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Original Article

Hypercalciuria, Hyperphosphaturia and Growth Retardation in Children with Diabetes Mellitus

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Abstract

Background: Previous studies have demonstrated that patients with insulin-dependent diabetes mellitus (IDDM) have a high prevalence of osteopenia. Hypercalciuria has also been well documented in human diabetes and many children with insulin-dependent diabetes mellitus have short stature.

Objective: To investigate the relationship of hypercalciuria and hyperphosphaturia with growth retardation in patients with IDDM.

Methods: Forty patients with IDDM aged between 6 and 12 years whose mean heights were less than their 32 non-diabetic siblings of similar age group were enrolled in this study. Urinary and plasma calcium, phosphorus and creatinine levels were measured in both groups. Meanwhile, the height and body weight were determined.

Results: Both, the mean height and weight percentiles of subjects with IDDM were significantly less than those of non-diabetic siblings ($p<0.001$). The height percentile of children with IDDM had negative correlation ($r=-0.75$, $p<0.001$) with the disease duration. The mean urinary calcium to creatinine (Ca/Cr) and phosphorus to creatinine (P/Cr) ratios were significantly higher in IDDM patients compared to their normal siblings ($p<0.001$).
The growth in the group of diabetic children correlated inversely and significantly ($p<0.001$) with hypercalciuria and hyperphosphaturia, duration of diabetes and HbA_1C level.

Conclusion: It is concluded that hypercalciuria and hyperphosphaturia may play a role in growth retardation of diabetic children.
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Keywords • Diabetes mellitus, insulin-dependent • growth retardation • hypercalciuria • hyperphosphaturia

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Introduction

Many children with insulin-dependent diabetes mellitus (IDDM) experience a decrease in growth rate and a decline in height growth velocity to a lower percentile within seven years of the onset of diabetes.[1] Jackson reported that growth veloc

Table 1: Measured parameters in 40 diabetic and 32 non-diabetic siblings

Parameter	Non-diabetic children (n=32)	Diabetic children (n=40)	
		Eucalciuria (n=10)	Hypercalciuria (n=30)
Age (Yrs)	11.4±0.42	11.81±0.31	11.72±0.28
Duration of diabetes (yrs)		3.92±0.48	4.18±0.32
Height (Percentile)	46.95±4.37	38.27±2.81	22.27±3.95†*
HbA_1C (%)[1]	4.2±0.08	8.81±0.15	11.01±0.3*
Serum calcium (mg/dl)[2]	9.90±0.05	9.61±0.04	9.45±0.05
Serum phosphorus (mg/dl)[3]	5±1.3	4.99±0.9	4.73±0.7
Urine Ca/Cr[4]	0.14±0.01	0.23±0.02	0.48±0.01†
Urine P/Cr	0.71±0.07	1.9±0.08	1.62±0.14†

†Differs from control (p<0.001), *Differs from eucalciuric (p<0.001), [1]Normal range = 3.0-6.9 (%), [2]Normal range = 8.5±10.8 mg/dl. [3]Normal range = 3.6±5.7 mg/dl. [4]Normal range ≤0.15

ity increased in children with diabetes whose metabolic control was improved.[2] Hypercalciuria and hyperphosphaturia impair growth in non-diabetic children and are known to occur in children with poorly controlled diabetes.[3-5] This cross sectional survey was conducted to determine whether there might be any association between the height of children with IDDM and the amount of urinary loss of calcium and phosphorus.

Materials and Methods

From the Diabetic Center of Fars Province, all diabetic children, aged between 6 and 12 years (n=40) were enrolled in this study. Duration of diabetes in this group of patients ranged from 8 months to 10 years. Thirty-two age-matched non-diabetic siblings were also selected as control group.

After obtaining information from children and their parents, the height of each child was determined, standing fully erect by a stadiometer.

Then we determined the height percentile of each child and compared it with standards of the United States National Center for Health Statistics (NCHS).[6] Blood and urine samples were obtained randomly from the non-diabetic siblings between 10 am and 12 pm, and from the children with IDDM between 7 and 8 am before having their insulin injected and breakfast.

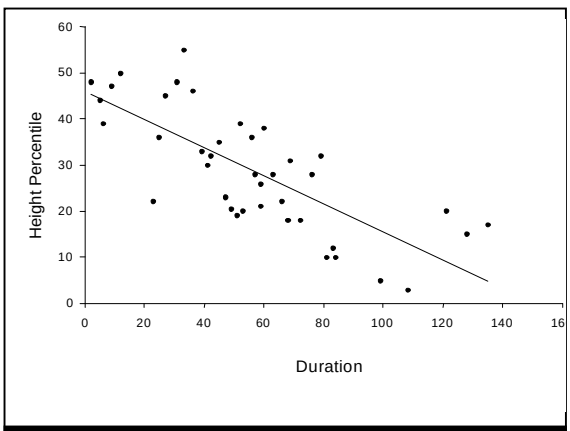

Figure 1: Correlation of duration of diabetes to height percentile

Serum level of total calcium (Ca), phosphorus (P), glucose, BUN and creatinine (Cr) was measured by automatic analyzer (TECHNICON RA 1000).

The measured serum levels of Ca and P were used to show the effect of dietary intake on urine calcium and phosphorus levels.

