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Schimke Versus Non-Schimke Chronic Kidney Disease: An Anthropometric Approach

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ABSTRACT

Schimke-immuno-osseous dysplasia is a rare autosomal-recessive multisystem disorder with the main clinical features of disproportionate growth deficiency, defective cellular immunity, and progressive renal disease. It is caused by mutations of *SMARCAL1*, a gene encoding a putative chromatin remodeling protein of unknown function. Because a detailed description of the clinical features is an essential first step in elucidating the function of SMARCAL1, we present the first detailed anthropometric data for Schimke-immuno-osseous dysplasia patients. By comprehensive anthropometric examination (28 parameters) of 8 patients (3 females) with the typical findings of Schimke-immuno-osseous dysplasia (mean age: 14.8 years; range: 4.9–30.5 years) and 304 patients (117 females) with congenital and hereditary chronic kidney disease (mean age: 10.7 ± 4.8 years; range: 3–21.8 years), we show that Schimke-immuno-osseous dysplasia patients differ significantly from those with other forms of chronic kidney disease. *z* scores were calculated with reference limits derived from 5155 healthy children (2591 females) aged 3 to 18 years. The key finding was that, in the latter group, median leg length was significantly more reduced than sitting height, whereas in Schimke-immuno-osseous dysplasia patients, the reduction of sitting height was significantly more pronounced than for leg length. Therefore, the ratio of sitting height/leg length might be a simple tool for the clinician to distinguish Schimke-immuno-osseous dysplasia from other chronic kidney disease patients. Schimke-immuno-osseous dysplasia is very likely if this ratio is <0.83. However, other forms of chronic kidney disease have to be discussed in case of a ratio >1.01.

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Key Words
anthropometry, Schimke-immuno-osseous dysplasia, chronic renal failure, chronic kidney disease

Abbreviations
SIOD—Schimke-immuno-osseous dysplasia
CKD—chronic kidney disease
SDS—standard deviation score

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SCHIMKE-IMMUNO-OSSEOUS DYSPLASIA (SIOD; Mendelian Inheritance in Man 242900) is a rare autosomal-recessive multisystem disorder. Spondyloepiphyseal dysplasia with disproportionate growth failure, typical facial appearance, nephrotic syndrome with focal and segmental glomerulosclerosis and progressive renal failure, recurrent lymphopenia, and defective cellular immunity, as well as pigment naevi, are typical clinical findings in SIOD.[1–4] Two forms of the disease have been described.[4–6] Patients with the severe infantile form of SIOD are thought to be dystrophic at birth, develop early renal insufficiency, and suffer from neurologic complications, such as transient ischemic attacks or cerebral infarctions. Mutations of the chromatin remodeling protein (SMARCAL1) causes SIOD; the function of SMARCAL1 remains undefined.[7] Furthermore, the correlation between the genotype and the clinical course of the disease seems to be weak.[8]

Key findings in SIOD are progressive renal failure and disproportionate growth failure. A few reports describe the typical radiologic skeletal findings in SIOD; these include ovoid, dorsally flat vertebral bodies; hypoplastic pelvis; and laterally displaced femoral heads with small epiphyses in SIOD.[4,9] Others have also reviewed the physical findings, which include a triangular face, short neck and trunk, lumbar lordosis, and protruding abdomen.[4,9–11] However, anthropometric measurements are missing.

Disproportionate growth failure also occurs in children with chronic renal failure.[12] Therefore, to determine whether the disproportionate growth observed in SIOD patients could be ascribed to renal failure (alone) or was a complication of the *SMARCAL1* mutations, we compared the anthropometric measurements of patients with SIOD and patients with non-SIOD chronic kidney disease (CKD).

