In 20.68% of the patients hypercalciuria was determined. The serum calcium, phosphorus and alchalen phosphatase (ALP) levels in diabetic children with hypercalciuria did not differ from the levels found in those children with normal calcium excretion. PTH values were within normal ranges for all the patients. No significant correlation was found between duration, onset of diabetes, PTH, osteocalcine, ALP, TPR levels and urinary excretion of calcium. Tubular phosphate reabsorption was found above 85% in 26.66% of the subjects. A significant difference was defined between normocalciuric and hypercalciuric subjects for the values of TPR ($p<0.05$). We revealed that the percentage of hypercalciuria and hyperphosphaturia is increased in IDDM. Metabolic control, onset and duration of diabetes did not have any influence on hypercalciuria.

Key words: IDDM, hypercalciuria, hyperphosphaturia, BMD

Introduction

Hypercalciuria can occur as a result of a number of disorders including hypercalcemia, hyperparathyroidism, hypervitaminosis D, Cushing disease, immobilization, renal tubular acidosis and furosemid administration. In the absence of these conditions if hypercalciuria occurs it is considered to be idiopathic. Under these circumstances the urinary abnormality is attributed to either a primary renal leak of calcium or intestinal hyperabsorption of this cation (1). Hypercalciuria in medullary sponge disease, a syndrome associated with total parenteral nutrition and diabetes is referred to as hypercalciuria of unknown cause (2).

In insulin dependent diabetes mellitus (IDDM), the increased urinary output of calcium is much greater than any other electrolyte. The precise cause of the hypercalciuria of diabetes is not known. In IDDM hypercalciuria probably results from a reduction in tubular reabsorption of calcium. In diabetic patients its shown that calcium absorption is independent of alterations in glucose concentrations whereas in idiopathic hypercalciuria calcium reabsorption is dependent on glucose. Garland et al. (3) revealed that the mechanism

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of the reabsorptive defect responsible for hypercalciuria is in the loop of Henle.

With this study we aimed to determine the incidence of hypercalciuria and its relationship with metabolic control and duration of diabetes.

Material and Method

Thirty diabetic outpatients seen at Ege University Faculty of Medicine, Pediatric Endocrinology department participated in this study. There were 15 male and 15 female patients aged 13.5±3.1. All children were receiving insulin therapy. None had diabetic nephropathy, proteinuria, albuminuria or any other renal disease and all serum creatinine levels were normal. All the subjects ingested a calcium restricted (300 mg/day) diet for 72 hours before the initiation of study. 24 hour urine collection was carried out in all children. Each patient's diabetic control was performed by taking a fasting blood sample of serum glucose and HbA_{1c}. Metabolic control was evaluated with parathormone, osteocalcine, serum calcium, phosphorus, 24 hour urinary calcium, phosphorus and tubular phosphate reabsorption.

Calcium excretion in 24 hour urine was studied by the Cresolphthalein Complexon method with an autoanalyzer where an ion selective method was used for the serum ions. Chemilimunassay and electrophoresis were used for intact PTH and HbA_{1c} respectively.

Statistical analysis was evaluated with student-t test, correlation analysis and variance analysis.

Results

Our study consisted of 30 IDDM patients, aged 7-19 years. The mean age of onset of diabetes was 2.5-15 years and average duration of the disease was 3 months-15.5 years. 56.6% of our patients were under 50 percentile whereas the remainder was between 50-75 percentile. The physical and biochemical data obtained for the patients are presented in Table 1.

In 20.68% of the patients hypercalciuria was found. The hypercalciuric patients did not reveal any pathology in renal USG. Biochemical findings were found normal in this group of patients. Neither hematuria nor nephrolithiasis were seen in the patients. Table 2. shows serum calcium, phosphorus, albumin, ALP, PTH, osteocalcine and total phosphorus reabsorption (TPR) values of hypercalciuric and normocalciuric patients.

The serum calcium, phosphorus and ALP levels in diabetic children with hypercalciuria did not differ from the levels found in those children with normal calcium excretion. PTH values were within normal ranges for all the patients. No significant correlation was found between duration, onset of diabetes, PTH, osteocalcine, ALP, TPR levels and urinary excretion of calcium. Although we could not find a correlation between serum calcium

Table 1. Physical and Biochemical Parameters of Diabetic Children.

Parameter	Age (year)	Height (cm)	Weight (kg)	Onset of IDDM (year)	Duration of IDDM (year)	HbA_{1C} (%)	Glucose (mg/dl)	Creatinine (mg/dl)	Calcium (mEq/lt)	Phosphorus Mg/dl
Mean	13.5 ± 3.18	150.9± 15.0	42.15 ± 3.1	10.4 ± 3.5	3.2 ± 3.1	9.3 ± 0.15	223 ± 93.2	0.66 ± 0.11	5.02 ± 0.35	3.04 ± 0.98

Parameter	PTH (ng/ml)	Osteocalcine (ng/ml)	ALP (Ü/Lt)	Albumin (g/dl)	TPR (%)	Ca (24 hr Urine) (mg/kg/d)
Mean	0.42 ± 0.14	10.16 ± 3.4	629.4 ± 270	4.74 ± 0.53	75.0 ± 15.0	3.5 ± 1.4

Table 2. Biochemical data of the patients with hypercalciuria and normocalciuria.

	Case (%)	Calcium (meq/lt)	Phosphorus (mg/dl)	Albumin (gr/lt)	PTH (ng/ml)	Osteocalcine (ng/ml)	TPR (%)*
Hyper Calciuria	20.68	5.1 ± 0.28	3.8 ± 0.87	4.74 ± 0.6	0.39 ± 0.1	11.18 ± 3.1	60 ± 3.0
Normo Calciuria	79.32	4.9 ± 0.35	4.5 ± 1.1	4.72 ± 0.4	0.43 ± 0.1	9.55 ± 3.5	86 ± 3.0

* $p < 0.05$

and PTH levels, as urinary excretion of calcium increased serum PTH increased. A negative correlation was found between serum phosphorus concentration and urinary calcium ($p<0.05$). Mean height and weight percentiles of the subjects with IDDM did not show correlation with urinary calcium excretion ($p>0.05$).

