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A Review: Short Stature in Renal Disease

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Introduction

Factors contributing to short stature in children with renal disease have been investigated by several groups [1, 2, 10, 13]. Acidosis and chronic malnutrition were believed to be among the most important causes of the growth failure. A critical discussion of the contributing causes has been presented by Bergstrom and coworkers [1].

Previous studies, while mentioning clinically evident renal rickets as a cause of growth failure, failed to note the possibility that subtle impairment of bone metabolism also may be an important factor which contributes to growth failure in renal disease.

We wish to point out that renal rickets may be the most important factor for short stature in renal disease.

Our Series

A search was made of the records of all patients who were less than 15 years old when they were first seen at the Mayo Clinic between 1950 and 1968 and who fulfilled the following criteria: (*1*) history of renal disease of a minimum of 2 years' duration; (*2*) a blood urea value of more than 50 mg/100 ml; (*3*) disease processes classified as cystinosis, bilateral hydronephrosis, nephrotic syndrome, and renal tubular dysfunction (not treated with steroids), familial renal disease, chronic glomerulonephritis, glomerulonephritis with anaphylactoid purpura, and renal failure of unknown cause. No cases were excluded from the study. The following patient data were obtained at the time of their last examination: (*1*) height and weight, (*2*) blood pressure, (*3*) hemoglobin level, (*4*) urea value, (*5*) CO_2 content, (*6*) alkaline phosphatase level, (*7*) specific gravity of urine (first morning voided specimen), and (*8*) serum inorganic phosphorus.

This retrospective study was limited by the use of levels of urea in blood as a measure of renal function and of CO_2 content as a measure of acid-base buffer. Urea in blood is not as precise a measure of renal function as is serum creatinine or creatinine clearance, and serum pH is a more reliable indicator of the acid-base balance than is the CO_2 content. However, these less reliable indicators were the only ones available in retrospect.

The alkaline phosphatase is uniformly recorded in international units per liter, yet until 1956 it was expressed in Bodansky units (the correction factor to international units per liter is 17), and from 1956–1966, in King-Armstrong units (correction factor to international units per liter is 7.08).

The heights of the patients were compared with normal values for height established by Reed and Stuart [8]. Deviations from normal were expressed as standard deviation from the mean for age and sex.

Children were considered to have rickets if they had positive roentgenographic evidence in addition to elevated alkaline phosphatase values.

Results

Total Group

Of the 64 patients who met the criteria for inclusion in the study, those with cystinosis were the shortest and those with chronic glomerulonephritis were the tallest (Table I). There were patients with very short stature in all disease categories but that of chronic glomerulonephritis.

The patients were separated into two groups according to height: those whose heights were within 3 SD of the mean and those whose heights were 3 SD below the mean. The first group represented normal growth whereas the second represented profound growth failure. No differences were found between children with profound growth failure and those with normal growth (Table II) in regard to (*1*) blood pressure, (*2*) presence or absence of anemia, (*3*) azotemia, (*4*) sever-

Table I. Short stature in renal diseases

Disease	No. of patients with height			Total
	Within 2 SD of mean	Between 2 and 3 SD below mean	More than 3 SD below mean	
Cystinosis	0	2	3	5
Hydronephrosis	4	8	3	15
Nephrotic syndrome (long duration)	2	0	4	6
Renal failure (cause unknown)	9	3	8	20[1]
Familial renal disease	4	1	3	8[2]
Chronic glomerulonephritis and anaphylactoid purpura	9	1	0	10[3]

[1] Includes 3 patients with hypoplastic kidneys, 5 with end-stage kidney (type unknown), and 12 with probable chronic pyelonephritis.

[2] Includes one patient with Alport's syndrome, one with oxalosis, one with familial nephrosis, one with Lowe's syndrome, and four with juvenile nephronophthisis.

[3] Proved by biopsy (five patients), autopsy (three patients), and clinical examination (two patients).

