Densitometric test in differential diagnosis of short stature children[*]

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ABSTRACT   The aim of the study is to compare the dimensions and optical density of the second metacarpal bone in children with short stature caused by idiopathic growth hormone deficiency (IGHD), and children with short stature, but normal level of growth hormone. The diagnostic importance of the obtained results is assessed.

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Aim, materials and methods

The densitometric method described by WOLAŃSKI [1967] is used as an additional diagnostic tool in children with growth and developmental disturbances [ŁYSOŃ-WOJCIECHOWSKA *et al.* 1984, 1991*a, b, c*; ŁYSOŃ-WOJCIECHOWSKA & ROMER 1987; DZIECHCIARZ *et al.* 1996].

The X-rays (done with a special technique [WOLAŃSKI 1967]) of bones of the left hand of 200 children with short stature, non-treated, were assessed with densitometric method. Children, 53 girls and 147 boys, were from 3 to 17 years of age. The X-rays were also used to assess the skeletal age with the Greulich-Pyle method [e.g., KOPCZYŃSKA-SIKORSKA 1969]. The dimensions and optical density of the second metacarpal bone were evaluated with Zeiss fotodensitometer. The optical density error was 8-10 %, and the bone dimensions were assessed with pinpoint caliper with 5 % error.

The children were divided into five clinical subgroups. The obtained results were standardized by the DENSITY software [ŁYSOŃ-WOJCIECHOWSKA *et al.* 1992] and presented as standard deviation scores (SDS). The bone dimensions were compared with reference data [BECKER 1984]. For optical density evaluation the authors used their own reference data collected with the use of Zeiss fotodensitometer. The patients' results were later compared with healthy children reference data: (a) of the same skeletal age, (b) of the same height, and (c) of the same chronological age. The results of these comparisons allowed for

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the proposition of new differential diagnostic test, which is refered as densitometric test.

Clinical material

(**I**) The first subgroup consisted of 10 girls and 12 boys with idiopathic growth hormone deficiency (IGHD). In two stimulation tests, the peak of growth hormone level was below 5 mg/l.

(**II**) The second subgroup consisted of 6 girls and 24 boys with partial growth hormone deficiency (PGHD). In two stimulation tests the peak of growth hormone level was between 5 and 10 mg/l.

(**III**) The third subgroup consisted of 18 girls and 47 boys with familial growth retardation (FGR). The following criteria were used: A) Normal body mass at birth [KORNAFEL 1995]; B) Children of 2 to 9 years of age, if their body stature was above the 25th percentile on the TANNER *et al.* [1979] chart (which takes into account the parents' stature) and below the 3rd percentile on the standard percentile chart. In case of children older than 9 years their standardized body stature had to be within 1 SDS of the mean parents' stature. Patients with FGR have usually low, but within the normal range, growth rate, and their skeletal age is close to their chronological age [RYMKIEWICZ-KLUCZYŃSKA 1993].

(**IV**) The fourth subgroup consisted of 10 girls and 45 boys with constitutional delay of growth and development (CDGD). Their parents (usually fathers) had delayed pubescence and long period of short stature. The characteristic features of this subgroup were delayed of about 2 to 4 years height age and skeletal age, and pubescence in accordance to skeletal age. The body mass and body stature at the birth were normal in these children, and growth rate was in along the 3 percentile, the minimum value of the normal range. The level of the growth hormone was normal, pubescence delayed, and final body stature around the minimum value of the normal range.

(**V**) The fifth subgroup consisted of 9 girls and 19 boys with intrauterine growth retardation (IUGR). This subgroup was heterogeneous, some patients had genetic growth disorders, some had growth retardation due to intrauterine fetus traumas, although their growth hormone level was normal. The following criteria were used: decreased body stature and body mass (below 2500 g) at birth while birth occurred on time, or body stature and body mass at premature birth (from 30 week of gestation) below 10 percentile.

Table 1 shows the mean chronological age, height age and skeletal age of all subgroups, together with relation of skeletal age to chronological age.

Table 1. Age of children with the growth retardation in five clinical groups

Clinical group	Number of patients	Growth hormone	Chronological age		Stature age		Skeletal age		Skeletal age/ Chronological age
			M	SD	M	SD	M	SD	%
IGHD	22	↓↓	8.2	2.6	5.0	1.7	5.1	2.4	59.6
PGHD	30	↓	10.1	3.4	7.4	2.7	7.9	3.1	77.9
FGR	65	N	10.0	3.2	7.2	2.9	7.6	3.3	76.0
CDGD	55	N	11.9	2.5	8.9	2.4	9.2	3.3	74.9
IUGR	28	N	9.5	3.0	6.7	2.5	7.2	3.6	73.9

Results

Tables 2 & 3 show five parameters of the second metacarpal bone in all five clinical subgroups standardized to skeletal age (Tab. 2) and to chronological age (Tab. 3). These data were further analyzed with analysis of variance.

