Critical Evaluation of the Different Ultrasound Methods of Imaging Techniques applicable to the Bone

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Owing to changes in the age structure of the population, osteoporosis today is the most frequently occurring generalized skeleton disease. It belongs to the most common metabolic changes accompanying the aging process. Postmenopausal osteoporosis (type I) affects approximately one third of all women. However, both sexes sooner or later develop clinically relevant osteoporosis (type II) [1, 2].

Basic problems lie in the biochemical and mechanical changes occurring in the tissue and – resulting from it – in a loss of function of the locomotor system. Following more recent physiological findings, especially on collagen and its impact on bone loss, pertinent diagnostic methods are gaining importance [3–5].

Whereas low-frequency ultrasound transmission techniques, comparable to other X-ray bone density measurement methods, are used in order to determine bone mineral loss, high-frequency ultrasound methods, similarly to laboratory-chemically applied markers, render data on the properties of the organic matrix which contains high collagen portions.

The choice of the appropriate method should not only depend on medical aspects, but should also take into account economic aspects, i.e. effort and effect as well as affordability by the social insurance system.

The multitude of diagnostic options available for early detection of such alterations, i.e. for detection of changes before they become clinically manifest, already suggests that there are to date no pathognomically detectable parameters.

Substantial progress in early diagnosis seemed to have been scored when radiological and scintigraphical methods were developed, allowing determination of bone mineral structure. Due to the method applied, implementation of the so-called osteodensitometry was confined to specialists. Spread by the media, the diagnostic news created demand in the population, hardly sparing any doctor's practice. In the long run, however, this led to an increasingly critical evaluation of measurement methods and their affordability [6]. Today, SPA (single photon absorptiometry), DPA (dual photon absorptiometry), DEXA (dual energy X-ray absorptiometry) and QCT (quantitative computer tomography) continue to be in use whereas the first two methods have lost significance. DEXA and QCT, by contrast, are of practical relevance. The latter is the most sensitive and best method, however, it involves the highest rate of exposure to radiation [7]. In recent times, spiral-QCT has also gained importance. A variant of QCT applied to the peripheral skeleton (pQCT) involves less radiation. The advantage of QCT methods contains especially the differentiation between mineral density in both cortical and trabecular bone. One source of error, however, lies in the measurement of collapsed bone. Such measurement will yield false negative results.

In order to ensure comparability of measurement results, there must be reliable progress controls based on always the same method. Measurement errors can only be avoided if each examination is preceded by carefully recording medical history and clinical examination.

Methods solely based on measuring the attenuation of X-rays through bone hydroxylapatite yield a surrogate parameter for bone mass and bone strength, from which clinical conclusions are drawn by implementing mathematical methods based on standard deviations. However, this approach fails to consider the extremely important, all-supplying and all-connecting organic matrix which ensures both bone elasticity and quality. In recent studies, this aspect is being emphasized more strongly than before. The bone consists of an organic matrix which is strengthened and mechanically stabilised by a mineral phase. The organic matrix itself, which accounts for approximately 40 % of the dry weight, consists of 90 % of collagen type I and of 10 % of non-collagen proteins [4].

The organic or extracellular matrix, resp., of the connective tissue is derived from undifferentiated mesenchymal cells. It contains the following components:

- basic substance
- collagen and elastic fibres
- non-collagen proteins
- water

It has a connective, supportive, protective, informing, transporting and nourishing function. All local cells of the extracellular matrix descend embryonically from mesodermic mesenchyme cells, and hence there is a close connection between the dermis (skin) and the bone.

In order to avoid exposure to radiation completely and to nevertheless detect postmenopause-related physiological changes in the bone, as alternative physical techniques the ultrasound transmission method as well as the ultrasonic reflection methods have been introduced. They use mechanical waves instead of the electromagnetic waves of X-rays. The mechanical waves were formed by triggered oscillation of the individual material particles.

In the case of the ultrasonic *reflection method*, ultrasound waves are partly reflected at interfaces and at density variations of the examined medium, returning as echoing waves and hit the piezo-electric crystal as mechanical impulses. The crystal's thus triggered mechanical oscillations are converted into electric impulses. Based on the temporal course and the energy implied, the well-known A-mode (amplitude) and B-mode (brightness) images are generated. They are computerized so as to render C- or even 3D images. Over the past decades, the reflection method has proved its value in all medical disciplines and has become an indispensable diagnostic tool.