Table II. Comparison of patients with normal or short stature in renal disease

Factor	Patients with height within 3 SD of mean (normal stature)	Patients with height more than 3 SD below mean (short stature)
Systolic blood pressure, mm Hg	140.6 ± 39.2	116.6 ± 15.6
Diastolic blood pressure, mm Hg	96.9 ± 32.1	76.0 ± 19.0
Hemoglobin, g/100 ml	9.4 ± 2.6	9.0 ± 2.2
Blood urea, mg/100 ml	175.9 ± 86.6	193.9 ± 119.08
CO_2 content, mEq/liter	15.9 ± 4.8	12.6 ± 3.9
Specific gravity of urine	1,008.4 ± 3.9	1,007.3 ± 3.7
Alkaline phosphatase, IU/liter	252.9 ± 171.1[1]	530.2 ± 341.6[1]

[1] Statistically significant difference: $P \approx 0.01$.

ity of acidosis, and (5) concentrating ability of the kidney. Most patients in each group had specific gravities below 1.010, and all patients had specific gravities below 1.018. The only statistically significant difference between the two groups was in the increase of alkaline phosphatase (Table II). The mean values for blood pressure tended to be higher in the normal-sized children, but this was not statistically significant.

Seven patients whose heights were within 3 SD of the mean had roentgenographic evidence of renal rickets on the basis of hand and wrist roentgenograms (Table III), and all seven were more than 10 years old, whereas patients with profound growth failure who had such evidence were as young as 1.5 years of age. Six patients who were short had no roentgenographic evidence of rickets. Figure 1 shows the relation between age and height in roentgenographically proven rickets. The difference in the severity of growth failure between children with rickets and those without rickets was significant ($P < 0.01$). Furthermore, there was evidence that younger children with renal insufficiency tended to be shorter than older children with the same degree of disease.

Among the patients with roentgenographic evidence of rickets, two had genu varum and nine had genu valgum. These probably are minimal numbers because more subtle deformities may not have been noted on clinical examination.

There was no relation between the level of inorganic phosphorus and either patient age or the presence or absence of rickets. Children who had a very short stature had phosphorus values ranging from 2.1–12 mg/100 ml in various age groups, regardless of whether or not they had rickets. Also there was no relation between the level of phosphorus and short stature.

We utilized West and Smith's [13] formula (in which chronic renal failure is assumed to be a cause of significant anorexia and failure to gain weight) to determine the nutritional status of the children in our

Table III. Height in relation to roentgenographic evidence of rickets

Height	No. of patients	With rickets	
		No.	%
Within 2 SD below mean (normal)	43	3	7
Between 2 and 3 SD below mean	15	4	27
More than 3 SD below mean	21	15	71

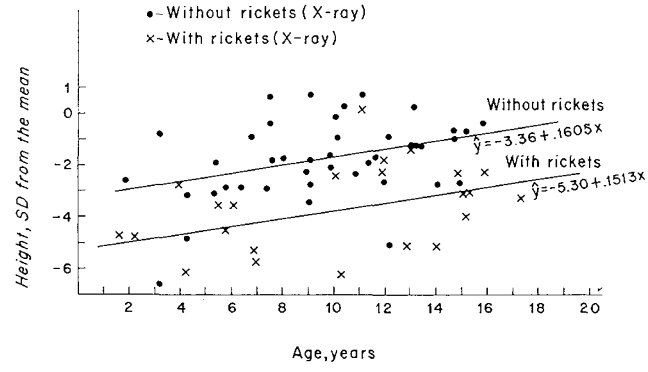

Fig. 1. Comparison of height and age of children who had renal disease with or without rickets.

Table IV. Relation among clinical renal rickets, short stature, and weight for height index (WHI)

Clinical rickets	Short stature	Cases		
		Total	Above 0.95 WHI	Below 0.95 WHI[1]
No	No	24	7	17 (71)
Yes	No	3	0	3
No	Yes[2]	15	6	9 (60)
Yes	Yes[2]	16	7	9 (56)
Total		58	20	38

[1] Percentage is shown within parentheses.
[2] More than 2 SD below mean.

series: weight for height index (WHI) = (actual weight/ideal weight for 50th percentile of height age). In this formula, a normal child has a WHI of 1. West and Smith [13] considered that the index was abnormally low if it was under 0.95 and considered that children with low WHIs had suggestive evidence of malnutrition leading to growth failure.

In order to allow comparison with West and Smith's [13] data, the patients in our series were divided into those with normal height (mean ± 2 SD) and those with small stature (2 SD or more below mean). Of 26 patients with normal height, 19 (73%) had a WHI of less than 0.95. Of 34 short patients, 20 (59%) had a WHI of less than 0.95. Unlike West and Smith [13], we included patients with clinically apparent renal rickets. None of the patients was edematous. When we classified patients according to the presence or absence of clinically proved renal rickets, no significant differences were found in the percentages of children in the low WHI (Table IV). There were fewer patients with relatively low body weights in the group with short stature than in those of normal height. Therefore, patients of normal height had WHIs in the hypocaloric range with the same (or greater) frequency as did short patients, regardless of whether renal rickets was present or not.

