Comparison of quantitative bone ultrasound and osteodensitometry in different metabolic osteopathies

1. Introduction

According to demographic studies, the population is rapidly increasing worldwide and the estimated life expectancy is put off. This change will result in growing of diseases depending on age in the next decades. The prognosis shows an extremely increase of osteoporotic fractures. In 2050 the number of hip fractures will be four times more than it was in 1990; the affected persons will be 6.26 million in comparison with 1.66 million. All this data reveal that metabolic bone diseases are considered widespread disease in our ages.

The bone mineral content decreases in metabolic bone diseases. Determining bone mineral content for the diagnosis of metabolic bone disease is crucial, because these diseases do not cause any specific symptoms. The measurement of bone mineral content is important because bone mass is the most significant factor predisposing bone fracture, however other factors are also influence fracture risk. The remaining factors are the changes of bone architecture and bone quality. It is more correct to state that the increased bone fragility caused by the heterogeneous changes affecting loading capacity. The osteodensitometry using photon absorption to determine bone mineral density is the first line method for the diagnosis of osteoporosis. However, there are increasing need for other methods which are able to measure other determinants of bone fragility, than bone mass alone. The quantitative bone ultrasound method tries to fill the above mentioned requirements.

In my dissertation I discuss the quantitative ultrasound method. I discuss some aspects of the metabolic bone diseases, and then I describe my methodical investigations. Later on I show the usefulness of quantitative ultrasound on diagnosis of calcipenic bone diseases and on fracture risk prediction. At the end of my thesis some short chapters discuss the changes of quantitative ultrasound and densitometric parameters in diseases affecting bone metabolism.

My work may help to acknowledge this diagnostic method. Taking into account that this method is differ from osteodensitometry in methodical features, in the procedure of the medical/biological information gathering and in the information content.

2. Aims

The calcipenic osteopathies are important diseases for the patients and for the population also, because they affect several persons and they have serious and costly consequences: the increased bone fragility and the increased fracture rates. The endocrine system which preserve extracellular calcium level and the regulation of mechanical properties of bone are affect the same mechanism, that is bone remodelling. Therefore the abnormality in one system affects the other also. Nowadays it is obvious that
the decreased loading capacity is caused by decreased bone mass and deteriorated bone quality.

Osteodensitometry is fundamental for the diagnosis of metabolic bone diseases. This is a non-invasive method to determine bone mineral content in a precise and accurate way.

Architectural and quality parameters are also important predicting bone fragility. These parameters can be determined by several methods. According to theoretic considerations and results the quantitative ultrasound is one of these methods. The method could objectively determine bone quality in its complexity. The data are promising for the understanding of the process of bone fracture and to recognise patients with high risk of bone fracture. Therefore I chose this topic in my investigations. We have examined this method in vivo and in vitro and the diagnostic application in different calcipenic osteopathies in comparison with osteodensitometry.

The aims of the investigations:
1. to determine the accuracy of the different quantitative ultrasound devices in Hungary and to compare them in clinical circumstances
2. to accomplish cut off values for heel ultrasound devices on the analogy of photonabsorptiometric cut off values determined by WHO study groups
3. to determine the possible differences of QUS parameters between the left and right heel taking the densitometric values and hand dominance into consideration
4. to apply the quantitative ultrasound
   4.1. recognising osteoporosis
   4.2. fracture risk prediction
   4.3. vertebral deformity prediction
5. to determine quantitative ultrasound parameters and osteodensitometric results in different conditions affecting bone metabolism
   5.1. among smokers
   5.2. among patients with primary hyperparathyroidism
   5.3. among patients with chronic hemodialysis
   5.4. among postmenopausal women suffering from pollen allergy

3. Patients and methods

3.1. Patients
The patients were enrolled in our studies from the osteology/ endocrinology outpatient department of 1st Department of Medicine. They were recruited from Budapest and from Hungary. The data which characterise the patients are shown in the Results chapter of the thesis.

