New considerations on the management of osteoporosis in Central and Eastern Europe (CEE): summary of the “3rd Summit on Osteoporosis—CEE”, November 2009, Budapest, Hungary

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Abstract

Introduction In November 2009, the “3rd Summit on Osteoporosis—Central and Eastern Europe (CEE)” was held in Budapest, Hungary. The conference aimed to tackle issues regarding osteoporosis management in CEE identified during the second CEE summit in 2008 and to agree on approaches that allow most efficient and cost-effective diagnosis and therapy of osteoporosis in CEE countries in the future.

Discussion The following topics were covered: past year experience from FRAX® implementation into local diagnostic algorithms; causes of secondary osteoporosis as a FRAX® risk factor; bone turnover markers to estimate bone loss, fracture risk, or monitor therapies; role of quantitative ultrasound in osteoporosis management; compliance and economical aspects of osteoporosis; and osteoporosis and genetics. Consensus and recommendations developed on these topics are summarised in the present progress report.

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Conclusion Lectures on up-to-date data of topical interest, the distinct regional provenances of the participants, a special focus on practical aspects, intense mutual exchange of individual experiences, strong interest in cross-border cooperations, as well as the readiness to learn from each other considerably contributed to the establishment of these recommendations. The “4th Summit on Osteoporosis—CEE” held in Prague, Czech Republic, in December 2010 will reveal whether these recommendations prove of value when implemented in the clinical routine or whether further improvements are still required.

Keywords Bone turnover markers · Central and Eastern Europe · Diagnosis and therapy of osteoporosis · FRAX® · Quantitative ultrasound · Secondary osteoporosis

Introduction

Osteoporosis is one of the most widespread chronic illnesses. In Europe, the prevalence of vertebral osteoporosis averages out at approximately 12% [1]. With an estimated population of 250–350 million people in Central and Eastern Europe (CEE), up to 42 million individuals are affected by this incriminating condition and its far-reaching consequences. Considering this huge number of patients, osteoporosis causes an enormous financial burden to this region. Particularly, costs for the treatment of fragility fractures and their sequelae, including disability or work loss, contribute to these expenses [2, 3]. Hence, reliable diagnostics and early interventions to reduce the incidence of fractures are vital not only to reduce the patients’ burden but also to decrease treatment and follow-up cost.

Despite comprehensive improvements in the knowledge of osteoporosis and its management, in countries of CEE as well as elsewhere, there are still significant gaps in awareness and prevention. The regularly held “Summits on Osteoporosis—CEE” approach these very issues.

With regards to contents, the major aim of the last conference (“2nd Summit on Osteoporosis—CEE”, Warsaw, Poland, November 2008) was to identify and discuss state-of-the-art diagnostic, prophylactic and therapeutic measures used in CEE countries to prevent and treat osteoporosis. Based on the information gained, issues concerning the management of osteoporosis in these countries were identified to provide the basis for the development of suitable support and development strategies [4, 5]. Building up on this information, the “3rd Summit on Osteoporosis—CEE” in Budapest, Hungary, in November 2009 was meant to eventually tackle these issues. Issues involved:

- Past year experience from FRAX® implementation into local diagnostic algorithms;
- Causes of secondary osteoporosis (SOP) as a FRAX® risk factor (new);
- Bone turnover markers (BTMs) to estimate bone loss, fracture risk or monitor therapies;
- Role of quantitative ultrasound (QUS) in osteoporosis management (new);
- Compliance and economical aspects of osteoporosis (new);
- Osteoporosis and genetics (new);
- Consensus and recommendations for the clinical practice.

Representatives from CEE to non-CEE countries took part. Besides those who had already participated in the second summit in 2008 (Austria, Czech Republic, Hungary, Poland, Romania, Slovakia, Slovenia), several new countries joined the conference in 2009 (Belgium, Bulgaria, Italy, Serbia, Switzerland, Russia, Ukraine). Through this, the sphere of influence of this conference considerably broadened. In addition, it mirrors the increased interest in this clinical field in CEE as well.

In the current progress report, conclusions and recommendations developed during the “3rd Summit on Osteoporosis—CEE” are summarised. The report is structured according to the intention of the distinct lecturers to present either pro or contra positions on the selected topics.

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Summary and conclusions of the “3rd Summit on Osteoporosis—CEE” in November 2009

Past year experience from FRAX® implementation into local diagnostic algorithms

The session started with a short introduction on the development, advantages and disadvantages of FRAX® by Hans P. Dimai, Graz, Austria. He pointed out the clear relationship between bone mineral density (BMD) and fracture risk that facilitates the use of BMD as a predictive factor for the development of osteoporotic fractures. This approach, however, has two drawbacks: Its predictive value is rather low in general [6] and its sensitivity further decreases with the patients’ increasing risk and age. To achieve a higher sensitivity that is not affected by age, additional clinical risk factors independent of BMD, e.g. prevalent rheumatoid arthritis, smoking or excessive alcohol consumption, have been added to the evaluation. Through this, an algorithm could be developed that allows predicting the absolute 10-year fracture risk with a much higher predictive value than the evaluation of BMD or clinical risk factors alone [7, 8].

The algorithm is now widely available and well known as FRAX® and is available free of charge at www.shef.ac.uk/FRAX®. After calibration of the FRAX® algorithm to local hip fracture and death rates, it is applicable to any geographical region. This has already been done in 26 countries worldwide, with Argentina and New Zealand joining just recently. In addition, FRAX® is already recommended by local diagnostic guidelines in Canada, UK and the USA and is mentioned in guidelines in Austria and Germany. Still, FRAX® has to deal with one drawback: Although several local retrospective analyses and prospective cohort studies exist, FRAX® has not been validated in a prospective randomised clinical trial. However, deliberations on this point made clear that even with the existing validated risk factors, the algorithm of FRAX® is already stretched to its limits regarding the prediction of fracture risk. