

Acid-base Homeostasis in Children With Growth Hormone Deficiency

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To determine whether children with growth hormone deficiency (GHD) have lower mean serum bicarbonate concentrations than do children with short stature due to other causes.

Materials and Methods: We evaluated one hundred short stature children, aged 5 to 15 years, attending the children's endocrine clinic at Motahari clinic, Shiraz, Iran, over a 6 month period. Demographic data and clinical features were recorded, laboratory investigations were performed, and bone ages were calculated. GHD was defined as serum GH concentration ≤ 10 ng/ml in response to L-dopa and clonidine, in addition a thorough work-up was performed to exclude any other known clinical conditions that might lead to growth retardation.

Results: Thirty one patients (31%) had GHD, 69 (69%) were not GH deficient, and one case had panhypopituitarism. Serum bicarbonate concentrations were significantly lower in GHD compared with non-GHD patients (15.68 ± 2.79 versus 17.98 ± 3.79 mEq/l, $P=0.003$). On the other hand, 52 (75%) GHD subjects and 22 (71%) non-GHD had arterial blood pH values below 7.35, the difference not being statistically significant. All GHD patients had abnormal serum bicarbonate levels versus 87% of non-GHD cases ($P<0.05$). GHD and non-GHD groups were comparable regarding mean age, sex, height SDS, BMI, severity of bone age delay, fasting blood sugar, serum cortisol level, and thyroid function test results.

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Conclusion: The lower plasma bicarbonate concentrations in patients with GHD as compared to with idiopathic short stature patients demonstrate a possible role for growth hormone in the modulation of acid-base homeostasis.

Key Words: Growth hormone, Serum bicarbonate, Short stature, Acid-base homeostasis

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Introduction

Although the primary use of growth hormone (GH) is to promote linear growth, it is known to affect many metabolic processes and renal function as well; GH affects renal growth, glomerular filtration rate, sodium and fluid retention, phosphate retention, and generation of calcitriol.¹⁻⁴

Studies carried out on laboratory animals have proposed a role for GH in acid-base homeostasis, indicating that growth hormone deficiency (GHD) causes a mild metabolic acidosis correctable with GH therapy.^{5,6} There are also some reports that patients with GHD initially present with metabolic acidosis, with resolution of the acidosis after GH therapy.^{1,2}

The aim of the present study was to determine whether children with GHD have lower mean serum bicarbonate concentrations than do children with short stature due to other causes.

Materials and Methods

In a cross-sectional study, 100 short stature children, aged 5 to 15 years, attending the children's endocrine clinic at Motahari Clinic, Shiraz, Iran over a six-month period, were evaluated. Short stature was defined as measurement of height falling below the 3rd percentile for age.

Demographic data and clinical features of the study population at the time of initial evaluation including age, gender, height, height SDS (standard deviation score), weight, and body mass index (BMI: weight in kg/ [height in meters]²) were recorded. None of the patients had malnutrition (weight for age less than 3rd percentile) or any known clinical condition that might alter serum electrolyte concentrations including renal tubular acidosis, renal failure, dehydration, and chronic diarrhea.

The results of initial laboratory investigations including serum electrolyte concentrations (sodium, potassium, chloride, calcium, and phosphor), fasting blood sugar, blood urea nitrogen, creatinine, and urine analysis were recorded. Thyroxin (T₄) and cortisol levels were measured by radioimmunoassay (RIA) (RIA kit, Kavoshyar Iran, Tehran; cortisol kit, Orion Diagnostica, Finland). Thyroid-stimulating hormone (TSH) was measured by immunoradiometric assay (IRMA) (IRMA kit, Kavoshyar Iran, Tehran), and serum GH by IRMA (Immunotech, France). Results of arterial blood pH and calculated serum bicarbonate concentration by performing an arterial blood gas measurement (by AVL Automatic Blood Gas System model 995) were recorded. Radiographs for bone age (Greulich and Pyle method⁷) were also obtained.

In addition, all subjects underwent provocative GH test with combination of L-dopa and clonidine following priming with gonadal steroids. GHD was defined as serum GH concentration ≤ 10 ng/ml in response to the provocative agents and a less than two centimeter growth over a six-month follow-

up. Any other known clinical condition that might lead to growth retardation was excluded by performing a thorough work-up.

Clinical and laboratory measurements in the GHD group were compared with non-GHD cases using Student's t test for continuous variables and the X² test for categorical variables. P values ≤ 0.05 were considered significant. Statistical analyses were performed by SPSS package.

Results

Of 100 patients evaluated for short stature, 31(31%) had GHD, 69 (69%) were not GH deficient, and one case had panhypopituitarism, showing deficiency in all pituitary hormones. (Table1).