3.2. Diagnostic methods
Osteodensitometry

The measurement of bone mineral density was carried out in the Osteodensitometry Laboratory of the 1st Department of Medicine. The bone mineral density (BMD, g/cm²) means the amount of minerals divided by area scanned by the electromagnetic radiation. The BMD was determined at lumbar II-IV vertebrae and femoral neck by dual photon absorptiometry method (DXA). DPX-L (Lunar, Madison, WI, USA) device was used at the lumbar vertebrae (coefficient of variation was 0.67%) and at the left femoral neck (coefficient of variation was 0.68%) and PIXI device (Lunar, Madison, WI, USA) was applied at the heel (coefficient of variation was 0.91%). The forearm bone mass measurements were carried out by single photon absorptiometry method (SPA) by NK-364 device (Gamma, Budapest, Hungary, coefficient of variation was 2.1%) and by DXA method by pDEXA (Norland-Stratec, Fort Atkinson, WI, USA) at the distal third of the forearm. All devices automatically calculated the Z-score value, which means a comparison of the measured value to the average value of the gender and age matched healthy population expressed by standard deviation. T-score values means a comparison of the measured value to the average value of the gender matched young healthy population expressed by standard deviation. Diagnostic criteria were determined according to the World Health Organisation (WHO) recommendation. Normal density was determined if T-score value was higher than -1.0. Osteopenia was diagnosed if T-score was between -1.0 and -2.5. Osteoporosis was diagnosed if T-score was lower than -2.5.

Quantitative bone ultrasound

DBM Sonic Bone Profiler (IGEA, Capri, Italy) measures at the non dominant side at the proximal phalanges II-IV, near to the distal metaphysis. The measurement occurs at one point. The contact is established by gel. The measured parameter is amplitude dependent speed of sound (AdSOS).

Achilles Express (Lunar, Madison, WI, USA) device measures in room temperature and dry medium. The contact medium between the source / detector and the patient's leg is gel (dry device). Under the device's membrane water layer assures the transmission of ultrasound. Broadband ultrasound attenuation (BUA) and speed of sound (SOS) are directly determined during the measurements and the Stiffness value is automatically calculated by the device.

Achilles InSight (Lunar, Madison, WI, USA) is a newly developed four generation device. The device uses dry contact medium and 500 KHz ultrasound. Under the contact medium a membrane covered water layer appears. The contact between the heel and the device can be assured by gel as well as by isopropyl alcohol 70%. The device automatically determines the BUA and SOS and calculates the Stiffness index.

Sahara (Hologic, Waltham, MA, USA) device has fixed source and detector and uses 0.2-0.6 MHz frequency ultrasound. Gel contact media is applied. Heel BUA and SOS are determined. The device calculates the stiffness or quantitative ultrasound index (QUI) which is used to estimate bone mineral density (estimated BMD, eBMD, g/cm²).
DTU-ONE (Osteometer, Roedove, Denmark) device is working in room temperature water bath with fixed source and detector distance without automatically water changing system. It applies 0.3-0.65 MHz frequency ultrasound. The device generates a scan about the calcaneus and a manual or an automatic determination of the region of interest can be performed. This area is used for BUA and SOS determinations.

Laboratory methods
Parathyroid hormone level (PTH) was determined by measuring the intact molecule using electrochemiluminescence immunoassay (ECLIA, Roche, Elecsys) method. Serum 25-OH vitamin D3 level was measured by two different methods: at the end of our studies high pressure liquid chromatography (HPLC, Bio-Rad, München, Germany) method was used, and at the beginning RIA technique was applied. Serum dehydroepiandrosteron-sulphate (DHEA-S) level was measured by RIA. Parathyroid hormone level (PTH) was determined by microparticular immunoassay using Abbott device. Serum Osteocalcin measurement was performed by N-MID Ostecalcin (OC) ECLIA kit (Roche Diagnostic GmbH, Mannheim, Germany) and type I collagen C-terminal crosslinks (β-CTx) level was measured by β-CrossLaps CalSet immunoassay (Roche Diagnostic GmbH, Mannheim, Germany). The above mentioned measurements were performed by Elecsys 2010 (Hitachi, Japan) device. The basic laboratory tests were made by EKTCHEM 750 XRC device. Serum and urine calcium level were measured by colorimetry, serum phosphorus was determined by ammonium molibdate reaction, alkaline phosphatase (ALP) was measured by P-nitrophenyl-phosphate reaction, bone specific alkaline phosphatase (bALP) was determined by lektin-precipitation, serum and urine creatinine were measured by modified Jeffe-reaction. Calcium excretion was expressed by the ratio of urine calcium /creatinine.