In children with IGHD the bone thickness (BT), cortical thickness (CT), and cortical area (CA) were statistically significantly diminished in comparison to healthy children of the same skeletal age, but the corrected bone density normalized (CBDN), i.e., optical density was normal. On the contrary, the relative optical bone density (optical density to cortical thickness and to cortical area – CBDN/CT and CBDN/CA) was increased in this group (Tab. 2, Figs. 1 & 2).

In children with PGHD the cortical thickness, osteopetrosis index (CT/BT x100), optical bone density and relative optical density were statistically significantly increased in comparison to healthy children of the same skeletal age.

In children with FGR bone thickness and medulla diameter (MD) were statistically significantly diminished in comparison to healthy children of the same skeletal age, although the cortical thickness was normal. The osteopetrosis index was increased, as was optical density and relative bone density.

In children with CDGD, like in children with FGR bone thickness and medulla diameter were statistically significantly diminished in comparison to healthy children of the same skeletal age, although the cortical thickness was normal. The osteopetrosis index was increased, as the length of the second metacarpal bone (BL), optical density and relative bone density.

In children with IUGR, like in children with CDGD and FGR, bone thickness and medulla diameter were statistically significantly diminished in comparison to healthy children of the same skeletal age, although the cortical thickness was normal. The osteopetrosis index, optical bone density, and relative bone density were increased (Tab. 2, Figs. 1 & 2).

Table 2. Second metacarpal bone. Differences (in standardized values SDS) between children with the growth retardation and standards of skeletal age

Clinical group	Number of patients	Bone Lenght BL	Bone Thickness BT	Cortical Thickness CT	Cortical Area CA	Optical Density CBDN
IGHD	22	−0.06	−1.19***	−0.70*	−0.87***	0.00
PGHD	30	+0.15	−0.04	+0.54*	+0.23	+0.81***
FGR	65	0.00	−0.74***	+0.24	−0.27	+0.56***
CDGD	55	+0.28*	−0.49**	+0.13	−0.19	+0.61***
IUGR	28	−0.18	−0.72*	+0.17	−0.33	+0.67*

Table 3. Second metacarpal bone. Differences (in standardized values SDS) between children with the growth retardation and standards of chronological age

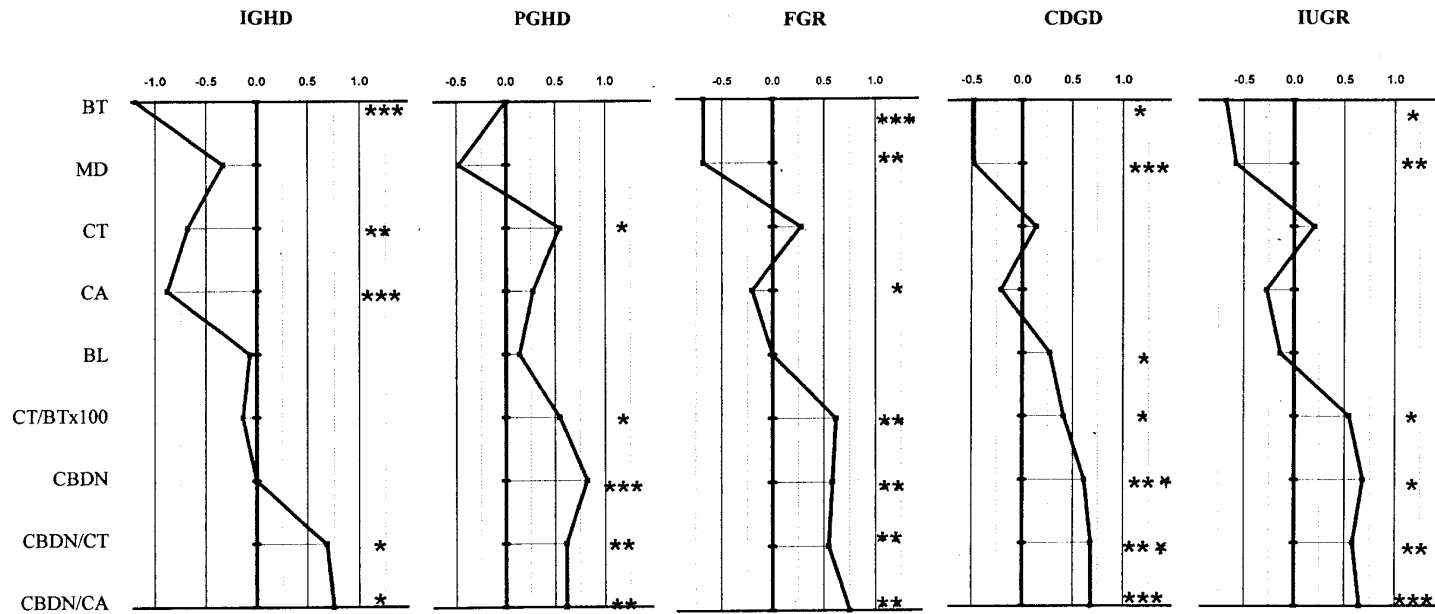| Clinical group	Number of patients	Bone Length BL	Bone Thickness BT	Cortical Thickness CT	Cortical Area CA	Optical Density CBDN
IGHD	22	−2.70***	−2.79***	−2.23***	−2.40***	−0.77**
PGHD	30	−1.35***	−1.11**	−0.33*	−0.87**	+0.23**
FGR	65	−1.81***	−1.88***	−0.93**	−1.49***	−0.16
CDGD	55	−1.48***	−1.57***	−0.96**	−1.38***	+0,03
IUGR	28	−1.97***	−1.75***	−0.91**	−1.38***	−0.12

