Hand radiograms as an alternative for bone mass screening in cystic fibrosis

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ABSTRACT

Purpose: Cystic fibrosis (CF) is a genetic, metabolic disease. Long-term therapy often leads to inappropriate calcification of bones. Dual X-ray absorptiometry (DXA) is considered a „gold-standard" for bone mineral density (BMD) assessment, but high usage costs can limit its availability. This paper compares two methods for BMD assessment in CF patients: hand radiograms method and densitometry using DXA method.
Materials and methods: The study was performed in a group of 26 CF patients (10F, 16M), aged 7-30 years. In all cases, DXA measurements were performed, along with bone mass assessment using DENSY2004 system for digital assessment of hand radiograms. Stepwise binary logistic regression was used to examine the contribution of bone age, BMI, Cole's index and hand radiograms parameters to low BMD expressed as Z-score ≤-1SD.
Results: Statistical analysis of the gathered data revealed that hand radiograms method allow for estimation of Z-score below -1SD with accuracy of 84.62% comparing to DXA. Sensitivity and specificity of this estimation in the studied group of CF patients was 86.67% and 81.82%.
Conclusions: Hand radiograms method has good accuracy, sensitivity and specificity; therefore, it can be an alternative for DXA in BMD assessment. It can be implemented in chronic diseases affecting BMD like cystic fibrosis.
Key words: cystic fibrosis, bone mineral density, osteoporosis, dual X-ray absorptiometry, hand radiograms

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INTRODUCTION

Cystic fibrosis (CF) is a genetically determined metabolic disease. Multisystemic and long-term therapy often leads to malnutrition and inappropriate calcification of bone tissue. Low physical activity, frequent hospitalization and chronic hypoxemia, due to evolution of lung disease, also impacts bone mineralization [1]. Dual X-ray absorptiometry (DXA) is considered as a „gold-standard" for bone mass assessment. But high usage costs can limit the availability of this method. Increasing mean of life of CF patients makes osteoporosis a growing problem for clinicians. Screening of bone mineral density (BMD) is necessary for application of proper therapy (biphosphonates) [2]. In European and US guidelines for CF management, assessment of BMD is an important point of the diagnostic process. Therefore simple but accurate methods are needed for screening of BMD. Although hand radiograms method is well know for almost 80 years, modern modifications implemented nowadays allow to improve the precision and accuracy of this diagnostic tool [3, 4].

This paper is a comparative study of two methods for bone mass assessment in patients with cystic fibrosis: hand radiograms method and densitometry using DXA method in CF patients. Furthermore we tried to answer the question, if the hand radiograms can be used as a preliminary method for further diagnosis of bone mass disturbances in CF patients.

MATERIALS AND METHODS

Study group. The study was performed in a group of 26 CF patients (10F, 16M), aged 7-30 years (x=14.3 ± 5.6 yrs), treated in Outpatient Clinic for Cystic Fibrosis, Children's University Hospital, Białystok, Poland (Table 1).

Cystic fibrosis was diagnosed on the basis of clinical symptoms and double, positive sweat test (pilocarpine iontophoresis and Wescor method). Clinical diagnosis was confirmed in molecular examination of the *CFTR* gene.

The dual-energy X-ray absorptiometry examination was conducted as a part of standard, annual clinical assessment of CF patients. Additionally, hand radiograms were used in current study were obtained from patients who gave their informed consent.

Physical development. For somatic development the measurements of growth and weight were performed. Nutritional status was assessed using body mass index (BMI) and Cole-Stanfield score. Additionally, measurements of hand thickness (TT, Total Thickness) between second and third metacarpal bone of non-dominant hand were performed.

Table 1. Studied group characteristics.

	n	mean
Total number of patients	26	-
males	16	-
females	10	-
Age	-	14.3 ± 5,6
Bone age	-	13.3 ± 4,2
Body Mass Index	-	16.9 ± 2,8
Cole-Stanfield Index	-	89.9 ± 13,5
BMD TOTAL	-	0.841 ± 0,377
BMD SPINE	-	0.786 ± 0,164
Z-score		-2,596 ± 1.306
>-1SD	11	-
≤-1SD	15	-

Hand radiograms. X-rays of non-dominant hand were performed using mammographic cassette MIN R-2, with exposition settings as follows: U=48 KV, 2 mAs, distance form x-ray source – 1 meter. Aluminium step pattern (10 steps, 1 mm each) was placed by the side of photographed hand. Absorbed dose was 1 cGy (permissible dose 5 cGy in accordance to Polish National Atomic Energy Agency).