Due to the impedance properties of the examined medium, not all waves are reflected as echoing waves; parts of them travel further. This fact is taken advantage of ultrasound transmission methods which measure the transit time of this sound portion through the medium within the known distance between emitting and receiving probe.

Parameters of mechanical waves are wave frequency, i.e. the number of oscillations of particles per second, and wave length. The latter corresponds to the distance between two levels in which the particles are in the same state of movement, caused by the physical principle whereas wavelength is inversely proportional to frequency. High frequencies have short wave lengths with low penetration depths; low frequencies have large wave lengths with greater penetration depths. Since wave propagation behaves similar to light in terms of refraction, diffraction and scattering, the same regularities apply as in optics.

Transmission method: In transmission measurement (according to the Anglo-American nomenclature Speed-of-Sound (SOS) [8] or Broadband Ultrasound Attenuation (BUA) [9, 10]) a spectrum of sound waves of different frequencies is emitted from a transducer. Thereby a part of the waves is diffracted, absorbed, deflected or scattered away into the surrounding soft tissue and within the corticalis. Only a fraction, in the frequency range between 200 and 300 kHz, reaches the receiving probe directly and can be used for the evaluation of ultrasound transmission time (figure 1).

Osteoporosis type I mainly affects the trabecular bone. In the case of reduced cancellous bone or otherwise damaged trabecular bone, characterized, for example, by partially collapsed trabecular structures and deposited fat, sound propagation in the bone is of course slower. The difference between sound velocity in healthy bone tissue on the one hand (fast) and propagation of sound in defective bone tissue on the other hand (slow) serves as a reference for the degree of lesion. Example: Through intact trabeculae, sound will travel fast, in the case of deficient trabeculae, i.e. when there are depositions of organic soft material, sound will travel slowly.

Of course, appropriate for examination are only measuring sites at the bone where the probes have to be positioned in a reproducible and definite manner, e.g. at the patella. In the case of measurements, e.g. at the calcaneus, the transmission of sound is impaired by various acoustic impedances of different tissue structures. In detail, these read as follows:

- locally different distribution of densities;
- locally different geometric forms;
- locally different surfaces of the surrounding softer tissues equally ultrasound-exposed, such as skin, tendons and periost, as well as,
- due to locally different portions of compact and cancellous bone content.

Also the appearently achieved additional measurement improvement by means of water baths does not lead to a reduction of the above-mentioned sources of errors, as even minor differences in the water bath temperature will cause measurement errors.

Due to these facts, the term "Quantitative Ultrasound Measurement" (QUS) cannot legitimately be maintained. Thus also the results obtained to date do not show more than a moderate correlation to X-ray densitometrical methods [8, 10, 12, 13]. Similar arguments speak against the application of the ultrasound transmission technique at the finger and at the radius as measurement sites.

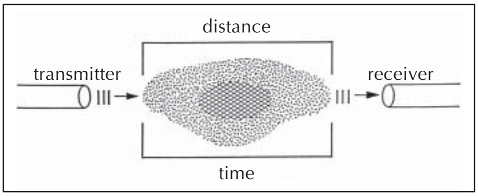

Figure 1. Ultrasound transmission method in patella (after [11], with Osteoson® KIV, Minhorst Company, Meudt, Germany)

Set against the reference values yielded by the radiological radiation-exposing methods, which we may consider "well established" [8–10], SOS, and BUA do not yield any correlating data in terms of age and clinical picture of osteoporosis.

The *reflection method* refers to the evaluation of collagen in the skin, especially in the dermis and at the dermal-subcutaneous interface. For a precise differentiation of epidermal, dermal and subcutaneous structures, a broad frequency band of > 20 MHz yielding an identification precision of 0.016 mm is emitted into the skin. The high portion of collagen and elastic fibres in the extracellular matrix (ECM) reflects the soundwaves more strongly than the surrounding medium will do, thus allowing to evaluate the connective tissue properties of the skin.