Fig. 1. Diagram of the standardized measurements and optical density of the second metacarpal bone of children with: IGHD (idiopathic growth hormone deficiency), PGHD (partial growth hormone deficiency), FGR (familial growth retardation), CDGD (constitutional delay of growth and development), and IUGR (intrauterine growth retardation) according to normal values for children of the same skeletal age.

Bone thickness (BT); Medulla diameter (MD); Cortical thickness (CT); Cortical area (CA); Bone length (BL); Osteoporosis or osteopetrosis index (CT/BT x100); Corrected bone density normalized (CBDN); Relative bone density (CBDN/CT); Corrected bone density/area (CBDN/CA). Significance level: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

STANDARD   PATIENTS

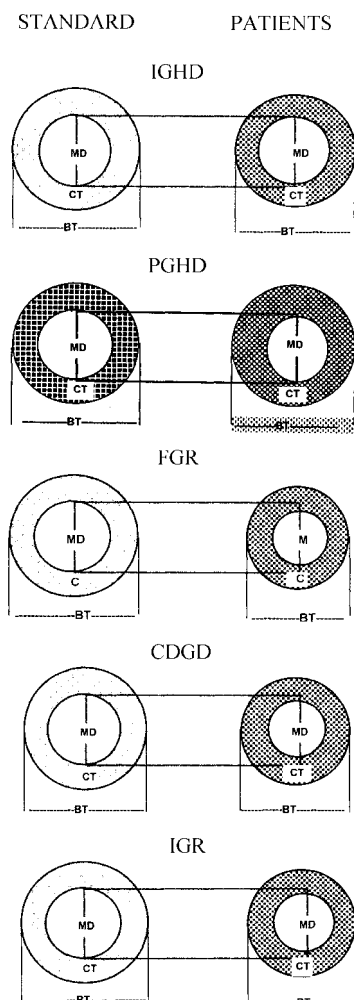IGHD

PGHD

FGR

CDGD

IGR

Fig. 2. Cross-section of the second metacarpal bone of children with IGHD, PGHD, FGR, CDGD, and IUGR (patients) in comparison with healthy children (standard)

Three subgroups of short stature children with normal growth level hormone (FGR, CDGD, and IUGR), although etiologies of their disorders are different, exhibit many similarities in second metacarpal bone structure: diminished bone thickness, increased optical density and normal cortical thickness. Apart from children with CDGD, who have in-creased bone length, the length of second metacarpal bone is normal in these groups.

Children with IGHD have decreased skeletal age in relation to chronological age. They reach about 59.6 % of chronological age, while children with PGHD, as children with normal level of growth hormone (FGR, CDGD and IUGR), reach 73.9-77.9 % of chronological age.