Radiograms were used for bone age assessment, afterwards they were scanned and corrected (because of background luminosity). Digital images of x-ray pictures were used for geometrical and densitometrical measurements of second metacarpal bone. Geometrical measurements (bone length, bone thickness, marrow cavity diameter, cortex layer thickness) were performed in the midst of the bone (Fig. 1).

Optical density, which emerges from bone mineralization, was measured in the same point of the bone. Geometrical parameters of the bone, thickness of soft tissues (TT) and luminosity of step pattern and bone images were used for calculation of normalized, relative optical density of bone (CBD/N/CT) and corrected bone density normalized (CBDN) [4-6]. These data along with bone age and sex of each patient were compared with reference values for polish population of healthy children (Fig. 2) [5].

This method of densitometrical assessment was first developed in mid 1960' by Wolanski and Eagen [9]. In Poland, studies on practical usage of hand radiograms was performed by Children's Health Center Hospital in Warsaw. Computer system and original software (DENSY 2004, Fig. 3) for assessment of skeletal system using this method was developed in Industrial Institute of Electronics in Warsaw, Poland (expedient grant of Polish State

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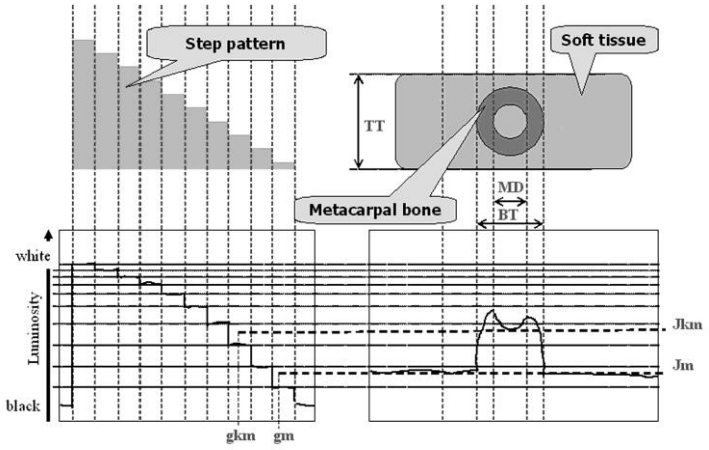

Figure 1. Determination of basic parameters of second metacarpal bone on the basis of scanned hand radiogram.

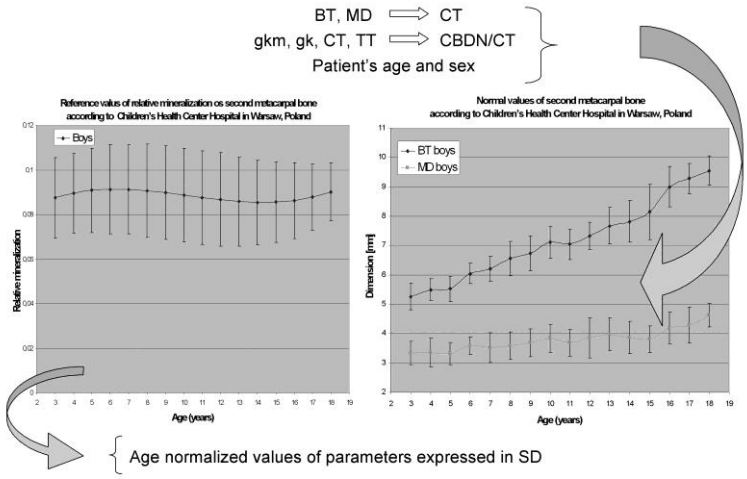

Figure 2. Determination of normalized parameters of second metacarpal bone.

The abbreviation used in this system are explained in Table 2.

Table 2. Abbreviations used in hand radiograms method description.

BL	length of the bone;
BT	bone thickness;
MD	marrow cavity diameter;
CT	cortex layer thickness;
CBDN	corrected bone density normalized;
CBDN/CT (CBDN2CT)	corrected bone density normalized related to cortex thickness;
CT/BT*100	bone proportion ratio;

DXA. Bone mineral density (TOTAL BMD and BMD SPINE in region L_2 - L_4) was assessed using dual-energy x-ray absorptiometry (DXA) on DPX-L system (LUNAR Radiation Corp, USA). Obtained resulted were expressed as Z-score. Osteopenia was defined as Z-score between -1SD and -2SD at least in one localization. Osteoporosis was diagnosed when Z-score was below -2SD with accompanying clinical symptoms [6]. In this study our goal was to estimate decreased BMD ≤-1SD using hand radiograms in comparison to DXA. to low BMD expressed as Z-score ≤-1SD (osteopenia or osteoporosis). Statistical analyses

were performed using SigmaStat 2.03 (SPSS Inc., Chicago, IL, USA).