METHODS

Patients

Eight patients (5 boys and 3 girls; mean age: 14.8 years; range: 4.9–30.5 years), all with chronic renal failure (2 prerenal transplant and 6 postrenal transplant) and with the clinical findings of SIOD were included in the study. Two patients (brothers) underwent a longitudinal follow-up (4 and 5 measurements in yearly intervals). One of these brothers was treated with growth hormone. This patient had measurements performed before and after renal transplantation. The anthropometric characteristics of SIOD were compared with those of 304 patients (117 females) with congenital or hereditary CKD. These patients had mean age of 10.7 ± 4.8 years (range: 3–21.8 years) and a mean glomerular filtration rate of 40.28 ± 28.97 mL/min per 1.73 m^2; 142 (48%) patients had received a renal transplant, and 84 (28%) patients had been treated with growth hormone.

Measurements

A total of 28 anthropometric measurements were performed as recommended by the International Biological Program.[13] The anthropometric measurements included 4 parameters of longitudinal body dimensions, 6 parameters of transversal body dimensions, 6 circumferences, 6 skinfolds, and 5 parameters of the head. Each measurement was made using standardized equipment (Dr Keller I Stadiometer, Limbach-Oberfrohna, Germany; Siber Hegner Anthropometer, Zurich, Switzerland; electronic scale, Seca, Vogel & Halke, Hamburg, Germany; growth monitoring and promotion skinfold caliper). The accuracy of the measurements was within 1 mm for all of the parameters except for body weight, which was within 100 g, and skinfolds, which were within 0.2 mm. *z* scores (SDS) were performed based on reference limits derived from 5155 healthy children (2591 females) aged 3 to 18 years.[14]

Statistical Analyses

SDS values for the observed parameters were calculated according to the equation $SDS = (x_i - x_s)/SD$, where x_i is the individual value of patient, and x_s and SD are the mean and SD values for age and gender-matched healthy peers, respectively. The normality of distribution was evaluated by the Kolmogornov-Smirnov test for each parameter. Because the distribution of each anthropometric parameter in CKD patients did not differ significantly from normal, we applied parametric methods for our analysis. If the variance of the groups was equal as assessed by the Levan test of homogeneity of variance, the means of variables were compared with the paired sample *t* test; however, when the variance of groups was unequal, we applied the Welch and Brown-Forsythe test. To compare parameters among SIOD patients, we used the Wilcoxon signed rank test as an alternative to nonparametric statistics. The Mann-Whitney U test was used to compare anthropometric parameters between SIOD and CKD patients.

To describe group characteristics, we used the median (M) as the measure of central tendency and the semi-interquartile range (Q) as the measure of variability, $Q = (Q_3 - Q_1)/2$ where Q is one half of the distance between the first and third quartile points).

Differences between healthy and CKD patients were evaluated using *t* test; differences between healthy and SIOD patients were evaluated using Wilcoxon rank sum test. Because changes of muscle mass and fat mass are observed in males during the age-span from 20 to 30 years, we excluded our adult SIOD patient from the analysis of skin folds and body circumferences.

RESULTS

Longitudinal dimensions were the most affected in both SIOD and CKD patients. Each parameter was significantly different from that of healthy peers (Fig 1). In