Children with stature deficiency differ statistically significantly from healthy children of the same chronological age (Tab. 3) in diminished dimensions of the second metacarpal bone. The biggest differences (below −2 SDS) were found in children with IGHD, in other groups these differences were smaller, from −1 to −2 SDS.

In comparison to healthy children in the same chronological age optical bone density is diminished in children with IGHD, increased in children with PGHD and normal in children with normal level of growth hormone (FGR, CDGD, IUGR).

Densitometric test

The results were analyzed with ANOVA method (F statistics, Halperin's test, Duncan's multiple range test, matrix of correlation, factor analysis were applied). The biggest differences and biggest similarities of standardized parameters of second metacarpal bone were found. The results of the analysis were later used for statistical analysis.

In all five clinical subgroups the parameters which exhibit the best differentiating power were the following: bone length, bone thickness, cortical thickness, cortical area, and optical bone density

Table 4. Concordance (in %) between clinical classification and the classification based on densitometric analysis (according to skeletal age)

Clinical group	Classification based on densitometric analysis		
	PGHD	CDGD+FGR+IUGR	IGHD
PGHD	**55.56**	25.93	18.52
CDGD +FGR+ IUGR	32.21	**38.03**	26.76
IGHD	11.76	17.65	**70.59**

Table 5. Concordance (in %) between clinical classification and the classification based on densitometric analysis (according to chronological age)

Clinical group	Classification based on densitometric analysis		
	PGHD	CDGD+FGR+IUGR	IGHD
PGHD	**50.00**	36.67	13.33
CDGD +FGR+ IUGR	32.99	**45.89**	21.23
IGHD	9.09	13.64	**77.27**

standardized to skeletal age and chronological age (Tab. 2, 3). These parameters were used for densitometric test.

The parameters which exhibit the smallest differentiating power were the following: cortical thickness, cortical area, and proportion of cortical thickness to bone length standardized on height age. These parameters were not included into densitometric test.

Through the discriminative function analysis it was found, that parameters standardized on skeletal age had smaller discriminative power than parameters standardized on chronological age. Thus densitometric test was based on five parameters standardized on chronological age. The chosen parameters were as follows: bone length, and thickness; cortical thickness, and area of the second metacarpal bone; and optical bone density.

The densitometric test can differentiate children with IGHD from children with normal level of the growth hormone (PGHD, FGR, CDGD and IUGR) and the same skeletal age with 70.6 % accuracy (Tab. 4), and from children of the same chronological age with 77.3 % accuracy (Tab. 5). The densitometric test cannot differentiate children with partial growth hormone deficiency (PGHD) from children with normal level of the growth hormone (FGR, CDGD, and IUGR).

The results from densitometric test were used for creating special computer software for differentiation diagnostics of short stature children.

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In conclusion one can say that diminished dimensions and decreased optical bone density of the second metacarpal bone of children with idiopathic growth hormone deficiency (IGHD) could be used for screening tests of short stature children.

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Streszczenie

Dzieci z somatotropinową niedoczynnością przysadki (IGHD) mają zmniejszoną grubość warstwy korowej kości w porównaniu z dziećmi niskimi z prawidłową czynnością przysadki. Celem tej pracy była ocena wymiarów i gęstości optycznej drugiej kości śródręcza u dzieci niskich o różnej etiopatologii zaburzeń wzrastania oraz przydatności diagnostycznej uzyskanych wyników. W badaniu zastosowano metodę densytometryczną, którą oceniono drugą kość śródręcza u 200 dzieci niskich, nie leczonych w wieku od 3 do 17 lat (53 dziewczęta i 147 chłopców).

Standaryzację badanych cech drugiej kości śródręcza w stosunku do norm dla populacji polskiej wykonano programem komputerowym DENSITY w 5 grupach klinicznych: somatotropinowej niedoczynności przysadki (IGHD), częściowej somatotropinowej niedoczynności przysadki (PGHD), z konstytucjonalnym nioedoborem wzrostu (CDGD), rodzinnym niedoborem wzrostu (FGR) i wrodzonym niedoborem wzrostu (IUGR). W oparciu o 5 cech drugiej kości śródręcza: długość, szerokość trzonu kości, grubość warstwy korowej, powierzchnię przekroju warstwy korowej i gęstość optyczną opracowano test diagnostyczny, nazwany przez autorów testem densytometrycznym, różnicującym dzieci niskie. Prawdopodobieństwo poprawnego rozpoznania somatotropinowej niedoczynności przysadki u pacjentów przy zastosowaniu testu densytometrycznego wynosiło 77,7%.