Metacarpal index in short stature before and during growth hormone treatment

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Abstract

Aims—To assess the usefulness of the metacarpal index (MCI) as a radiographic measure of the proportions of the metacarpals in the differential diagnosis of short stature. To investigate the significance of the MCI in following the longitudinal growth and proportions of individual long bones during growth hormone stimulated catch up growth in children with short stature with and without growth hormone deficiency.

Subjects—124 children, including 65 children with short stature caused by growth hormone deficiency, 13 with familial short stature, 29 with idiopathic short stature, and 17 with Ullrich-Turner syndrome.

Methods—Retrospective analysis of the MCI in five posterior-anterior radiographs of the left hand of all patients, which were performed sequentially for routine bone age determinations (Greulich and Pyle) before and during the first three years of growth hormone treatment.

Results—The MCI was similar in all patient groups, resembled that of healthy children, and correlated significantly with chronological age, bone age, and height before and during growth hormone treatment. Despite a remarkable growth hormone stimulated catch up growth, the MCI did not change significantly during growth hormone treatment.

Conclusions—The role of the MCI is insignificant in the diagnosis of short stature, but the MCI can serve as an auxological measure of osseous proportions during longitudinal growth. Growth hormone treatment accelerates longitudinal growth without affecting the proportions of the long bones, indicating that growth hormone stimulated bone growth closely resembles spontaneous bone growth.

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Keywords: metacarpal index; growth hormone; linear growth; osseous proportions

The benefits of growth hormone treatment to the promotion of longitudinal growth in various disorders with growth failure are well recognised.¹ The effect of growth hormone treatment on body shape and proportions—for example, sitting height and subischial length—has been evaluated, and possible disproportionate growth in patients with and without growth hormone deficiency has caused concern.^{2,3} The impact of growth rate with respect to the timing of the onset of puberty on

the ratio of upper to lower body segments and on the proportions of individual long bones remains to be determined. Treatment with growth hormone probably stimulates growth rate rather than maturation, but the consequences of catch up growth on the osseous proportions of short children with and without growth hormone deficiency have not been investigated.

The metacarpal index (MCI), a radiographic measure of the proportions of the metacarpals, was introduced to diagnose arachnodactyly in patients with Marfan's syndrome.⁴ The index is the ratio of the mean length to the mean width of the second to fifth metacarpal bones, measured at their midpoints. The MCI has been examined in adults and children with Marfan's syndrome, but its clinical significance has been questioned.^{5–7} Normal values have been published for infants, children, and adults.^{5,8}

We previously reported that the MCI in children with constitutional tall stature was higher than that found in normal children.⁷ Therefore it seemed intriguing to speculate that the MCI is smaller in children with short stature than in normal children, as brachymetacarpia have been observed to be prevalent in various forms of short stature.^{9,10} So far, the MCI has not been examined in children with short stature and its usefulness in following the growth and proportions of individual bones remains to be evaluated.

This retrospective study aimed to evaluate the MCI longitudinally in children with short stature with and without growth hormone deficiency before and during growth hormone treatment to investigate the proportions of the metacarpals as a measure of long bone proportions during growth hormone stimulated linear growth.

Patients and methods

The patient population consisted of 124 children with short stature (81 boys, 43 girls) who were evaluated and consequently treated with growth hormone at the University of Heidelberg, department of paediatric endocrinology, between 1974 and 1993. Table 1 gives the patients' characteristics at the initial evaluation of short stature. The diagnosis of short stature was established and growth hormone treatment initiated as recommended by national and international guidelines.^{11,12} The patients were grouped according to the appropriate diagnosis: 65 patients with growth hormone deficiency; 13 with familial short stature; 29 with idiopathic short stature; and 17 with Ullrich-Turner syndrome.

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Table 1 Clinical data from 124 patients at the initial evaluation of short stature

Patients	Male	Female	CA (years)	BA (years)	Height SDS (CA)	Height SDS (BA)
Growth hormone deficiency (n = 65)	55	10	6.7 (2.9)	4.5 (2.9)	-3.8 (0.9)	-0.8 (1.8)
Familial short stature (n = 13)	5	8	8.4 (2.7)	6.4 (2.5)	-4.1 (0.6)	-1.9 (1.5)
Idiopathic short stature (n = 29)	21	8	7.3 (2.5)	5.2 (2.3)	-3.6 (0.8)	-1.0 (1.6)
Ullrich-Turner syndrome (n = 17)	-	17	9.3 (2.6)	7.7 (2.3)	-3.5 (0.7)	-1.9 (1.4)

Values are mean (SD).

CA, chronological age; BA, bone age; SDS, standard deviation score.