Ethical issues. In accordance with the Helsinki 2nd Declaration each patient was informed verbally and in writing about the purpose of the study and methods used. All patients gave their written consent. The study was approved by the Bioethics Committee of medical University of Bialystok, Poland.

Statistical analysis. In comparative analysis stepwise binary logistic regression (Wald's test) was used to examine the contribution of bone age, BMI, Cole-Stanfield index and hand radiograms parameters (BL, BT, MD, CT, NBT, NMD, CBDN2CT, NCBDN, CT/BTx100, CBDN).

Table 3. The results of DXA and hand radiograms analysis in studied group.

Patient	Sex	Age [yrs]	TT [mm]	BL	BT	MD	CT	100x CT/BT	CBDN2CT	CBDN	NBL	NBT	NMD	NCBDN	NCBDN2CT
1	F	7.33	20	46.2	4.7	2.1	2.6	54.89	0.1171	0.302	-0.1	-1.7	-2.4	0.9	0.2
2	F	11.00	16	56.6	8	4.3	3.7	46.26	0.1277	0.475	-0.9	1.8	0.7	2.5	1.4
3	F	14.25	16	61.8	6.4	4.1	2.4	36.85	0.1291	0.305	-3.3	-1.1	0.8	-2.2	0.3
4	F	12.50	21	63	6.8	2.6	4.2	61.29	0.1139	0.472	-0.1	-0.9	-1.8	0.9	0.2
5	F	16.75	20	55.2	6.4	3.6	2.8	44.28	0.1239	0.35	-3.2	-17	-2.8	-1.3	1
6	F	18.00	20	64.2	6.9	3.4	3.6	51.15	0.1018	0.361	0.1	-1	0	-1.4	-0.5
7	F	10.50	23	57.7	5.9	3.6	2.3	38.61	0.1479	0.338	-0.1	-1.7	-0.3	0.8	2.5
8	F	30.00	18	66.7	6.9	2.5	4.4	63.4	0.1457	0.641	-1.3	-2.4	-5.9	2.4	1.5
9	F	14.42	16	60	5.8	3.4	2.5	41.95	0.1501	0.367	-5.6	-2	0.2	-1.5	1.3
10	F	8.75	19	45.1	5.7	3	2.7	47.79	0.1094	0.296	-1.6	-0.8	-1.1	0.2	-0.2
11	M	7.67	22	40.1	7.2	4.6	2.6	36.52	0.1136	0.298	-0.6	3.2	2.4	1	0.3
12	M	10.42	16	43	5.9	3.3	2.6	44.35	0.0995	0.261	-1.1	-0.2	-0.7	0.2	-0.2
13	M	15.17	21	62	8.1	5.8	2.3	28.65	0.1386	0.322	-2.2	-4.4	3.4	-1.3	-1.3
14	M	12.67	23	56.5	7.5	5.1	2.4	32.09	0.1048	0.253	-1.8	-0.7	1.1	-1	0.2
15	M	7.25	21	41.6	5.6	3.8	1.8	32.07	0.1338	0.238	-2.7	-1.4	0	-0.4	0.7
16	M	19.00	28	71.1	7.4	2.5	4.9	66.62	0.1128	0.553	-0.5	-1.7	-1.3	0.9	7.6
17	M	20.00	21	70.4	8.1	2.8	5.4	66.17	0.1055	0.567	-0.7	-1.2	-1.1	1	5.4
18	M	27.00	30	72.2	7.5	3.6	4	52.78	0.138	0.549	-0.2	-1.6	-0.7	0.8	15.2
19	M	12.33	23	56.3	6.6	4.2	2.4	35.9	0.1431	0.339	-1.3	-1.4	-0.1	0	1.5
20	M	22.00	21	74.2	8	3.9	4.1	51.13	0.1438	0.585	0.4	-1.3	-0.5	1.2	17
21	M	15.83	30	64.7	8.9	5.6	3.3	36.83	0.094	0.306	-0.6	0.6	1.5	-0.9	-0.3
22	M	12.92	27	61	7.1	5	2.1	29.67	0.1117	0.246	0.6	-0.2	1.5	-0.9	0.5
23	M	12.33	18	56.2	6.6	3.7	2.9	44.24	0.1706	0.498	-1.3	-1.4	-0.9	1.7	2.5
24	M	10.25	20	55.2	6.4	3.6	2.8	44.28	0.1239	0.35	-3.2	-17	-2.8	-1.3	1
25	M	14.42	23	64.7	7.3	3.9	3.4	47.11	0.1265	0.433	-1.1	-11	-1.9	-0.4	1.1
26	M	11.12	20	53.2	6.9	3.7	3.6	51.44	0.125	0.446	-0.8	-0.1	-0.6	1.4	1

RESULTS

The results of measurements of BMD using DXA and parameters of second metacarpal bone using studied hand radiograms system are presented in Table 3.