Radiologic studies
Thoracic and lumbar vertebrae were X-rayed from two directions, according to the standard protocols. Lateral scans were focused on the thoracic VII and lumbar II vertebrae, the tube distance was 120 cm. Vertebral deformities were determined according to the Minne's method. The anterior, medial and posterior high of the thoracic IV-XII. and lumbar I-IV. vertebrae were measured. Radiomorphometric index values were calculated (vertebral deformity index, VDI). Variation coefficients were calculated for a vertebra (standared deviation divided by mean) for anterior high (1.46%) middle (2.42%) and posterior (2.25%) high.

Statistical methods
Our results are shown as number (n), means, standard deviation (SD) of the mean, standard error (SE) of the mean. One and two sample t-tests and Mann-Whitney tests, variance analysis, Chi-square test, Pearson correlation test, linear regression test were used and Odds-ratio was calculated by SPSS version 10.0 (Chicago, IL, USA) statistical programme. Statistical significance was determined by p<0.05.
4. Results

4.1. Precision of five quantitative ultrasound devices operated in Hungary

Precision error was determined in vivo and in vitro. The phantom made by the manufacturer for the daily calibrations was measured eleven times after reposition during the in vitro studies. The same measurements were performed without repositioning the phantom, if the device's software allowed this protocol. In vivo precision error was determined measuring 14 patients (7 healthy and 7 osteoporotic) three times at the same day. If it was possible the measurements were made with and without reposition. All the measurements were made by the same operator.

The in vitro precision errors had never exceeded 2%. The Achilles Express and Achilles InSight devices allowed the measurements without repositioning the phantom. We found that reposition elevated the CV% both for BUA and SOS values.

In vivo studies by Achilles InSight showed 0.34% for SOS values and 3.19% for BUA and 2.92% for stiffness without reposition. The following data were calculated after reposition: 0.67%, 4.56%, 3.49%, respectively.

4.2. Quantitative bone ultrasound for the diagnosis of osteoporosis

192 women (37-69 years) and 41 men (33-72 years) were enrolled in our first study. Lumbar spine, left femoral neck and radius bone density were measured and heel QUS parameters were determined by DTU-ONE device. According to the T-score values normal (T-score >-1.0), osteopenic (-1.0 >T-score >-2.5) and osteoporotic (T-score < -2.5) groups were distinguished. The arrangement in groups was made for the spine density, femoral neck density and radius density, separately. The BUA and SOS values of these groups were compared after variance analysis by t-test. Both the BUA and the SOS differed between the normal and osteoporotic groups, and in most cases the osteopenic group distinguished from the other two categories.

Similar observational study was made among 106 women (28-69 years) and 44 men (23-72 years) separately. 30 women and 20 men suffered from bone fracture in the past. Osteodensitometry was performed by DPX-L and NK-364 devices, and QUS measurements were made by Achilles Plus at the heel. The patients' groups with normal or pathologic values determined by osteodensitometry always differed in QUS parameters. Sometimes the osteoporotic and osteopenic groups had divided. Fractured and non-fractured subjects had significantly differed in BUA (women : 107.2±2.2 vs 97.9±2.4 dB/MHz, p<0.01; men 121.2±3.9 vs 106±4.0 dB/MHz, p<0.05) and in SOS (women : 1558±4.4 vs 1538±6.5 m/s, p<0.05; men 1590±11.7 vs 1540±12.1 m/s, p<0.05) in both gender.

4.3. Quantitative ultrasound for fracture risk determination

The relationship between QUS results and bone fractures were examined among patients described in chapter 4.4 (106 women and 44 men). Logistic regression analysis of densitometric and QUS values
proved the independent effect of heel stiffness on fracture risk.

Odds ratio (95% confidence intervals):  
- Women: 2.09 (1.2-3.66)
- Men: 2.12 (1.2-3.76)

Area under the ROC curve:  
- Women: 0.716 (0.583-0.849), p=0.004
- Men: 0.803 (0.641-0.965), p=0.007

After this study we had an opportunity to examine the relationship between fractures and QUS and osteodensitometric parameters in an enlarged patients' group. QUS measurements were performed in 537 women (mean age ± SE 57.8±1.5 years, mean BMI ± SE 25.5±0.41 kg/m2) at the heel by DTU-ONE and at the proximal phalanges by DBM Sonic. Femoral neck, lumbar spine and radius bone mineral density were also measured. 163 patients suffered from bone fracture (78 forearm, 3 hip region, 61 other sites). 21 patients had known about vertebral compression fracture. 413 postmenopausal women were separately analysed (mean age ± SE 59.5 ± 0.5 years, mean BMI ± SE 25.9 ± 0.32 kg/m2) and 137 bone fractures were found.