More recent findings show that connective tissue weaknesses entail high risks for the patients affected. This also concerns postmenopausal osteoporosis where, due to menopause-related ovarial insufficiency going along with declining estrogen production, the rate of collagen synthesis is reduced, which means that not only the connective tissue of the skin is affected, but also the organic bone matrix [12, 14–19]. For several years now, OSTEOSON® Skin Thickness Measurement (OST) for early diagnosis of the risk of osteoporosis has therefore become the prevailing diagnostic method in gynaecologic practices. This high-frequency and high-resolution sonographic reflection method has received an award from the German Menopause Society [15].

The OST-method not only produces images, but is also a highly accurate pachymetric measuring device, e.g. for quantifying the layer thicknesses of the skin and of the vessel walls. Further it is not only an appropriate early warning and risk evaluation system regarding connective tissue degeneration and suspected osteoporosis (correlation between the rate of collagen synthesis both in the skin and in bone matrix), but it is also suitable for progression control under cortisone treatment and HRT.

Undeniably the skin is a very sensitive, endocrine organ, with its properties depending noticeably on the estrogen level [16, 20–22]. Since both fibroblasts, myoblasts, chondroblasts, osteoblasts and osteoclasts derive from the embryonic parent tissue collagen and collagenic structures – irrespective of their localisation – according to today's view are considered to be of major importance concerning the development of osteoporosis [23, 24]. Both nutrition and stabilization of individual bone trabeculae are conditioned by collagen fibres in the bone; because bone formation and resorption solely depend on the metabolism in the organic matrix. Collagen originates from the basic substance, a mucopolysaccharide protein complex, as well as from tropocollagen. The latter is considered a component of collagen fibres of type I. They are responsible fo r the formation of a dense network – the intercellular matrix. The term collagen is derived from ancient Greek and stands for "glue-producing".

In a net-like manner, collagen envelops the built-up deposited mineral substance. Together they form the equally **elastic** and hard substance of the bone. In this process, both pH value and electrostatic processes play an important role: The specific charge is responsible for bone formation and for bone resorption. This is why physical exercise is so important in order to prevent osteoporosis. In the pathogenesis of osteoporosis and especially of post-climacteric osteoporosis, a decline in the estrogen level plays an important part. This also means that in case of insufficient estrogen production in juvenile age this will lead to an insufficient formation of bone substance. Consequently at this time already, the formation of bone substance has to be set on the right track.

Estrogen deficiency in adolescents leads to insufficient formation of both collagen substance and bone mineral substance. The demineralized bone still contains 90–95 % of collagen, whereas the skin contains 68–72 %. Both systems are comparable in their formation and resorption activity regarding their metabolic dependence on estrogens. With high frequency ultrasound (> 20 MHz) an accurate recognition 0.016 mm precise and identification concerning the epidermis, corium and dermal-subcutaneous interface is possible (cf. figure 2).

In clinical chemistry, similar methods are now being adopted for evaluation of osteoporosis by determining hydroxyproline and pyridinium cross links, which reflect the amount of disassembled collagen directly via urine analyses.

Just like sole measurement of the bone, sole evaluation of collagen does not suffice to establish a clear diagnosis of osteoporosis or to determine a fracture risk. Comparable to the cases of other imaging methods, also in this case one further diagnostic mosaic piece of significant importance to the patient is found concerning the early detection of this metabolic change. Considering the individual anamnestic findings, the today therapeutic methods available can be used for treatment.

Personally conducted long-term examinations show furthermore that OST, similar to osteodensitometry, offers monitoring options allowing economization of the entire therapy (figure 3).

The positive effect of parathormone and of adrenaline as well as of estrogen and testosterone on the skin is well-known [14]. The glycosaminoglycan content of the connective tissue increases under estrogen therapy. Thus the content of hyaluronic acid, i. e. of the largest glycosaminoglycan, increases. The hence increased water content of the skin can easily be seen from an improved skin turgor, especially in women under hormone replacement therapy.