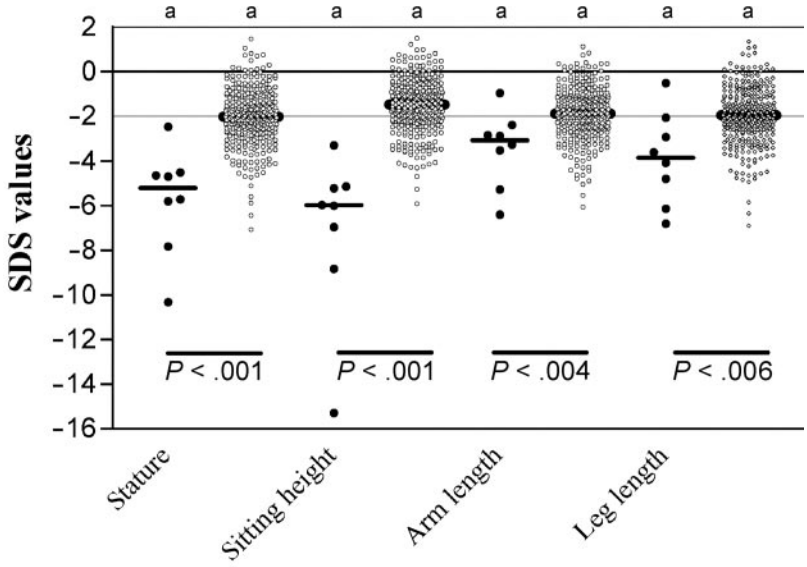

FIGURE 1
Longitudinal dimension of the body (stature, sitting height, arm length, and leg length) in SIOD versus CKD patients. [a]Statistically significant differences from healthy peers ($P < .05$).

addition, compared with CKD patients, SIOD patients showed significantly more impairment of linear growth in each body segment; median SDS was −5.98 for sitting height, −3.08 for arm length, and −3.85 for leg length in SIOD patients compared with −1.46, −1.88, and −1.95 SDS in CKD patients. The short stature of SIOD patients (−5.2 SDS) resulted primarily from impaired growth of the trunk (sitting height), whereas the short stature among CKD patients (−2.01 SDS) resulted primarily from reduced leg growth (Figs 1 and 8). These results did not change significantly when growth hormone-treated patients were excluded from the CKD cohort (Fig 8).

Transversal body dimension, particularly the biacromial, transverse chest, and biiliocristal diameters, was more affected in SIOD than in CKD patients (Fig 2). In the CKD patient group, the median SDS of each parameter was above −2, whereas in SIOD patients, only the median transverse chest, anteroposterior chest, and bicondylar humerus diameters were above −2 (Fig 2). As we observed for the longitudinal dimensions, transverse thoracic growth was most severely compromised among SIOD patients; they had median biacromial and biiliocristal diameters at −2.97 SDS and −2.78 SDS, respectively. In contrast, transverse leg growth was most severely affected among CKD patients; they had a median bicondylar femur diameter at −1.71 SDS. In SIOD patients the anteroposterior chest diameter (0.53 ± 0.98) differed from healthy peers, whereas in CKD patients neither the anteroposterior chest (0.02 ± 0.72) nor the

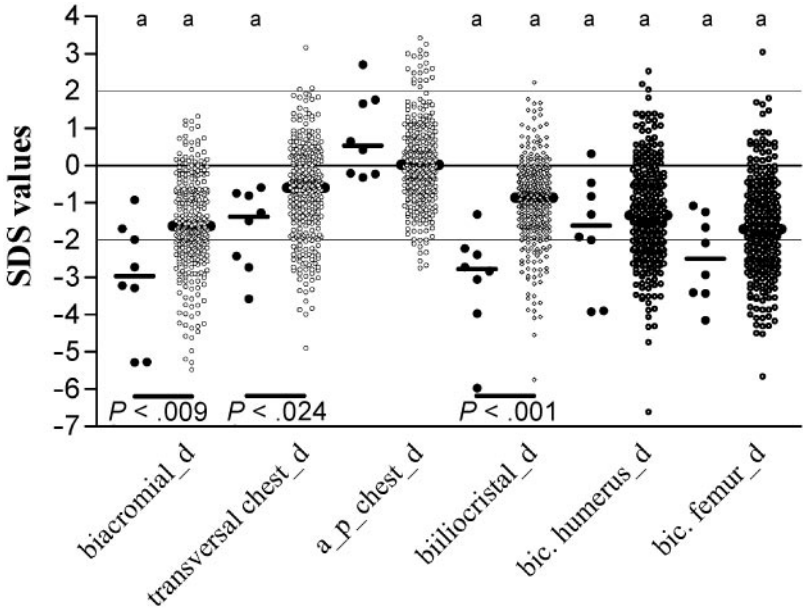

FIGURE 2
Transversal dimension of the body (biacromial diameter, transversal chest diameter, anteroposterior chest diameter, biiliocristal diameter, bicondylar humerus diameter, and bicondylar femur diameter) in SIOD versus CKD patients. [a]Statistically significant differences from healthy peers ($P < .05$).

transverse chest diameters differed significantly from those of healthy peers (Fig 2).