Table 2 Auxological data from 124 patients before and during growth hormone treatment

	Visit -1	Visit 0	Visit 1	Visit 2	Visit 3
Chronological age (CA)	7.4 (2.9)	8.3 (2.9)	9.3 (2.9)	10.4 (2.9)	11.4 (2.9)
Height SDS (CA)	-3.8 (0.8)	-3.8 (0.9)	-2.9 (1.0)	-2.3 (1.2)	-2.2 (1.1)
Bone age (BA)	5.3 (2.7)	6.2 (2.9)	7.3 (3.0)	8.6 (2.9)	9.8 (3.0)
Height SDS (BA)	-1.1 (1.7)	-1.3 (1.6)	-0.6 (1.6)	-0.7 (1.5)	-0.9 (1.5)
Δ BA/ Δ CA	-	1.0 (0.7)	1.1 (0.6)	1.3 (0.7)	1.3 (0.7)
Height velocity SDS	-	-1.9 (1.8)	3.8 (3.0)	2.3 (2.2)	1.0 (1.9)

Values are mean (SD).

SDS, standard deviation score.

Patients treated before 1985 were given pituitary growth hormone, 14 IU/m²/week subcutaneously in three doses/week. Thereafter, recombinant growth hormone, 14–24 IU/m²/week, was given in daily injections. Height measurements, which were all performed by the staff of the paediatric endocrinology clinic, were transformed to height standard deviation scores (SDS; Z scores) for chronological age and bone age according to the tables derived from the Dortmund longitudinal growth study.¹³ The SDS were calculated by subtracting the population mean for age and sex (cm) from the observed measurement (cm) and dividing by the SD around that mean. Using the SDS allows auxological data acquired in children of different ages to be compared. Bone ages were assessed by one investigator (JT) according to the method described by Greulich and Pyle.¹⁴ The ratio of the difference of two consequent bone age (BA) ratings to the respective difference of chronological age (CA) (Δ BA/ Δ CA) was calculated to establish an equivalent degree of skeletal maturation. Pubertal maturation was assessed by the method of Tanner and coworkers.^{15, 16}

Five posterior–anterior radiographs of the left hand of all patients, which were performed for routine bone age determinations at the initial work up of short stature (visit -1), at the start of growth hormone treatment (visit 0), and once a year during the first three years of treatment (visits 1–3), were available for this retrospective study. The mean (SD) time intervals between examinations were 0.92 (0.56) years, 1.03 (0.2) years, 1.02 (0.21) years, and 0.99 (0.25) years respectively. In these radiographs the MCI was evaluated by one investi-

gator (KG) as the ratio of the mean axial length of the second, third, fourth, and fifth metacarpals to the width of the same metacarpals at their midpoints.⁴ The rater was unaware of the patient's diagnosis and of the course of growth hormone treatment. The MCIs were transformed to SDS using the reference data on MCIs in normal children of Rand *et al.*⁸ All the results were expressed as mean (SD). Statistical analysis was performed by parametric tests as appropriate (ANOVA; Scheffé's S post hoc comparison; simple regression analysis).

Results

Table 2 summarises the auxological data of all patients before and during the course of growth hormone treatment. At all times the MCIs were similar in the four patient groups. Before growth hormone treatment the mean (SD) MCIs were 6.9 (0.9) and 7.1 (0.8) and increased after the initiation of growth hormone treatment to 7.3 (0.75) at visit 1, 7.4 (0.7) at visit 2, and 7.6 (0.7) at visit 3 ($p < 0.0001$). The MCI correlated significantly with chronological age, bone age, and height before ($r = 0.44$; $r = 0.37$; $r = 0.45$; $p < 0.0001$) and during ($r = 0.36$; $r = 0.34$; $r = 0.34$; $p < 0.0001$) growth hormone treatment, but no significant correlation between changes of MCI and height velocity could be calculated ($r = 0.02$; $p = 0.6$).

The overall MCI in girls (7.6 (0.8)) was higher than in boys (7.1 (0.7); $p < 0.0001$). No overall significant difference could be detected in girls with Ullrich-Turner syndrome (7.8 (0.9)) and girls with normal karyotype (7.6 (0.7); $p = 0.6$). Patients with signs of puberty showed a higher overall MCI (7.5 (0.8)) than infantile patients (7.0 (0.8); $p < 0.0001$).

Table 3 The metacarpal index of 124 patients with short stature expressed as mean (SD) standard deviation scores (SDS) for chronological age (CA) and bone age (BA) before (visits -1 and 0) and during (visits 1–3) the first three years of growth hormone treatment

Patients	Visit -1		Visit 0		Visit 1		Visit 2		Visit 3	
	CA	BA	CA	BA	CA	BA	CA	BA	CA	BA
GHD (n = 65)	-0.6 (1.1)	0.4 (1.3)	-0.6 (1.2)	0.3 (1.3)	-0.7 (1.1)	-0.02 (1.1)	-0.6 (1.1)	-0.03 (1.2)	-0.6 (0.9)	-0.2 (1.0)
FSS (n = 13)	-0.5 (1.1)	0.1 (1.4)	-0.6 (1.1)	-0.1 (1.5)	-0.5 (1.3)	-0.3 (1.2)	-0.1 (0.8)	-0.1 (0.7)	-0.2 (0.7)	-0.1 (0.7)
ISS (n = 29)	-0.8 (1.4)	0.2 (1.7)	-0.8 (1.5)	0.1 (1.9)	-0.5 (1.7)	-0.3 (1.5)	-0.8 (1.1)	-0.3 (1.5)	-0.6 (1.4)	-0.3 (1.4)
UTS (n = 17)	-0.2 (1.2)	0.1 (1.5)	-0.1 (1.8)	0.7 (1.8)	-0.04 (1.2)	0.2 (1.4)	-0.1 (1.6)	0.1 (1.3)	0.04 (1.2)	0.2 (1.4)
Total (n = 124)	-0.6 (1.2)	0.3 (1.4)	-0.6 (1.3)	0.2 (1.5)	-0.5 (1.3)	-0.1 (1.2)	-0.5 (1.2)	-0.1 (1.3)	-0.5 (1.1)	-0.1 (1.1)