The urine was stored at –20 °C for 10 days until Ca, P and Cr concentrations were measured. The Ca/Cr and P/Cr ratios were calculated to permit an estimation of Ca and P losses in urine samples.

Results

The characteristics of diabetic subjects and their normal siblings are presented in Table 1.

The mean age of the diabetic children did not differ from non-diabetic siblings.

Both the mean height and weight percentiles of the subjects with IDDM were significantly less than those of the non-diabetic siblings (p<0.001).

The height percentile of children with IDDM had a negative correlation (r=-0.75, p<0.001) with the disease duration (Fig 1).

Those with IDDM compared to their normal siblings, had a significantly (p<0.001) higher mean Ca/Cr (0.41±0.13 *vs.* 0.14±0.01), and P/Cr (1.69±0.15 *vs.* 0.71±0.07) ratios, although the mean serum Ca and P levels in both groups were similar.

About 75% of diabetic subjects had significant hypercalciuria (Ca/Cr>0.25).

The growth impairment was significantly (p<0.001) more pronounced in diabetic patients with hypercalciuria than those with eucalciuria.

The growth in the diabetic children correlated inversely with the level of hypercalciuria (Fig 2) and

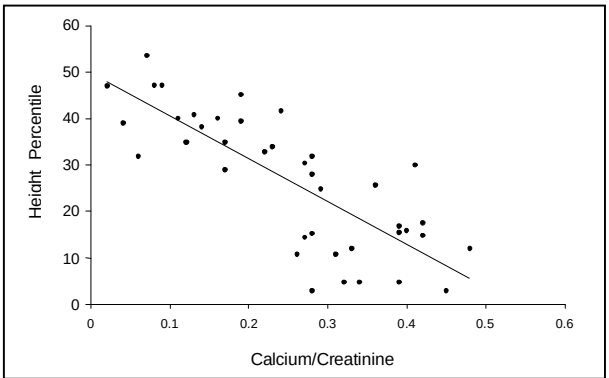

Figure 2: Correlation of hypercalciuria to height percentile in diabetic children

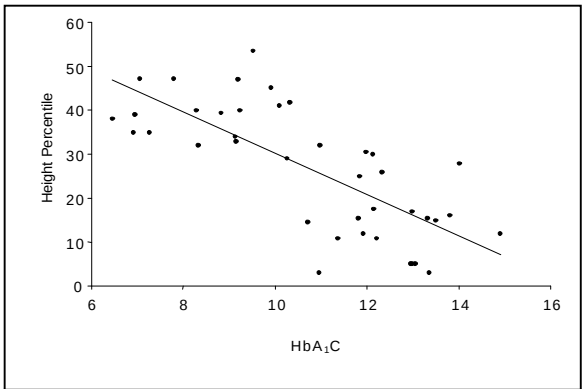

Figure 3: Correlation of HbA_1C to height percentile in diabetic children

hyperphosphaturia, duration of diabetes and the level of Hb A_1C (Fig 3).

Discussion

The etiology of the abnormalities in bone and mineral metabolism that occur in diabetes mellitus is probably related to the complex metabolic and hormonal derangements associated with the disease.[5]

Hypercalciuria is characteristic of early diabetes mellitus in human and experimental animal that may contribute to alteration in calcium hemostasis in the disease.[7]

Hypercalciuria and hyperphosphaturia are recognized as isolated causes of growth failure in certain non-diabetic children.[8]

A report from Malone, *et al.* indicated that there was an association between the height of children with IDDM and the amount of urinary excretion of calcium and phosphorus.[9]

In the present group of children with IDDM, the height correlated inversely with the levels of calciuria and phosphaturia, glycemic control, and the disease duration (Figs 1, 2 and 3).

Loss of excessive amounts of both Ca and P in urine in our IDDM patients is in agreement with previous reports.[4,9,10]

The elevated level of glucose in diabetes seems to alter the renal tubular reabsorption of both Ca and P; induction of diabetes in rats has been associated with increased urinary excretion of Ca, P and proteins correctable by insulin therapy.[7,11,12]

Similar phenomena have been described during uncontrolled human[13,14] and animal diabetes and are usually ascribed to osmotic diuresis; increased glomerular permeability, decreased tubular reabsorption and reduced vitamin D-binding protein concentration.

Although the growth of children with IDDM correlates inversely with the duration of hyperglycemia, a direct influence of high blood glucose concentration on growth has not been well established.

Bongnettie, *et al.*[14] analyzed the changes in the growth of children and adolescents with IDDM. They found no statistically significant retardation in the height standard deviation scores (HSDS) of the IDDM patients compared to those of normal population, at the disease onset. However, they found that HSDS decreased significantly over the first 3 years of the diagnosis.[14] Similar findings were reported by Gunczler, *et al.*[15] after 5 years of IDDM in poorly controlled patients.

In children with diabetes, divergence exists between GH secretion and IGF-1 production; increased GH with decreased IGF-1 concentration are found in the prepubertal and pubertal diabetic patients.[16]

The relative importance of low IGF-1 as a cause of short stature in diabetes is currently unknown.

In conclusion, if children with IDDM have excessive loss of Ca and P in urine during the growth spurt, it is reasonable to assume that these losses may contribute to their growth failure.

To shed light over this issue, a controlled clinical trial of P, vit D or Ca treatment for growing children with IDDM is warranted.

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