Compared with healthy peers, all of the body circumferences were significantly less in the SIOD and CKD patients except for abdominal circumference in CKD patients. In both groups, the circumferences of the upper body were better preserved than those of the legs. The reduction in circumferences was more pronounced in SIOD than in CKD. The thigh and calf circumferences of SIOD patients were clearly below −2 SDS, and these measures, as well as the median chest circumference of SIOD patients, were significantly less than those of CKD patients (Fig 3).

Skinfolds were the best-preserved parameters ranging from −1.11 SDS (subscapular) to −0.68 SDS (suprailiacal) in SIOD patients and from −0.97 SDS (medial calf) to −0.58 SDS (subscapular) in CKD patients (Fig 4). Differences from healthy peers were more pronounced in CKD than in SIOD patients. Furthermore, as reflected by the variability in the SDS, the deviation of skinfold measures from normal was more variable in the CKD group than in the SIOD group.

Each head anthropometric measurement for both SIOD and CKD patients was significantly different from healthy peers. Furthermore, the SIOD group differed significantly from the CKD group in all of the parameters except for head length. In addition, head length was the only parameter in which the median SDS was above −1 SDS in both cohorts of patients (−0.53 and −0.76 for CKD and SIOD patients, respectively). SIOD patients had a narrower head and shorter face compared with CKD patients (forehead width: −1.97 SDS; bigonial diameter: −1.97 SDS; and face length: −2.17 SDS in SIOD vs −0.51 SDS, −1.03 SDS, and 0.42 SDS in CKD, respectively; Fig 5).

Growth Dynamics

The typical anthropometric profile of SIOD patients seems to be age and gender independent. We did not find significant differences between SIOD patients at different years of age. Furthermore, the anthropometric parameters of a patient with severe SIOD did not change during 5 years; however, they did change after he was treated with steroids for renal graft rejection (Fig 6).

Sitting Height/Leg Length Ratio

A key finding of the study is that sitting height is the best-preserved parameter in CKD, whereas it is the most impaired in SIOD. Therefore, the ratio of sitting height/leg length might be a simple tool for the clinician to distinguish CKD patients from SIOD patients. Figure 7 indicates that if the ratio is >1.01, SIOD is very unlikely. However, if the ratio is <0.83, SIOD is very likely. Interestingly, the patients with the higher ratios (1.01 and 0.93) were the youngest of our SIOD patients (4.9 and 7.02 years, respectively). Although, as described above, the typical anthropometric profile in SIOD seems to be age independent, this ratio might have an age dependency; however, elucidation of this will require additional longitudinal studies.

DISCUSSION

We present the first comprehensive anthropometric study comparing SIOD patients to others with chronic renal failure. Because chronic renal failure itself leads to disproportionate growth failure,[12] we characterized the anthropometric differences distinguishing these 2 patient groups. However, the present article focuses on the anthropometry of SIOD. Because the SIOD patients were either on dialysis or transplanted, the patients of the CKD group had the same treatment modalities. Sub-