Taking all patients into consideration both heel BUA T-score (-2.58 vs -1.82, p<0.05) and lumbar spine T-score (-2.5 vs 1.44, p<0.05) were lower in patients with vertebral fracture than in patients without vertebral compression. Subjects with forearm fractures had lower QUS parameters at the phalanges than their non-fractured counterparts (AdSOS T-score -3.04 vs -2.63, p<0.05). Femoral BMD mildly differed between fractured and non-fractured without significance (0.772 vs 0.803, p=0.803), however, the small number of cases did not allow to draw conclusion from this result. Similar results were found among postmenopausal women.

The regression analysis resulted the following Odds-ratios in women; for femoral neck T-score: 1.2 (CI 95% 1.04-1.38), in vertebral compression for lumbar spine T-score: 1.44 (CI95% 1.09-1.89), heel SOS 1.32 (CI95% 1.05-1.74), in forearm fracture for phalangeal AdSOS: 1.17 (CI95% 1.02-1.34). Similar observations were made among postmenopausal subjects.

4.4. Quantitative ultrasound for assessing the risk of vertebral deformity

Bone density and non-mass bone parameters were examined in 117 men (mean age ±SE 56 ±0.8 years). Osteodensitometry, QUS (DTU-ONE) and vertebral morphometry were made. According to the WHO criteria the patients were divided into osteoporotic (n=25), osteopenic (n=58) and normal (n=58) groups by bone densitometric results.

No differences were found in age (57.1±2.1 vs 56.7±1.1 vs 56.0±1.5, respectively, p=0.89). The BUA values also differed in the three groups (p<0.0001) which were established according to the densitometric results. BUA in the in the osteoporotic group (mean ±SE 39.79±1.64 dB/MHz) were lower than in the osteopenic subjects (mean ±SE 45.2±0.99 dB/MHz) (p=0.02) and lower than it was found in the normal subjects (mean ±SE 50.92±1.23 dB/MHz, p<0.0001). No differences were revealed in SOS values.

Patients with vertebral deformities did not differ in BUA values from their non-fractured
counterparts (mean ±SE 44.96±1.14 dB/MHz vs 46.34±1.05 dB/MHz, respectively, p=0.38). In contrary
the SOS values were lower in patients with vertebral deformity. Further grouping was made and we
have compared the fractured and non-fractured patients by BMD, BUA and SOS values in the
osteoporotic and normal groups. Bone density and BUA did not differ between groups.

SOS was lower among patients (n=15) whose bone mineral density was within the normal range,
however they had suffered from vertebral deformities (mean±SE: 1538.9±5.8 m/s) than among those
non fractured patients whose BMD was normal (mean±SE: 1558.8±2.3 m/s, p=0.01). The same
observation was made among osteoporotic subjects with or without vertebral deformities (mean±SE:
1539.9±4.2 vs 1553.4±4.1 m/s, p=0.03). In conclusion we state that SOS value is able to differentiate
between groups with or without vertebral fractures.

In a further analysis we have examined the relationship between QUS and densitometric parameters.
Correlation coefficient between lumbar spine BMD and BUA was 0.43 (p<0.001), between femoral
neck BMD and BUA it was 0.55 (p<0.001) and between forearm BMC and BUA the correlation
coefficient was 0.43 (p<0.001). In contrary, no correlation was found neither between lumbar spine
BMD and SOS (r=0.13, p>0.1), nor between femoral neck BMD and SOS (r=0.16, p=0.08), and forearm
BMC also did not correlate with SOS (p>0.05).

We have determined the Odds-ratio to reveal the predictive value of QUS parameters to vertebral
fractures. The decrease of SOS by 1 SD multiplied the risk of vertebral fractures by 1.56 (95%CI 1.08-
2.62). Neither age, nor BMI changed the relationship between the two parameters (1.50 95%CI: 1.02-
2.22). Fracture risk was independent from lumbar spine BMD (1.43 95%CI: 0.6-1.52), from femoral
neck BMD (1.41 95%CI: 1.02-2.17) and from radius BMC (1.32 95%CI: 1.02-2.0).

4.5. Comparative evaluation of local and international reference databases in forearm
densitometry: Different impact for diagnostic decisions

Reference databases play a key role in the management of osteoporosis. The aim of the study was to
compare diagnostic consequences of using an international and a local reference database in
peripheral densitometry. For this purpose standard curves for bone mineral density at the distal and
proximal forearm by dual-energy X-ray absorptiometry were generated in healthy Hungarian men
and women.