GHD, growth hormone deficiency; FSS, familial short stature; ISS, idiopathic short stature; UTS, Ullrich-Turner syndrome.

Table 3 summarises the expression of the MCIs in SDS for chronological age and bone age. No significant difference of the MCI SDS was detected between patient groups and from one visit to the other. At all visits the SDS for bone age in the four patient groups corresponded better to the population mean than the SDS for chronological age.

Discussion

The height of an individual is determined by lengthening of the diaphysis, which depends on the progression of ossification within the epiphysis. Thus the major factor contributing to linear growth is the lengthening of the bones by endochondral ossification. This process occurs largely in the long bones of the extremities, but is also characteristic of the vertebral bodies. In contrast, the increase in the girth of bones results from membranous ossification.¹⁷ The MCI measured in normal children increases from relatively low values in infants to reach the adult range by 10–11 years of age, after which the value is approximately constant.⁸

We previously reported that the MCI in children with constitutional tall stature is higher than that of children of normal height.⁷ The increase in the length to width ratio of the metacarpals with age and height shows that linear growth is characterised by a lengthening of bones that exceeds thickening. It remains speculative, however, whether height velocity and bone maturation correlate with changes in osseous proportions and whether exogenous growth hormone alters the osseous proportions of long bones.

This study evaluated for the first time the MCI in short children with growth hormone deficiency, familial short stature, idiopathic short stature, and Ullrich-Turner syndrome sequentially before and during the first three years of growth hormone treatment. At the initial evaluation of short stature the height of all the children was well below the third centile of the German reference population. The MCIs were not significantly different in the four patient groups, indicating comparable osseous proportions of the metacarpals in these growth disorders with and without chromosomal abnormalities. Shortening of metacarpal bones is frequent in children with Ullrich-Turner syndrome and in those with familial short stature.^{9–10}

Our present data therefore show that metacarpal shortening is accompanied by metacarpal thinning in these growth disorders and that metacarpal proportions are probably insignificant in the diagnosis of short stature. All the measured MCIs correlated significantly with chronological age, bone age, and height before and after the initiation of growth hormone treatment. The transformation of the measured MCIs to SDS to compensate for age differences showed a remarkable resemblance of the MCIs in children with short stature and children with normal stature.

In contrast, Cervantes *et al* reported that in patients with familial short stature the degree of stature reduction correlated with metacarpal

shortening, but bone width and proportions were not assessed in their study.⁹ More importantly, the SDS remained constant during growth hormone treatment despite a dramatic increase in the height velocity well above the normal population mean. No significant correlation could be detected between growth rate and changes in the MCI. Thus growth hormone treatment stimulates longitudinal bone growth without altering bone proportions, even in patients with inherent bone abnormalities. The SDS for bone age corresponded better to the normal population mean than the SDS for chronological age and the MCI was higher in girls than in boys. As girls are from birth onwards always more skeletally mature than boys,¹⁸ these findings suggest that bone maturation rather than growth rate influences metacarpal proportions.

The MCI was corrected for chronological age and expressed as SDS using the data of Rand *et al*, which were derived from children living in California.⁸ Unfortunately, no German reference data are available and these data may have to be applied with caution to German children. Other anthropometric methods—for example, assessing the skeletal age according to Greulich and Pyle¹⁴ and Tanner *et al*,¹⁸ using standards derived from US and British children—are commonly used worldwide and are successfully applied in children with Ullrich-Turner syndrome and with other growth disorders. Thus it seems justified to use reference values of metacarpal proportions accordingly.

The present data indicate that individual height measurements correlate with the MCI, but it is unknown whether metacarpal proportions represent the proportions of other long bones. Earlier studies provided substantial evidence, however, that maturation of the hand and wrist may be used as an index of the development of the rest of the skeleton.^{17–18} Therefore it seems reasonable to hypothesise that the MCI may be used as an index of the proportions of other long bones.

The MCI appears particularly well suited for repeated analysis of osseous proportions during linear growth because it can be assessed in radiographs of the left hand, which are routinely performed for bone age determinations in the evaluation and follow up of children with growth disorders. As a measure of long bone proportions the MCI can provide further insight into the effects of growth hormone on linear growth and bone maturation, and can be used as a tool to monitor proportionate growth as response to growth hormone treatment.

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