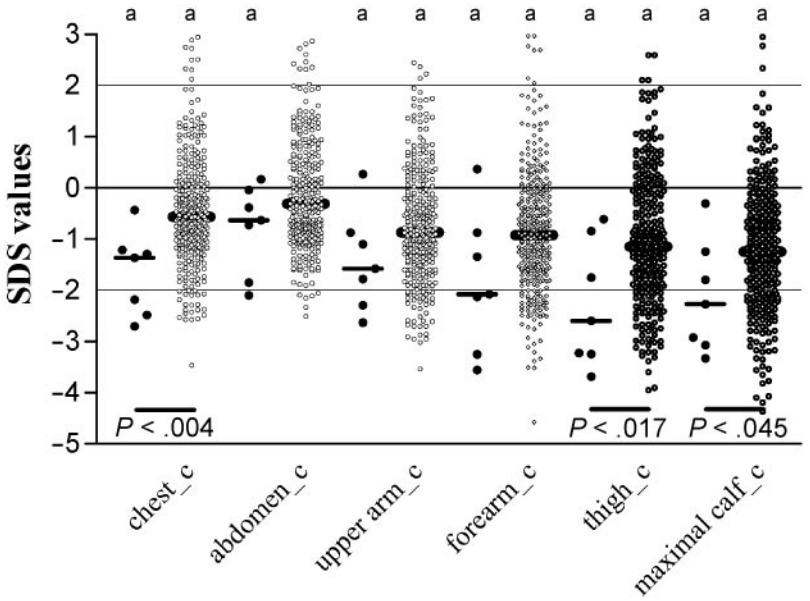

FIGURE 3
Circumferences of the body (chest, abdomen, upper arm, forearm, thigh, and maximal calf) in SIOD versus CKD patients. [a]Statistically significant differences from healthy peers ($P < .05$).

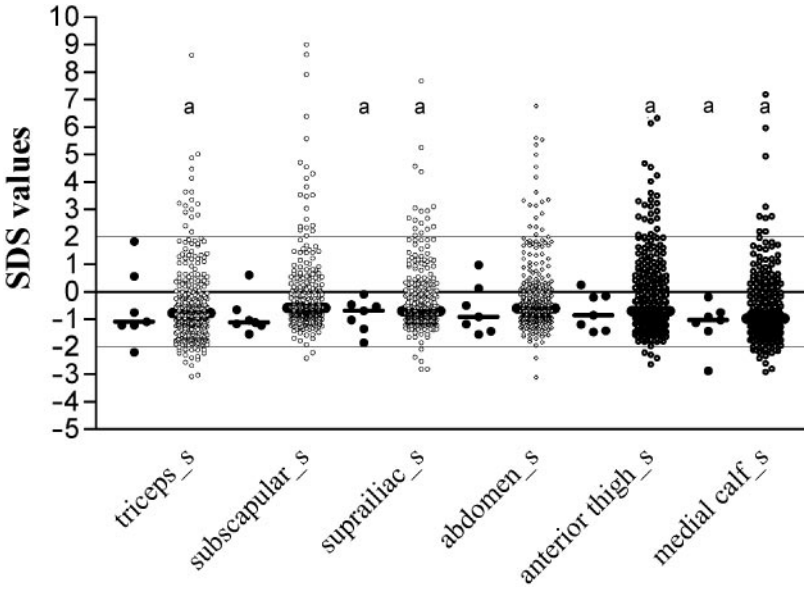

FIGURE 4
Body skinfolds (triceps, subscapular, supra-iliac abdominal, thigh, and medial calf) in SIOD versus CKD patients. [a]Statistically significant differences from healthy peers ($P < .05$).

group analysis in CKD concerning dialysis versus transplantation versus chronic renal failure will be presented in a further publication. Subgroup analysis in SIOD was impossible because of the small sample size.

We found that in nearly all of the parameters, SIOD patients differed significantly from those with non-SIOD chronic renal disease. The most marked difference in CKD patients without SIOD was that their median leg length was significantly more reduced than trunk length, whereas in SIOD patients, the reduction in trunk length was significantly more pronounced than that for leg length (Fig 8). The significant reduction in trunk length in SIOD is in line with the radiologic findings of ovoid, dorsally flat vertebral bodies and hypoplastic pelves in SIOD.[4,9] In contrast to CKD patients, SIOD patients had a significantly narrowed forehead, a shorter face height, and a preserved anterior posterior chest diameter. Based on these observations, we conclude that the disproportionate growth failure in SIOD does not result from early onset or severe renal failure.

The anthropometric findings in SIOD seem to be gender unspecific. However, the small number of SIOD patients and the unequal gender ratio (5 male to 3 female) did not allow us to define gender-specific differences. Our limited observations suggest that the typical body proportions found in SIOD are not modified by puberty. Ongoing studies will focus on aspects of puberty-onset and gender-specific growth patterns in SIOD.