In total, 303 healthy volunteers of both sexes aged 20-90 years were recruited in 4 Osteoporosis
Centres. Subjects having conditions or taking a drugs affecting bone metabolism were excluded.
Bone densitometry was performed using pDEXA (Norland-Stratec) devices of each centre after
cross-calibration of the machines. Precision error of the forearm measurement was also determined
(less than 1% in vitro, and 1.2%-2.5% in vivo, respectively).

In females, the peak of the forearm density was detected in the 30-39 years group. The density
decreased by 8% per five years in early postmenopausal females and 10% per ten years in late
postmenopausal females. In males, the highest bone mineral density was found in the 30-39 years
group for the distal forearm but one decade later for the proximal site followed by 5% decrease of
density per 10 years except the 8th decades showing 20% decrease.

1434 patients with suspected osteoporosis were classified by T-score on the basis of forearm
densitometry using both the new Hungarian reference database and the international database
provided by the manufacturer. The distal forearm measurements resulted in similar outcomes by the
two reference curves. However, at the proximal site one fifth of female patients were moved from
the low density groups to the normal group using the domestic normative database. An inverse
difference was observed in the males: the use of the Hungarian reference data resulted in 40% more
men with osteoporosis than the use of the international normal values.

Our results suggest that not only the geographic differences but also the origin of the
reference database influence the prevalence of osteoporosis.

4.6. Modifying WHO thresholds worked out for osteodensitometry in heel quantitative
ultrasound measurements
1574 women (age: 53.3±11.7 ys) and 363 men (age: 49.8±13.7 ys) were enrolled. Quantitative
ultrasound measurements at the heel were performed by different different devices: 293 women were
investigated by Sahara device and 1166 women and 284 men were measured by DTU-ONE. 465
women and 19 man were examined by DBM Sonic at the proximal phalanges and the speed os sound
was measured. The enrolled patients were split into „osteoporotic” (T-score ≤ -2.5) and non osteoporotic
(T-score > -2.5) groups according to the osteodensitometric results (spine, femur, radius). QUS
parameters were analysed by three different T-score threshold values (-2.5, -2.0, -1.0 and 0) to
determine sensitivity and specificity in comparison with osteodensitometry. Our results showed that
phalangeal SOS T-score below -2.0 considered the patients osteoporotic with 80% or even better
sensitivity and with 40-50% specificity taking the pathological DXA and SPA results as a basic. DTU
BUA cut off values were between -1.0 and -2.0 (specificity 60-70%). Sahara stiffness-like (QUI) T
scores were considered pathological below -1.0 (specificity 50%). T score of speed of ultrasound at the
heel below -1.0 showed pathological values by 40% sensitivity, however below 0 the sensitivity was
between 60 and 90%.

Similar study was performed by Achilles InSight bone ultrasound. 507 women (age [mean±SE]:
56.0±7.3 ys) were investigated. The values of sensitivity (70-80%) and specificity (60%) revealed that -
1,5 T-score should be threshold for the diagnosis of osteoporosis.

4.7. Comparison of quantitative ultrasound parameters and bone minera density at the left- and
right- hand-side considering the hand dominance.
Femoral bone mineral density and heel quantitative ultrasound parameters were measured in 106 women (age 28-68 years) and 44 men (age 23-72 years) at the left- and right-hand side.

Hand dominance was determined by questionnaire. Lower limb dominance was appointed to the dominance hand side, as it is usual in the every day practice. (E.g.: right leg was considered dominant in a man with right hand side dominance). Patients with diseases of calcium and bone metabolism and anatomic disorders of the lower limb were excluded from the study. Patients with risk factors of osteoporosis were also dropped out. Prior bone fractures were explored by questionnaire. Age of menopause was assessed and according to the data premenopausal and postmenopausal groups were established.

The premenopausal group included 42 women (age 28-57 years) and the postmenopausal group consisted 64 (age 44-68 years) subjects. Right hand dominance was found among 73% of the entire study population and left hand dominance was in 27%, accordingly. Mild, but significance difference was found between the two side in calcaneus BMD (0.504±0.009 vs 0.496±0.009 g/cm², p=0.001), BUA (109.9±1.5 vs 105.6±1.5 dB/MHz, p<0.001) and in QUI (89.3±1.8 vs 85.9±1.8 g/cm², p<0.001) considering all the enrolled subjects. However, we have not found difference neither in femoral neck BMD (0.931±0.01 vs 0.925±0.01 g/cm², p=0.261) nor in calcaneus SOS (1558.6±3.8 vs 1557.4±4.9 m/s, p=0.749). Heel BMD, BUA and QUI were larger at the non-dominant side in all cases.