In evaluating the effect of therapy and metabolic control, no significant correlation was found between urinary excretion of calcium, hemoglobin A_{1c}, fasting glucose and insulin doses. There was no significant difference in bone mineral density (BMD) in hypercalciuric patients compared with normocalciuric patients ($p>0.05$). Levels of HbA_{1c}, fasting glucose and insulin doses in hypercalciuric and normocalciuric patients did not differ (Table 3).

Table 3. Relationship of hypercalciuria, therapy and BMD.

	Serum Glucose (mg/dl)	Hb A_{1c} (%)	Insulin Therapy U/day	BMD Lateral
Hyper Calciuria	215. ± 80.1	8.5 ± 2.7	0.5 ± 0.3	0.528 ± 0.10
Normo Calciuria	225.1 ± 91.6	9.6 ± 3.3	0.6 ± 0.3	0.53 ± 0.09

Tubular phosphorus reabsorption (TPR) is used as a parameter of urinary phosphorus excretion and values below 85% were determined as pathologic. TPR was found above 85% in 26.66% of the subjects. A significant difference was defined between normocalciuric and hypercalciuric subjects for the values of TPR ($p<0.05$).

Discussion

In many studies it is reported that hematuria, hypercalciuria and hyperphosphatemia occurs more frequently in children with IDDM than normal children (1, 4, 5, 6).

The incidence of hypercalciuria was ascertained to be 27 % in children with IDDM compared with the general pediatric population which was found to be 3.8 % (1). In many studies, the frequency in healthy Turkish children was found to be 2.9-6.3 % (7-9). In our study group, we found the incidence of hypercalciuria as 20.68 % which is much higher than the frequency of the general pediatric population. In recent studies, it was reported that polakiuria was one of the main complaints in normal children with idiopathic hypercalciuria (10).

Although Malone et al. (4) reported strong association between hypercalciuria and gross hematuria, in our patients no hematuria was detected Kodama et al. (11) reported a case of nephrocalcinosis with renal failure in which hypercalciuria was associated with IDDM. There was no history of nephrocalcinosis and ultrasound pathology in our patients. The serum levels of Ca, P, ALP, PTH, and osteocalcine did not differ from each other in hypercalciuric and normocalciuric patients. Osteocalcine values were within the lower limits of normal level. Decreased PTH activity and alterations in circulating vitamin D metabolites were defined by Wit et al. (12) in hypercalciuric patients. Nyomba et al. (13) in one of their studies explained that low concentrations of $1,25\text{-}(OH)_2D_3$ were found in diabetic rats, associated with hypercalciuria and hyperphosphaturia which were due to insulinopenia caused by diabetes. In the study by Hough et al. (14) it is stated that long term diabetes induces hypocalcemia and PTH elevations.

In our study we defined that onset and duration of diabetes did not have any influence on urinary Ca excretion. In some animal models; the ratio of hypercalciuria in long standing diabetes was found to be elevated (1, 4, 12, 13).

In some studies it is indicated that hypercalciuria is the result of defective reabsorbtion of calcium and can be corrected by aggressive insulin therapy in poorly controlled diabetes (1, 4, 12, 13, 15).

On the contrary there are some reports implying that correcting glucosuria (good metabolic control of diabetes) will not affect hypercalciuria (12). We could not find any correlation between levels of HbA_{1c} and urinary excretion of calcium. Since there is no correlation in the values of fasting glucose and HbA_{1c} with hypercalciuria we can postulate that poorly controlled diabetes has no effect on hypercalciuria.

Diabetic children with hypercalciuria, however, did have lower serum phosphorus and parathyroid hormone levels than normocalciuric patients. Hypophosphatemia has been reported as a cause of hypercalciuria in association with normal parathy-

roid hormone and alkaline phosphatase levels (5). Although absolute hypophosphatemia was not observed in these children, there was a negative correlation between serum posphors and urinary calcium concentration in children with diabetes, suggesting that the hypercalciuria may be a renal response to functional phosphorus deficiency. The renal absorptive capacity for phosphate is the principal determinant of the serum phosphorus concentration. Under normal physiologic conditions approximately 80-97 % of the filtered load of phosphate is reabsorbed by the renal tubule (16). TPR was found significanly lower in hypercalciuric patients than normocalciuric. Serum phosphorus levels were lower in hypercalciuric patients, but there was no significant difference. In some studies, it was emphasized that the increased urinary phosphorus appears to result from competition with excess glucose for renal tubular absorbtion (5).

BMD values decreased as urinary calcium excretion increased as defined in other reports. (17).

Daragon et al. (18) measured bone mineral content (BMC) from the lumbar spine of children with idiopathic hypercalciuria (IHCU). It was found that there was no correlation between BMC and urinary calcium excretion. Thus individuals with IHCU showed no decrease in bone mass. On the contrary, in patients with diabetes, osteopenia occurs without hypercalciuria (19). We determined no significant decrease of BMD in diabetic children with hypercalciuria compared with diabetic children without hypercalciuria. As a result we revealed that the ratio of hypercalciuria and hyperphosphaturia are increased in IDDM. Metabolic control, onset and duration of diabetes did not have any influence on hypercalciuria. Glucosuria at the onset of diabetes interferes with and decreases reabsorbtion of calcium but in the course of the disease, elevation or reduction of glucosuria does not affect urinary calcium excretion.

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