To gain information with regard to acidosis as a possible factor causing short stature in renal disease, two additional groups of patients were analyzed: five with exstrophy of the bladder who had ureterosigmoidostomy early in life and four with distal renal tubular acidosis (Lightwood-Albright type).

Patients with Ureterosigmoidostomy (Five Patients)

Patients with ureterosigmoidostomy have been known to have chronic acidosis. This occurs if the patient is on a regular diet, probably because the free hydrogen ions in the urine that is excreted into the sigmoid are partially reabsorbed, thus resulting in accumulation of hydrogen ions and the production of acidosis. Three of the five such patients in our series had, for part of their observation period, been treated with sodium bicarbonate, and during other periods, no treatment was prescribed. To the best of our knowledge, the diet was not changed. Comparison of growth during the periods of sodium bicarbonate therapy and the periods without it showed that the growth rates did not differ regardless of therapy. All five patients had heights within normal limits, and none had renal failure or renal rickets.

Prader *et al.* [7] described a patient who had a ureterosigmoidostomy but failed to grow. He was acidotic at that time and had rickets. Alkali therapy was associated with catch-up growth and the healing of rickets. No statement was made whether the patient received vitamin D in addition to alkali. One may interpret the growth failure as being related to the rickets and not to the acidosis.

Patients with Distal Renal Tubular Acidosis (Lightwood-Albright Type) (Four Patients)

All four patients had acidosis at their first examination, and all four patients had a lowered titratable acidity in the urine. Each patient had impaired ammonia excretion and nephrocalcinosis.

The three patients with short stature had clinical, roentgenographic, and biochemical evidence of rickets. The fourth was treated with sodium bicarbonate only, and she had normal growth, no evidence of rickets, and only slight elevation of the alkaline phosphatase level. If CO_2 content is accepted as an indicator of severity, this patient had the least severe acidosis.

One of the three patients with short stature was treated with Shohl's solution, and she grew normally. A second patient was treated with sodium bicarbonate and vitamin D in a dose of 25,000 to 50,000 U/24 hr. He had a very severe genu valgum, but by the time he was 12 years 4 months old his legs were straight and the alkaline phosphatase level had decreased to 129 IU/liter. From then on, he did not adhere strictly to the treatment program and his growth was less than expected. When he was 16 years of age, the boy was short; there was no roentgenographic evidence of rickets or osteomalacia, but the alkaline phosphatase level had increased to 325 IU/liter. The serum pH at that time was 7.33. The rickets of the third patient healed on treatment with vitamin D and sodium bicarbonate given between the ages of 11 years 8 months and 13 years 9 months. For reasons not clear in retrospect, the

therapy with sodium bicarbonate was discontinued at that time and was not restarted until the patient was 16 years 11 months old. She had normal growth despite CO_2 contents of 15.8 and 17.7 mEq/liter in this period when no sodium bicarbonate was given.

Comment

The results of this study have to be evaluated in the light of several limitations. First of all, it was a retrospective study; furthermore, it was a cross-sectional rather than a longitudinal study. Growth acceleration and deceleration were not evaluated except in patients with ureterosigmoidostomies and renal tubular acidosis.

The fact that patients with cystinosis were found to have the shortest stature cannot necessarily be considered evidence that rickets was the only cause of their short stature. Although these patients all had rather severe rickets, other factors such as generalized metabolic derangement may have contributed to their failure to attain normal height.

The small number of patients in each disease category is another limiting factor in the interpretation of data. There may be other factors within each category of disease responsible for the short stature.

To isolate the factors leading to short stature is difficult, an observation confirmed by previous investigators, particularly Bergstrom *et al.* [1]. Acidosis was considered one important factor, and this has been supported by clinical as well as experimental evidence [2, 5]. In our study, acidosis did not seem to have a primary role in causing short stature of children with chronic renal disease. This view was supported by the observations in one of the patients with distal renal tubular acidosis whose rickets had healed after treatment with buffer and vitamin D; even after the use of sodium bicarbonate was discontinued for several years, she continued to grow at a nearly normal rate. Also, patients with chronic acidosis who had had ureterosigmoidostomy grew normally regardless of whether sodium bicarbonate was given or not. This normal growth rate in such patients also has been observed by Bergstrom and co-workers [1].

However, acidosis was a significant factor in seven boys who had proximal renal tubular acidosis described by Nash and associates [6]. Correction of the acidosis was associated with resumption of normal growth, and the prognosis for these patients was good. Five of the seven were not receiving medications 5–8 years after an initial period of buffer therapy, and all five continued to grow normally.