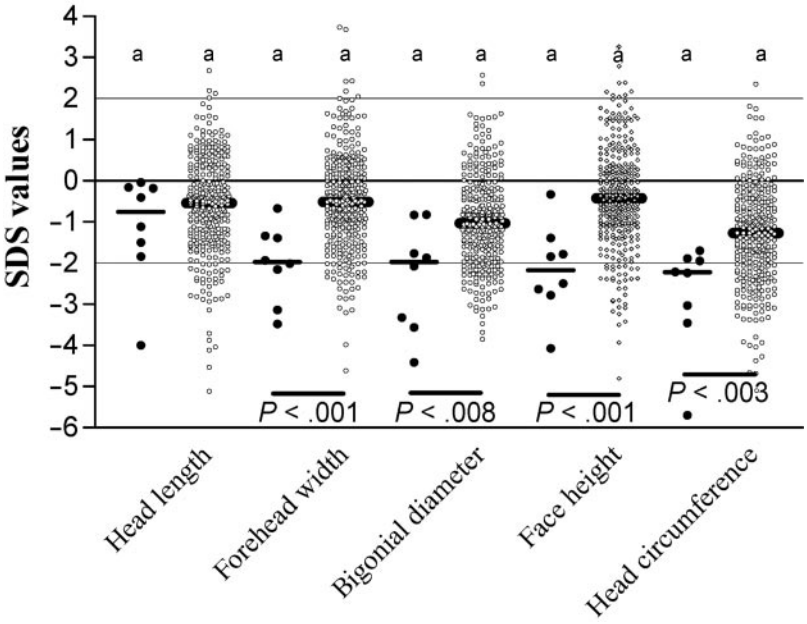

FIGURE 5
Head anthropometry (head length, forehead width, bigonial diameter, face height, and head circumference) in SIOD versus CKD patients. [a]Statistically significant differences from healthy peers ($P < .05$).