Experiences gathered to date regarding the sensitivity and specificity of the

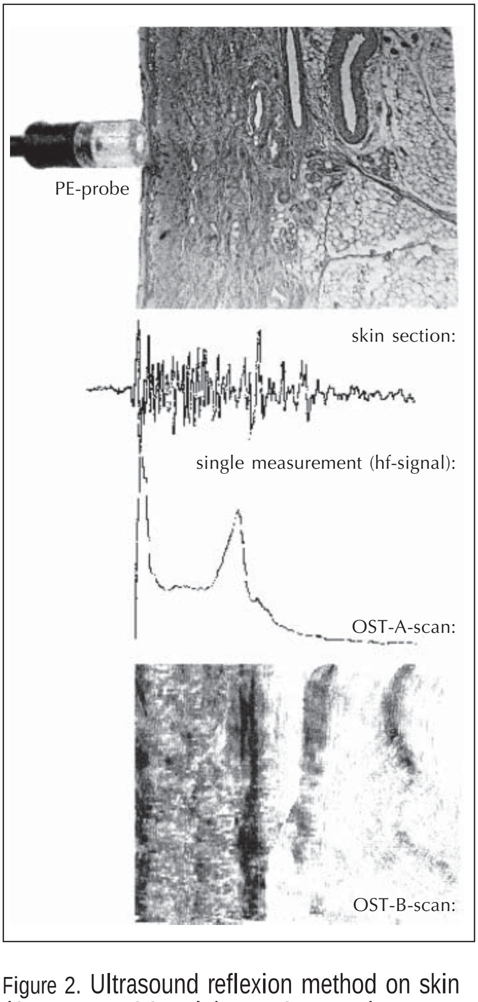

Figure 2. Ultrasound reflexion method on skin (Osteoson DCC, Minhorst, Germany)

OST method, when based on the individual anamnestic findings show that satisfying predictions can be made [17, 25–27] (figure 4). Direct comparison with other methods is only allowed to a limited degree.

