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OSTEODENSIOTOMETRY AN INNOVATIVE APPROACH TO OSTEOPOROSIS DIAGNOSTICS

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INTRODUCTION. *The generally accepted main method for diagnosing osteoporosis (OP) is axial X-ray densitometry. The high demand for densitometric studies with a small number of bone densitometers leads to a situation where doctors evaluate the results of studies performed on devices of different types and in different diagnostic centers. If densitometry is performed for the first time, the accuracy of the measurement is extremely important for diagnosing OP and initiating therapy. Reproducibility is of great importance for repeated densitometry. The accuracy of densitometers declared by manufacturers is 1%, and reproducibility is 2%, however, in real practice, taking into account the influence of all factors, the reproducibility of the results may be worse. Ensuring reproducibility and quality is important both in clinical trials of drugs, when the results of repeated observations are material for statistical processing, and in relation to a specific patient in order to assess the effectiveness of treatment.*

Keywords: *osteodensitometry, osteoporosis, trabecular bone tissue, menopause.*

In international multicenter randomized controlled trials (RCTs), high requirements are imposed on the accuracy of osteodensitometry, compliance with which is monitored by SYNARC, an international company for quality control of densitometric studies. Fulfillment of these requirements and interpretation of densitometric study results may be accompanied by certain methodological difficulties. The objective of this work is to analyze the methodological factors affecting the accuracy and reproducibility of densitometric studies. Accuracy and reproducibility of measurements. The capabilities of osteodensitometers are assessed by a number of characteristics, the main ones being the accuracy and reproducibility of measurement results. The technical guidelines indicate an accuracy of 1%, meaning the deviation of the in situ BMD assessment results from the data obtained by direct chemical analysis of an artificial sample. Densitometers have a built-in calibration and quality control program (Quality Control, QC). During operation of the densitometer, calibration (daily in some models) is performed using an anthropomorphic phantom, which is a homogeneous cast of a block of lumbar vertebrae (L1-L4), poured into a plastic cube or a stepped phantom consisting of aluminum plates of different thicknesses also poured into plastic. For each phantom, the required value of the IPC is known, a deviation from which during calibration by +1.5% is considered acceptable by both the manufacturers and SYNARC. Based on the calibration results, a graph is automatically generated for the entire period of operation. Reproducibility characterizes the spread of the results of repeated measurements performed over a short period of time. In addition to accuracy, the reproducibility of measurements is affected by circumstances related to the operator and the patient. During a repeated examination, the operator must lay down and establish the region of interest (Region of interest,ROI) as accurately as possible in relation to the previous one. The location of the ROI in the scanning field (offset relative to the center) and changes in the patient’s anthropometric parameters during the period between examinations can also affect reproducibility. The International Society of Clinical Densitometry Densitometry (ISCD) suggests using a special calculator in Excel that allows calculating the reproducibility of the operator-device complex by performing 2 repeated measurements on 15 patients (or 3 on 10 patients). If the reproducibility of the operator-device complex for ROI L1-L4 is 1.9%, this indicates that the densitometer is in good working order and the personnel are sufficiently qualified. The software (SW) of densitometers is constantly being improved and some models offer the definition of the least significant change (Least Significant Changes, LSC) for repeated observations. The LSC value will depend on the measurement accuracy for a given ROI and the version of the statistical software. Thus, in order to assess whether the BMD changes detected during a repeated examination after a long period of time (more than 1 year) are reliable, in practice, taking into account all factors, changes of less than 2% cannot be considered reliable. Information content of study areas during dynamic observation. According to the ISCD recommendations [1], to diagnose osteoporosis, it is necessary to measure BMD in two skeletal areas (lumbar vertebrae and proximal femur). To diagnose osteoporosis, it is sufficient to have a decrease in BMD in only one of the areas: the lumbar vertebrae segment (L1-L4), the femoral neck (Neck) or the entire proximal femur (Total). However, this does not mean that when a diagnosis of osteoporosis has been established and treatment has been prescribed, it is possible to limit ourselves to monitoring the effectiveness of only one area. The conclusions on densitometry of the proximal femur include data on the Ward area or Ward's "triangle" (a term extrapolated into osteodensitometry from radiology). In fact, this is the area of the lowest density, automatically found by the densitometer software. The BMD value in the Ward area is not recommended for use in diagnosing osteoporosis [1], since the rate of metabolic processes in this area is high, and its localization depends on the projection of bone structures and software of densitometers determines it with insufficient consistency. Sometimes, within the framework of clinical studies, repeated measurements are carried out only of the proximal part of the femur. This is due to the inclusion of very elderly patients and the presence of pronounced degenerative changes in the spine, as well as the fact that this ROI is determined in the same way on all densitometer models. Modern densitometers are equipped with the "Whole Body" program, which allows obtaining data on BMD in the entire skeleton and in its different sections. Due to the large size of the ROI, the study using this program is carried out with lower resolution and the accuracy usually does not exceed 2%. In addition, the implementation of this program takes much more time than measuring BMD in standard localizations, and the reference databases are less representative than for the lumbar vertebrae and proximal femur. Therefore, the "Whole Body" program is not used in clinical practice. Our experience in using the "Whole Body" program for research purposes shows that it can be used to detect reliable changes in BMD and its distribution by skeletal sections in healthy people who were immobilized for 0.5-1 year [2]. Also, the Whole Body program was used to assess the amount and distribution of fat and lean mass in women at different stages of the postmenopausal period [3]. It is difficult to predict in advance how quickly bone mass will change in a particular area of the skeleton with age, exposure to others, or during treatment in a particular person. We found that in healthy men (astronauts), the predominance of BMD losses in the lumbar vertebrae or femur under zero gravity conditions, as well as subsequent recovery on Earth, was individually specific and was repeated during repeated flights. In addition, it turned out that the maximum mineral losses were noted not in the lumbar vertebrae and femoral neck, but in the pelvic bones [4]. A BMD loss of 1-2% per year in postmenopausal women is considered physiological and primarily affects trabecular bone tissue in the vertebrae [5,6]. However, there are differences in the rate of loss of trabecular and cortical bone tissue in women with natural and surgical menopause. If in women with natural menopause bone loss begins in the vertebrae and the proximal femur joins later, then in women after oophorectomy, BMD loss occurs simultaneously in the vertebrae and femoral neck, and osteoporosis in the femoral neck develops 1.3 times more often [7]. With a positive effect of treatment, the average increase in BMD in different parts of the skeleton is 2% per year [8] and the greatest increase is observed in the lumbar vertebrae (Fig. 1). With such a ratio of possible BMD dynamics