Statistical analysis of the gathered data revealed that for interpretation of hand radiograms following parameters are of highest usefulness: bone thickness of cortical layer (BT), relative density (CBDN2CT), corrected bone density normalized (NCBDN), bone proportion index (CT/BTx100), corrected optical density normalized (CBDN).

These values allow for estimation of Z-score below -1SD (osteopenia or osteoporosis) with

accuracy of 84.62%. Sensitivity and specificity of this estimation in studied group of CF patients was 86.67% and 81.82% respectively (Table 4).

Table 4. The results of binary logistic regression with backwise conditional elimination.

		Reference method (DXA)	
		Positive	**Negative**
Analyzed method (hand radiograms)	Positive	13	2
	Negative	2	9

DISCUSSION

One of the clinical feature of cystic fibrosis is retardation of growth and mass. Nutritional status and somatic development in these patients are closely connected with mineralization of bones. Lowered quality of life in this chronic disease, limited physical activity (frequent hospitalizations, physiotherapy procedures), inhaled and systemic steroid therapy and finally impaired absorption impact the calcification of bones [6,7]. Decreased bone mineral density despite the vitamin D and calcium supplementation is related with disease duration and age of the patient. Among all of the methods used for assessment of bone mineralization, along with biochemical measurements, different imaging methods are known (radiological - DXA, QCT and ultrasonographic - QUS). The "gold standard" is dual x-ray absorptiometry (DXA), which is used for assessment of fracture risk and therapy monitoring in osteopenia and osteoporosis [6].

The densitometrical assessment of skeletal system using radiograms is an old technique developed for the first time in 1939 [8]. Hand radiograms methods used in our study was invented by Wolanski and Eagen for NASA in 1964 [9]. The modified version of hand radiograms method developed by Children's Health Center Hospital in Warsaw, Poland, and was used for densitometrical assessment in chronically ill children [11]. Last modification was performed by Industrial Institute of Electronics in Warsaw, Poland [10]. Lyson-Wojciechowska *et al.* using this method performed an assessment of bone age, bone mineralization and bone measurements in children with hyposomatotropism, hypocalcaemia in Williams syndrome and infant idiopathic hypercalcemia, celiac disease, in liver diseases [3, 4]. In this study, the organic changes in bone structure were assessed with the thickness of cortical layer of the bone. Optical density was used to assess the mineral status of bones. In this study authors conclude that the assessment of geometrical parameters of second metacarpal bone (thickness of cortical layer, marrow cavity diameter) along with optical density can be a useful tool for a preliminary diagnosis of mineralization disturbances, but this should be confronted with DXA examination [10].

Hand radiograms method has also its limitations. It is only useful for screening not for diagnosis. Hand radiograms are only the beginning of diagnostic process. Later on densitometry is inevitable. Moreover, a training in using a new method and of course the cost of implementation of new diagnostic system should be considered. Despite this inconveniences overall cost of single DENSY2004 examination is still much lower than DXA (pharmacoeconomical comparison not published yet). What differs this system from other previously developed in other countries is a possibility of its implementation even in very small centers. DENSY2004 requires only a single x-ray image to be scanned. The cost can be even lower if digital version of an x-ray is already available. Very important is also lower radiation level in this method, so the examination can be repeated and combined with other imaging examination during one hospitalization.

The DXA is a "gold standard" in diagnosis of osteopenia and osteoporosis, but this method requires sophisticated equipment, appropriate space and qualified personnel. This limits the use of DXA in general practice. The costs of densitometry can also be a barrier. Hand radiograms method can be an alternative, as it is cheaper and more available. Although that hand radiograms method have good accuracy, the time consumed by posting an x-ray and involvement of radiologist caused that this technique was not very popular [11]. Recent progress in imaging (high quality digital x-ray images, computer-allied image analysis) corrected most common errors like time of exposition and influence of soft tissues. According to recent findings patients with CF and lactose malabsorption are endangered in early osteoporosis incidence – the hand radiograms due to relatively low irradiation dose and low cost of performing could be valuable tool in osteoporosis screening in this group [12]. Hand radiograms can be useful for clinical practice, but studies on bigger groups of patients are needed.

Conflicts of interest: none declared.

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