We have proved that the differences were not derived from the precision error of the device. Knowing the precision error of all devices we have calculated the last significant changes (LSC, LSC=2.8 x CV%). LSC for the femoral neck BMD was 1.9%, for calcaneus BMD it was 2.55% and for calcaneus QUI the LSC value was 2.8%. We have expressed the percentage difference between the two side using the following mathematical formula: ((dominant – non-dominant) / (mean of dominant and non-dominant)) x 100%. The results were compared to the LSC of the given skeletal region measured by the same device applying t-test. The percentage differences differences between the two side of femoral BMD, calcaneus BMD and QUI were: 5.0±0.35%, 5.88±1.45% and 5.6±3.39%, respectively. All this values exceeded the LSC (femoral BMD p=0.001, calcaneus BMD p=0.001, calcaneus QUI p=0.001).

Heel BUA and stiffness values were larger at the non-dominant side than they were at the dominant side both among men and women. In the group of women the calcaneal BMD at the non-dominant side exceeded the value of dominant side. Femoral neck BMD and heel SOS have not differed between the two sides neither among women nor among men. The above mentioned differences were found both in the pre and postmenopausal groups. Fractured and non-fractured women differed only in SOS values at the dominant side (1529±6.5 vs 1547±5.2 m/s, p<0.05).

4.8. QUS parameters and bone density in different diseases influencing bone metabolism
The most interesting application of the QUS methods are the different calcipenic osteopathies which influence the organic and inorganic component of bones by different ways. How the BUA and SOS values changed in this diseases where the decreased bone density is well known and what kind of
relationship could be developed between these parameters and the background of this disorders.

4.8.1. Comparison of QUS and bone density parameters among smoker women

Osteoporosis is a multifactorial disease in most cases. In involution period several several risk factors add and drive to the bone disorders. One of these factors is smoking. Both smoking and osteoporosis affect was majority of peoples, therefore it could be interesting to examine the relationship between them.

45 smoker women were enrolled into our studies (age 25-72 years). These patients were compared with age and antropometric parameters adjusted non-smoker women. The subjects did not have any disease or risk factors influencing calcium and bone metabolism. Questionnaire was used with targeted questions of low trauma fractures in the past. Bone mineral density and QUS parameters (Achilles InSight) were determined. Age of menopausa was also assessed, and pre and postmenopausal subgroups were developed. 13 smoked and 12 non-smokers women suffered from low trauma fractures in the past.

BUA, SOS ans stiffness did not differed between smokers and non-smokers, however, smokers had slightly lower values. Moreover, this finding revealed in the pre- and postmenopausal groups separately.

Bone mineral density differed between the two groups, smokers had significantly lower density at the lumbar spine and slightly lower values were measured at the femoral neck and radius. In the postmenopausal group the difference was more obvious. The difference at the lumbar and femoral site achieved the significance.

Among fractured postmenopausal patients we had made a comparison of QUS and BMD parameters between smokers and non-smokers. Lower SOS was measured in the group of smokers (1508.9 vs 1525.3 m/s, p=0.01). BUA and regional BMD values did not differ, stiffness was slightly lower among smokers than among non-smokers. Similar finding was not revealed in the group of premenopausal patients.

4.8.2. Parameters describe bone quality and quantity in primary hyperparathyroidism

136 patients with primary hyperparathyroidism (pHPT) were enrolled: 97 postmenopausal women (mean age±SD 66.43±8.6 years), 23 fertile women (mean age±SD 39.44±12.3 years), and 16 men (mean age±SD 65.3±9.72 years).

Basic laboratory parameters characterised pHPT. No differences were found between groups. Fractured patients were almost in the same rate among fertile women (2/23) and men (1/16), however higher fracture rate was found among postmenopausal patients (29/97).