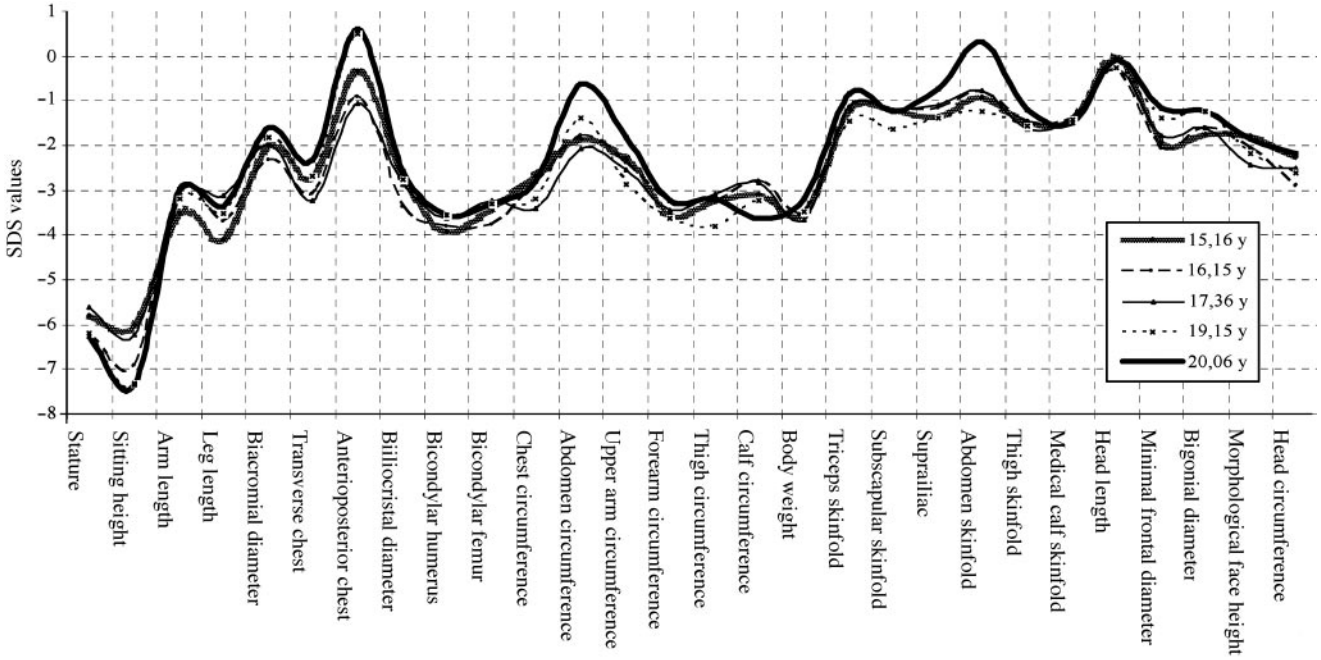

FIGURE 6
Growth dynamics over 5-year period (15–20 years) in a patient with severe SIOD. First measurement at 15.16 years and last measurement at 20.06 years. Last measurement was performed 0.8 years after renal transplantation.

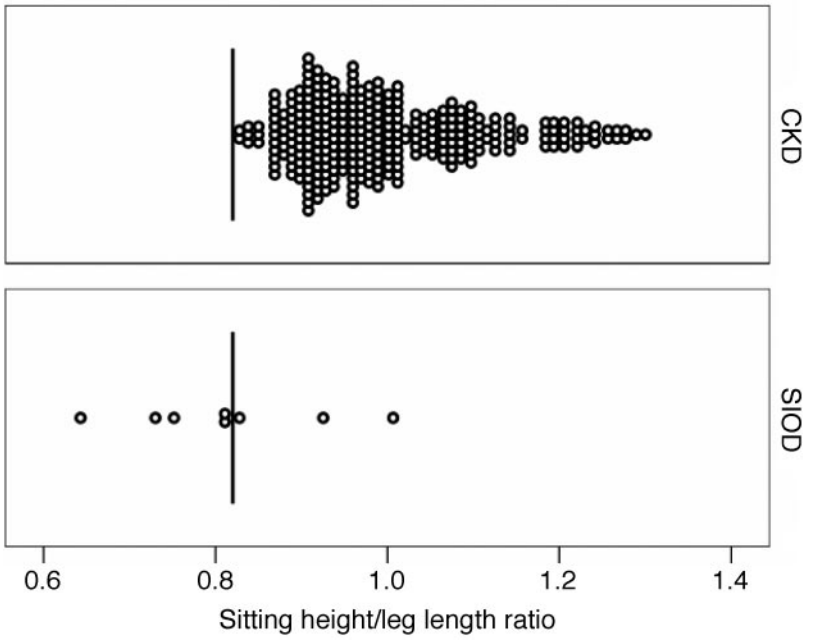

FIGURE 7
Sitting height/leg length ratio in CKD and SIOD patients. Black lines (0.82) mark the lowest ratio found in CKD patients.

Ludman et al[9] speculated that slowing of linear growth occurs during the second and third years of life. However, this suggestion was based on the clinical aspects of a single patient's habitus but not on anthropometric data; other studies found that, in some SIOD patients, the growth failure began prenatally.[4]

As described in the "Introduction" section, longitudinal data were collected in only 2 adolescent patients. Although the sample size is small, presentation of longitudinal anthropometric data are of importance in a rare disease like SIOD. This detailed anthropometric report will serve as a basis for further investigations into the growth dynamics of SIOD patients and models of SIOD.