and densitometry reproducibility, the issues of study quality are of particular importance. Taking into account the above, the question of the predominant information content of a particular skeletal area may not have an unambiguous solution. Methodological aspects of quality and reproducibility.Compliance with domestic clinical guidelines [9] and ISCD recommendations ensures the proper quality of densitometry. Since densitometry measures the projection BMD (g/cm2), the shift of the object of study in the ROI, changing the area of its projection, affects the result. Thus, an increase in the area leads to an underestimation of the BMD. The bone boundaries and the "bone map" are determined automatically, but can be changed by the operator. Let us consider common but non-standard densitometric situations that affect the quality and result of the measurement. Study of the proximal femur. The recommendations of manufacturers of densitometers of all types for patient positioning during hip examination are the same. Correctly performed scanning assumes a vertical position of the diaphysis and a visible lesser trochanter, meaning that the foot is rotated inward and, therefore, the femoral neck should be positioned parallel to the table. A special foot retainer is provided for this. However, mechanical fulfillment of these conditions is not always possible and can lead to undesirable consequences. There are patients in whom the lesser trochanter is visible only when the foot is not rotated. In turn, refusal to rotate the foot leads to a downward deviation of the femoral neck and an overestimation of the BMD and T-score values. The opposite situation is also possible, when the lesser trochanter is “too noticeable” when the foot is rotated. Refusal to fix the foot will negatively affect reproducibility in subsequent studies. Sometimes these features can cause SINARC claims to quality and prevent the patient from being included in the RCT. The location of the femoral neck area is affected by the tilt angle determined by the operator using anatomical landmarks. A low location of this area of interest leads to an underestimation of the BMD because the area of its projection increases. The vertical size of this area, automatically suggested by the densitometer program, is rarely changed, but differences in it during repeated measurements can make the results incomparable. The vertical location of the femoral diaphysis in the ROI is also very important. Current ISCD recommendations provide for the examination of only one femur. If the operator selects automatic sequential examination of two femurs, both shafts will be located at different angles. This will not lead to large errors in determining the BMD and T-score, but will affect reproducibility, since the position of the shaft at the same angle is more difficult to repeat during a repeat examination than a vertical one. The BMD indicator for the entire proximal femur "Total" depends on how much compact bone of the shaft part falls into the ROI, i.e. on its lower border, drawn along the lower part of the lesser trochanter (or its shadow) on Hologic densitometers or on the inclination of the femoral neck axis on Lunar densitometers. All these features should be taken into account by the operator when performing densitometry, especially if its purpose is to assess the effect of treatment.Lumbar Vertebrae Examination When performing a repeat examination to determine the dynamics of densitometric parameters, the operator should try to position the patient and set the ROI in the same way as in the first examination. The presence of the lumbosacral junction in the ROI helps to avoid errors in selecting the L1-L4 segment for analysis. In this case, the starting point and the center of the scan are determined. Failure to follow this rule, even on high-resolution densitometers, can lead to errors. When positioning the patient for examination of the lumbar spine, it is recommended to raise the legs on a special cube in order to straighten the lumbar lordosis. Unfortunately, operators sometimes neglect this, especially on densitometers with a short distance from the X-ray tube to the detectors, when the correct use of the device in obese patients is impossible. According to our observations, in some patients there is indeed no noticeable difference in the resulting scans. However, most often, failure to straighten the lordosis overestimates the BMD, and in some cases the last vertebra of the segment may be "hidden" in the projection of the vertebra located above and the sacrum, which complicates interpretation and worsens reproducibility. Anatomical features in the lumbar spine segment are not uncommon. An error in the numbering of the vertebrae will lead to the fact that the mineral density standards included in the reference databases will be applied to the vertebrae located above, and this will underestimate the T-criterion. Therefore, SYNARC recommends counting the vertebrae from below in atypical situations, taking the vertebra located above the sacrum as L5. The starting point of the scan, which determines the location of the ROI, is easily controlled and, if necessary, its position is corrected by a repeat scan. Since the patient's position along the axis of the device is determined visually, even with correct positioning, it may turn out that the position occupied by the lumbar segment is slightly different from that on the scan, with which it is important to compare. In cases with small deviations, the resulting scan is usually accepted for analysis by operators. We determined the effect of a 1.5 cm shift from the center of the ROI location during placement on the result. For this purpose, 15 scans of an anthropomorphic phantom of the L1-L4 vertebral segment were performed, located in the center of the scanning window and with a lateral shift of 1.5 cm (Table 1). Deviation from the central position led to a decrease in BMD by 0.06 g / cm2 or 0.61%. This effect is explained by an increase in the projection area of the segment. At the same time, the amount of mineral (g) in the segment did not change. The study was performed under "ideal" conditions, i.e. on a stationary object with a known mineral content at a constant thickness and composition of "surrounding tissues". In vivo, the effect of ROI shift could be greater. The measured difference in BMD values is small, but it should be taken into account that it is added to the usual parameters of accuracy and reproducibility. It is known thatthat due to the geometry of the fan beam, there are "edge effects" and other features that are overcome by the developers of densitometer software. The operator's task is to prevent a decrease in the metrological capabilities of the densitometer. The practice of densitometric studies shows that taking into account only quantitative indicators, which include the BMD, leads to the fact that in some cases osteoporosis remains undetected. For example, uniform compression of the vertebral bodies can remain unnoticed. At the same time, due to a decrease in the projection area of the L1-L4 section, the BMD values will be higher than in the previous examination, even in the presence of bone loss. This situation can be recognized by paying attention to the absolute amount of minerals (g) in the studied segment, the change in the projection area (cm2) and the height of the segment. Altered vertebrae cannot be used to diagnose osteoporosis: compressed, deformed, with traces of past injuries and surgical interventions, foreign inclusions and metastases. Diagnostics in the L1-L4 segment is carried out in the presence of 2 or more interpreted vertebrae. The densitometry results are presented in a report, the content of which is determined by the specialist conducting the study. Most specialists choose the option that includes all the indicators, but abbreviated versions are also possible. For doctors, the most interesting are the BMD and T-criterion. During dynamic observation, such indicators as the size of the ROI, the projection area of the site (cm2), the amount of minerals (g) can also be very important. Taking them into account will allow us to assess the reliability of the data obtained. A decrease in the height of the segment or individual vertebrae over the period between studies indicates the possible development of compression deformations.