West and Smith [13] have suggested that malnutrition is a significant factor related to the growth failure in renal disease; these authors studied only patients without clinical evidence of rickets. By using their criteria, we could not find any significant correlations between growth failure and malnutrition, and malnutrition was present regardless of whether there was clinical evidence of renal rickets or not. The incidence of malnutrition was higher in patients with normal growth than in those with profound growth failure. However, in evaluating these results, one has to remain somewhat skeptical in accepting the "weight for height index" as the best measure of nutrition.

The factor of malnutrition should not be overlooked, however, particularly in view of the data presented by Simmons and co-workers [10]. These authors studied growth rates of children who were on chronic dialysis and found that children who received more than 67% of the recommended daily caloric allowances grew much faster than children who had a lower caloric intake. Unfortunately, Simmons *et al.* did not report the status of the skeleton before or after renal transplantation. One wonders whether the better nutrition had an effect on calcium and bone metabolism.

The duration of the disease could not be correlated with the severity of the height deficit because, in some of the patients, the renal problems began at birth but did not lead to early renal failure, whereas in others the time of disease onset could not be determined. The duration of the disease may be an important factor to explain short stature in younger children with renal failure. Younger children with renal insufficiency were relatively smaller. This may be related to variations in growth velocity. Poor renal function early in life, when the growth velocity is greatest, probably causes a more profound growth failure.

Although acidosis, malnutrition, and the nature of the renal disease may contribute to growth failure, our study suggests that renal rickets is at least in part responsible for the short stature and that, even in the absence of severe skeletal deformities, more subtle forms of renal rickets are contributing factors to growth failure in renal disease. Although 6 of the 21 patients with the most severe growth failure had no roentgenographic evidence of rickets, these 6 may have had a more subtle form of the disease or other factors may have led to growth failure.

Stanbury [11] suggested that acidosis was not responsible for renal rickets. In 1968 he stated [11]

> It seems that the defective mineralization, the hypocalcaemia and the resulting secondary hyperparathyroidism in azotaemic

rickets and osteomalacia are all reasonably explained by the postulated state of vitamin D resistance; all are reversed when this resistance is overcome by the appropriately large dose of vitamin D.

We found in children, as did Stanbury in adults, that renal disease was associated with larger than normal losses of calcium and phosphorus in the stool and with lower urinary excretion of calcium and phosphorus. This appears to be true even in acute renal disease [12].

Recent work, particularly by Fraser and Kodicek [4], has been summarized in *Nutrition Reviews* [3], work that supports Stanbury's observations and extends them. The present hypothesis regarding vitamin D metabolism can be summarized as follows: cholecalciferol, which comes either from the diet or from 7-dehydrocholesterol in the skin, is converted in the liver to 25-hydroxycholecalciferol. This compound is then metabolized by the kidney into 1,25-dihydroxycholecalciferol. This metabolite is now believed to be the active substance with "vitamin D" activity on intestinal mucosa and bone. The vitamin D resistance (suggested by Stanbury [11]) may result from the renal inability to synthetize 1,25-dihydroxycholecalciferol. Whereas dialysis alone fails to overcome the vitamin D-resistant osteodystrophy in renal failure, renal transplantation corrects this in most instances. This would explain the observations by Simmons and co-workers [10] that children grow after transplantation if adequate nutrition is provided. Growth also depends on the steroid regimen after transplantation. Steroid given every other day to suppress the rejection phenomenon allows better growth than does the daily administration [9].

In our series, patients with chronic glomerulonephritis did not show growth failure. Perhaps only disease processes that affect parts of the kidney other than the glomerulus, such as tubular or interstitial disease, cause insufficient conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol. This may be one explanation why disease processes, such as severe hydronephrosis, cystinosis, nephrotic syndrome with tubular dysfunction, and forms of familial renal disease such as juvenile nephronophthisis, are usually associated with growth failure.

Summary

An analysis of factors possibly contributing to the short stature in 21 of 64 children with renal insufficiency, who had had renal disease for at least 2 years, was attempted. Increases in alkaline phosphatase level, most often with roentgenologic evidence of rickets, correlated with short stature. Other factors, such as malnutrition or acidosis, were not contributory factors. The hypothesis is advanced that forms of renal disease that interefere with vitamin D activation lead to rickets and eventually to short stature, whereas forms of renal disease (such as glomerulonephritis) that do not interfere with vitamin D activation may not cause short stature.

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