One SIOD patient received growth hormone therapy, but he did not differ in his anthropometric pattern com-

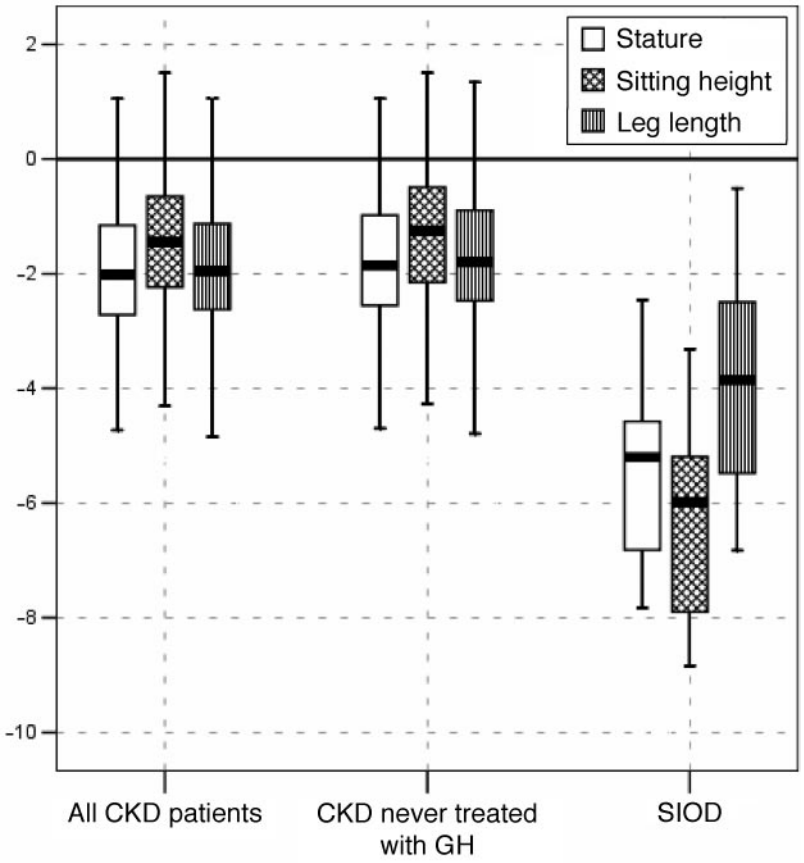

FIGURE 8
Key findings in longitudinal dimension (mean SDS, confidence interval 95%) of the body (stature, sitting height, and leg length) in SIOD versus CKD patients (all CKD patients and CKD patients never treated with growth hormones). In CKD, sitting height is the best-preserved parameter, whereas in SIOD patients, sitting height is the most impaired parameter.

pared with the other SIOD patients. In contrast, growth hormone therapy corrects the disproportionate body structure in children with CKD.[12] In this respect, several clinically important differences exist between CKD and SIOD patients. First, CKD patients frequently have a retarded bone age, a finding suggestive of hormonal deficiency, and this has not been observed in SIOD.[4] Second, in most patients (18 of 19) with SIOD, growth hormone studies have been normal, and an improvement of growth with growth hormone supplementation could not be demonstrated.[4,8] This finding is consistent with the anthropometric measures suggesting a different etiology for the growth failure in CKD and SIOD patients.

The growth failure in SIOD seems to differ from that of some other inherited diseases. In Ullrich-Turner syndrome, an aggravation of disproportionate growth has been described with growth hormone supplementation,[15] whereas in Prader-Labhart-Willi syndrome, growth hormone supplementation improved body shape.[16] In contrast, among SIOD patients. growth hormone supplementation seems to have no effect on body proportions. However, because this first study of anthropometric measures in SIOD focused on the basal physical parameters, the influence of growth hormone supplementation on growth parameters in SIOD remains to be elucidated by future studies.

CONCLUSIONS

The anthropometric measures presented here are standardized and relatively easy to perform. We have demonstrated that these measures can help to distinguish SIOD from other forms of CKD (Fig 8). In this respect the sitting height/leg length ratio seems especially to be a helpful diagnostic tool. As far as other diseases associated with dysmorphic growth retardation are concerned, further studies are necessary to detect a special anthropometric pattern. Finally, a more precise understanding of the growth impairment in SIOD may also help elucidate the hitherto unknown function of the SMARCAL1 protein on growth regulation.

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