Table 1. Characteristics of the study population (n=100)*

Mean age (years)	10.88±2.94
Age distribution: (years)	
4-7	17 (17) [†]
7.1-11	35 (35)
11.1-15	48 (48)
Male gender	51 (51)
Etiology of short stature:	
Familial short stature and/or constitutional delay	68(68)
Hypothyroidism	1(1)
Isolated GHD	30 (30)
Hypopituitarism	1(1)
Height SDS:	
-1 to -2	8(8)
-2 to -3	30 (30)
≤ -3	62(62)
Mean age (years)	10.88±2.94

GHD: Growth hormone deficiency, SDS: Standard deviation score; *continuous data are expressed as mean \pm SD; [†].Numbers in parenthesis denote percentage.

GHD and non-GHD groups were comparable regarding mean age, sex, height SDS, BMI, and severity of bone age delay. Bone age was considerably lower than chronological age in both groups but there was no statistically significant difference between the two groups. (Table 2) In addition, no significant differences were detected between the groups in

Table 2. Comparison of GHD and non-GHD short stature children

	GHD	Non-GHD	P value
Age (years)	11.24±2.87	10.72±2.97	0.412
Bone age (years)	8.47±2.66	8.58 ±3.10	0.862
Height (cm)	125 ± 14	122 ± 15	0.402
Height SDS (CI)	-3.08 ± 0.85(-6.00-2.00)	-3.22±1.28 (-6.50 -1.00)	0.568
Height SDS ≤ -3	19 (61.3%)	43 (62.3%)	0.260
Weight (kg)	25.68±8.90	23.03 ± 7.51	0.128
FBS(mg/dL) (CI)	85± 10 (63-111)	85±9 (69-107)	0.727
Arterial PH	7.30±0.04	7.31±0.07	0.425
Arterial PH<7.35	22 (71.0%)	52 (75.4%)	0.643
Bicarbonate (mEq/L)	15.68±2.79	17.98±3.79	0.003*
Cortisol > 10 µg/dL	25 (80.6%)	60 (90.9%)	0.192

GHD: Growth hormone deficiency; Continuous data are expressed as mean ± SD; * P value is statistically significant

arterial blood PH, fasting blood sugar, serum cortisol level, or thyroid function test results.

Serum bicarbonate concentrations were significantly lower in GHD compared with non-GHD patients (15.68±2.79 versus 17.98±3.79 mEq/l, P=0.003). All GHD patients had abnormal serum bicarbonate levels versus 87% of non-GHD cases (P<0.05). On the other hand, 52 (75%) GHD subjects and 22 (71%) non-GHD had arterial blood PH values below 7.35 the difference not being statistically significant.

Discussion

In the present study, serum bicarbonate levels were considerably lower in children with GHD compared with non-GHD short stature children, similar to results achieved by Glaser et al¹ and Jiang et al.²

Studies carried out on laboratory animals have demonstrated the same effect of GH on acid-base homeostasis. Hypophysectomized rats have renal acidification defects that are corrected with GH therapy.^{5,6} In addition, rats

subjected to surgical stress and maintained on total parental nutrition develop metabolic acidosis, which improves with GH treatment.⁸

As it has been postulated that patients with GHD have lower serum ketone concentrations than do normal controls adjusted for age and serum glucose,⁹ and since none of our patients were hypoglycemic at the time of serum electrolyte concentration measurements, it seems unlikely that in the current study excessive serum ketones had a substantial role in elevating organic acid concentrations.

It is proposed that current methods of provocative GH testing are not perfect and one cannot exclude the possibility that some patients were misclassified;¹ even though, the results would be expected to be biased toward a decreased likelihood of detecting differences in the studied population, the actual differences in bicarbonate values between GHD and non-GHD groups may be greater than observed in this study.

There was no detectable difference in blood PH between GHD and non-GHD subjects. This finding lends further support to some previous studies.^{1,2} One possible explanation could be that although serum bicarbonate concentrations were significantly lower in GHD patients compared with non-GHD children, activity of compensatory mechanisms and buffers adjust blood PH in these children.

A substantial number of cases in the non-GHD group also had low serum bicarbonate level that could be explained based on the no-

tion that malnutrition causes low serum bicarbonate concentrations¹⁰ and although we tried to exclude cases with malnutrition, it is probable that malnutrition was, at least to some degree, responsible for their short stature, leading to a decreased serum bicarbonate serum level.

In conclusion, lower plasma bicarbonate concentrations in patients with GHD compared with idiopathic short stature patients demonstrate a possible role for growth hormone in modulation of acid-base homeostasis.

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