CONCLUSION. The physician prescribing treatment for OP should inform the patient that its effectiveness can only be monitored using the same densitometer. The data obtained using the same densitometer will have to be compared “manually” and this can only be done by the operator, taking into account all the features of the first study. Even a software update on the same densitometer can affect the comparability of the results. Of course, there are algorithms for comparing the results obtained using different densitometers (HOLOGIC, LUNAR, NORLAND), cross-calibration procedures and formulas for recalculating readings are described, but they do not cover all the modifications released, cannot take into account all the technical features of densitometers and, moreover, factors introduced by the operator. If the patient's examinations were performed using different densitometers, and the need to have an idea of the dynamics of densitometric indicators is great, you can try to estimate the dynamics using the T-criterion. This approach is justified by the fact that all densitometers operating on the DXA principle (HOLOGIC, LUNAR, NORLAND) have been using a single NHANES III database since 2003, which includes ethnic groups of the US population. However, it should be taken into account that a small change in BMD can lead to a noticeable change in the T-score, since in accordance with the accepted standards, BMD is calculated with an accuracy of 0.001 g / cm2, and the T-score is up to 0.1. The compared areas should be the same, i.e. the ROI of the femoral neck is also oriented and have the same relative sizes. A lower location of the femoral neck area leads to an underestimation of BMD. The lumbar vertebral segment should consist of the same vertebrae in both studies and have no significant differences in the bone "map". These recommendations apply to a situation where dynamic monitoring is important. In the absence of osteoporosis and long intervals between examinations (several years), the current status is of decisive importance, not the dynamics. The data presented in the article do not mean that the accuracy and diagnostic value of modern densitometers are insufficient. For more than 30 years of improving osteodensitometers, from gamma-photon monoenergetic and dual-energy to X-ray with a point and fan beam, the accuracy of densitometers (1%) has not changed, and is unlikely to change soon. Ensuring the quality of the study and the correct interpretation of its results will always remain the main task of specialists. It is important that the high quality requirements imposed in international RCTs are maximally widespread in the practice of conventional densitometric studies.

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