Regarding these physiological and pathophysiological considerations, high

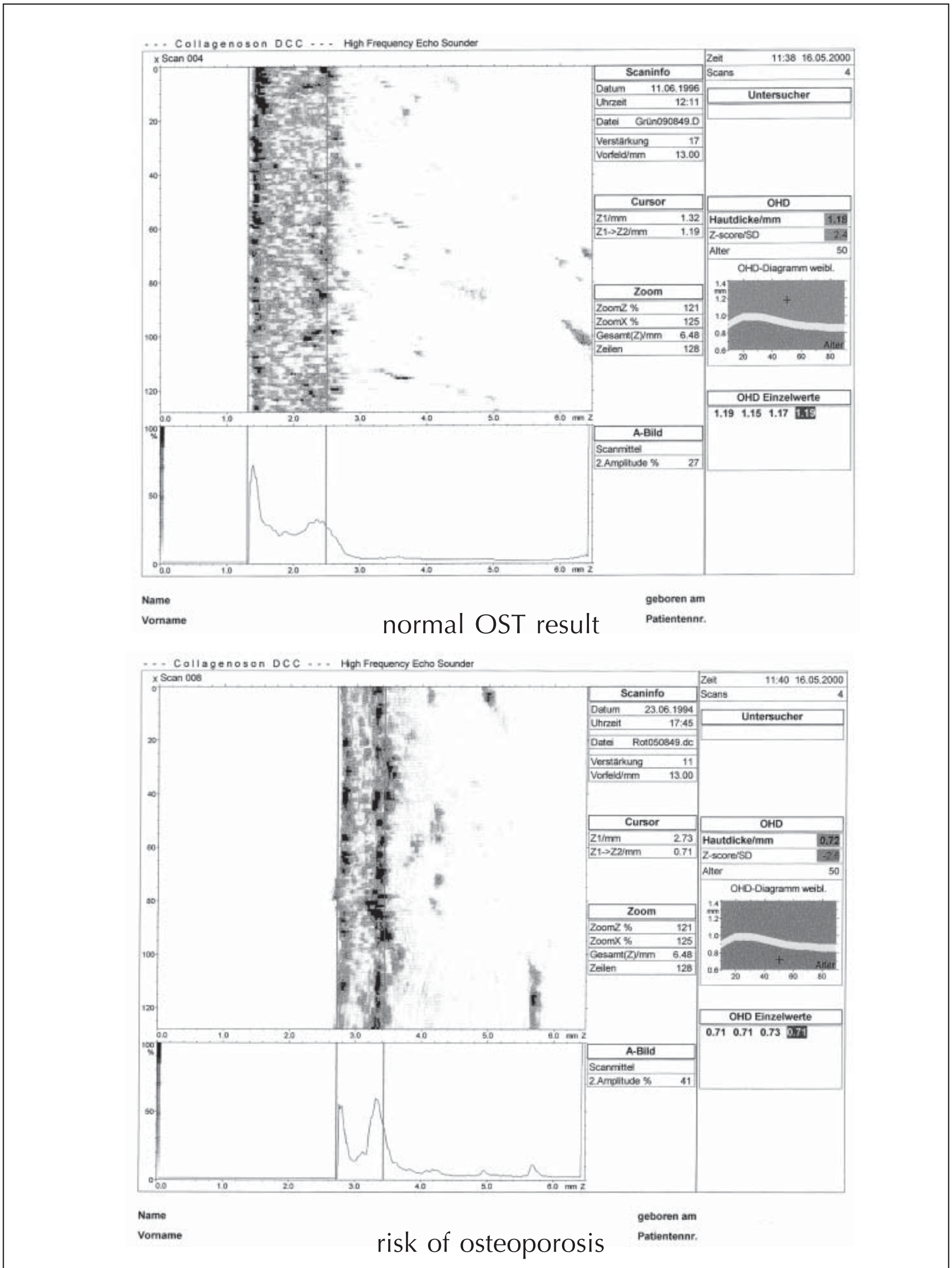

Figure 3. Evaluation of osteoporosis risk with A- and B-mode (skin)

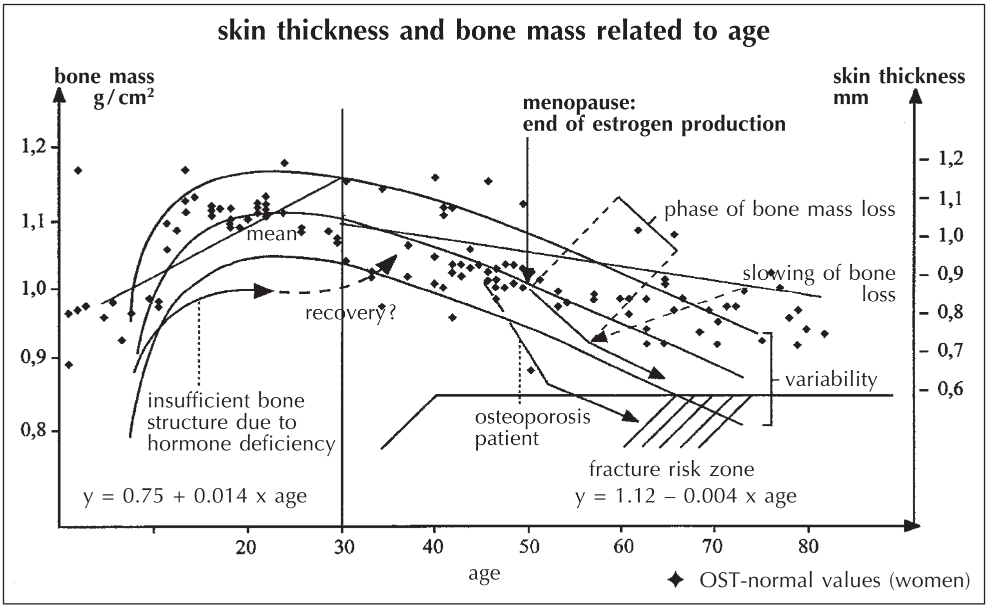

Figure 4. Safety of forecast with the OST-method (after [18] and [28])

frequency ultrasound methods will have their fields of application and will make determined statements concerning individual cases of potential osteoporosis.

Conclusion

Among the classic methods, QCT is undeniably the best method for determination of bone mineral content, although it involves high radiation exposure.

Biochemical markers indicate loss of collagen.

The high frequency and high sensitive ultrasound reflection OST-method evaluates collagen properties in the organic matrix at defined measurement sites of the skin and allows, irrespective of the age, a very early entry into the right diagnosis with the chance for prevention. At the same time, especially concerning HRT monitoring, it offers the possibility of a more dense therapy control. In older patients, the choice of low hormon dose may not change bone mineralisation immediately measurable, but bone nutrition and elasticity can be improved by noticeably increased collagen content. Only much later an increase in bone mineralization can be detected by means of bone density measurement methods. The knowledge of the individual medical history as well as the clinical evaluation and interpretation of obtained measurement results, in conjunction with the knowledge concerning the successful use of sexual steroids and of other widely known therapeutic tools, are the gynaecologist's indispensible help for responsibly enhancing their patients' quality of life.

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