BUA was pathological at the heel (DTU-ONE) among postmenopausal women (mean±SE T-score -2.67±0.61) and men (T-score -2.32±0.51). At the phalanges (DBM Sonic) low values were determined both among postmenopausal women (AdSOS T-score -3.84±0.69) and men (T-score -3.73±0.71). However, SOS had not showed difference neither in postmenopausal women (T-score -0.47±0.12) and men (T-score -0.40±0.13). No pathological QUS values were measured in fertile women nether at the
heel (BUA T-score -1,4±0.85, SOS T-score -0,47±0.13) nor at the phalanges (AdSOS T-score -1,61±0.2).

Measuring the BMD values in every group pathological low BMD was revealed at the radius (T-score -3,19±0.33) and at the femur (T-score -3,62±0.41) among men and slightly lower bone density was found at the lumbar 2-4 vertebrae (T-score -1,91±0.41). Radius and femoral neck BMD differed between fertile women and men, but no difference was found between postmenopausal women and men.

4.8.3. Bone ultrasound measurements at the phalanges in chronic haemodialysed patients

Diagnosing renal osteodystrophy accompanying chronic renal insufficiency is a target for osteodensitometric measurements. In the past the secondary and tertier hyperparathyroidim, osteomalatia dominated the pathophysiology, however, nowadays revealing adynamic bone disorders is more frequent. In this disease increased bone fragility was found beside slightly decrease bone mineral density.

32 haemodialysis patients and 21 gender, age and antropometric parameters adjusted healthy controls were investigated by QUS at the phalanges (DBM Sonic), moreover, osteodensitometric measurements were made at the spine, femoral neck and at the radius diaphysis. Routine and specific parameters characterizing calcium and bone metabolism were determined. All patients had normal calcium level, therefore tertier hyperparathyroidism was excluded.

AdSOS was lower among patients with chronic renal insufficiency in both genders than among healthy controls. Femoral neck BMD was lower in haemodialysis patients in both gender, however, the difference in lumbar spine bone density was revealed only among the group of women. In women the phlangeal AdSOS and age negatively correlated (r=-0.647, p<0.001), and positive correlation was found between AdSOS and femoral neck and forearm density (r=0.524, p=0.006; r=0.364, p=0.05, respectively), and between AdSOS and bone specific alkaline phosphatase (r=0.692, p=0.05). Among men the correlation between AdSOS and age and AdSOS and forearm bone density correlated at the level of significance. Femoral neck bone density positively correlated with AdSOS (r=0.571, p=0.002).

4.8.4. Bone quality and quantity parameters in postmenopausal women sufferig from pollen allergy

Some data suggest that enhanced histamine release may have adverse effect on bone metabolism, however, the pathomechanism is not fully understood. The mast cell is one of the important cells in the pathogenesis of allergic disorders and most allergic symptoms are associated with histamine release.

One hundred and twenty five postmenopausal women with pollen-allergy (mean age±SE: 61.26±0.57 years) were recruited from allergologist's practice for this cross sectional study. The diagnosis of allergy was based on characteristic clinical and laboratory findings (skin prick tests, specific IgE assays). Forty-
three allergic women received neither inhaled corticosteroids nor H1R antagonist. Fifty-three allergic women were treated only with H1R antagonist. Seventeen allergic patients received both H1R antagonist and inhaled corticosteroid. Twelve allergic women were treated only with inhaled corticosteroid.

One hundred non-allergic subjects served as controls, matched for age, body mass index (BMI) and age at menopause to the allergic subjects. Potential participants in both allergic and non-allergic control groups with secondary causes of osteoporosis or those on medication likely to affect skeletal metabolism were excluded.

Bone mineral density was measured for all allergic patients and controls at lumbar spine, left femoral neck and at radius add QUS parameters at the heel (Sahara) was also determined. The WHO guidelines were used for categorisation. BMD were categorised as normal (T-score 1.0 or above), osteopenia (T-score between −1.0 and −2.5) or osteoporosis (T-score 2.5 or below). Diagnosis of osteopenia or osteoporosis was set up if T-score values were lower than −1.0 or ≤2.5 at one or more measured sites.

Distal forearm, hip and vertebral fractures with clinical symptoms (validated by morphometry) resulting from mild to moderate trauma (typically a fall to the floor from standing height or less), occurred within ten years, confirmed by medical record were considered low-energy fractures.

Untreated allergic had almost triple the rate of prevalent low-energy fractures (34.9%, 15/43, 12 distal forearm, 1 clinical vertebral and 2 hip and fractures) compared to non-allergic women (13%, 13/100, p=0.003).

Allergic patients without treatment had significantly lower T and Z-scores at the femoral neck (T-score: -1.93±0.12 vs -2.33±0.13, p<0.05, Z-score: -0.27±0.09 vs -0.67±0.13, p<0.01) and most other DXA and QUS parameters were lower (not statistically significant) in them in comparison with non-allergic controls. Osteopenia was diagnosed more often among untreated pollen-allergic women than among controls and normal bone density was not found at all in the former group. No differences were found between allergic patients receiving H1R antagonist treatment and non-allergic controls neither in DXA nor in QUS results. Furthermore, some results of the allergic patients were slightly higher. Modest correlation was found between QUS and DXA results at all measurement sites (range, r=0.276 to r=0.584) in non-allergic controls, in untreated and H1R-only treated allergic women. However, no correlation was revealed between QUS and DXA results in corticosteroid treated allergic subjects, irrespectively of H1R antagonist treatment.

In the control group BMI-adjusted values for a 1 SD reduction in lumbar 2-4 vertebral T-score predicted prevalent low-energy fractures with significant (p=0.034) odds ratios of 2.01 (95% CI, 1.06 to 3.82). More fractured patients were found with higher BMD in the untreated allergic group. Neither DXA, nor QUS values were able to predict bone fractures in any allergic groups. Fractured control patients had lower lumbar and forearm BMD and QUS values. In contrast, the fractured untreated pollen-allergic patients did not differ from non-fractured untreated allergic women neither in BMD at
any skeletal sites, nor in QUS values. The fractured allergic women were, however, older, more obese and they had earlier menopause than their non-fractured counterparts. The fractured untreated allergic women had higher lumbar BMD and higher lumbar T-score than the non-allergic non-fractured women. The non-fractured allergic patients were younger and they had lower femoral neck Z-score than the non-fractured control patients.

VI. Conclusion and new statements
1. Our observations showed that the in vivo quantitative bone ultrasound examinations also had two or three fold greater precision error for all the parameters than the in vitro tests measuring the phantom. Variation coefficients for SOS were lower both in vivo and in vitro than for BUA, because SOS values were in narrower range among the examined population. Our results confirmed that the QUS method also had precision error which derives from positioning the phantom or the examined part of the body, similar to DXA method.
2. The different quantitative ultrasound methods have not the same T-score threshold values which clinically distinguish the normal and osteoporotic subjects, measuring by DXA, with an appropriate sensitivity. The results are almost the same in the two genders, therefore we expect the same threshold values in men as they are in women. Our studies sowed, that we should determine the T-score thresholds for each QUS methods.
3. We have shown that the bone mineral density were different between the two side at the distal part of the lower limb similar to the difference at the forearm. It is important to mention that SOS at the heel which reflects the elasticity did not differ between the two side, however BUA which correlate with bone mass showed similar difference to bone density.

Our observation has practical consequences for the diagnosis of osteoporosis measuring the peripheral bones at the lower limb by QUS or DXA methods. We should not randomly choose the measured side, but to determine according to hand dominance or according to a general consensus. Moreover we should assess the results according to a side specific T-score thresholds.
4. We have found that quantitative bone ultrasound clearly distinguishes between subjects with normal or pathological bone density. Therefore, the method is able to diagnose osteoporosis based on bone quantity. QUS results differed between healthy and fractured patients with osteoporosis for peripheral fractures, independently from bone density. Our results revealed that 1SD decrease of Stiffness at the heel was accompanied by two fold fracture risk.
5. No difference was revealed between men with or without vertebral deformities in bone density and BUA values, however SOS values, reflecting bone elasticity, were lower among men with vertebral deformities. Our data showed that bone elasticity have grater role in vertebral fracture development, than bone mass among men.
6. Beside the well known effect of smoking on bone metabolism we have shown the adverse effect on bone quality among postmenopausal subjects.
7. Previous data showed increased fracture risk in primary hyperparathyroidism. The risk correlated with age and duration of disease. However, fracture risk did not mainly depend on bone loss. Our results revealed that PTH effect did not drive to bone fracture characterized by change in bone quality.

8. We found that QUS measurements at the phalanges are equivalent by DXA measurements at the hip in patients with chronic renal insufficiency to diagnose calcipenic osteopathy. Therefore we recommend the QUS method in the every day practice in this patient group.

9. Surprising result was that neither bone density nor QUS were able to predict the increased fracture risk among patients with allergic rhinitis. Further studies are indicated.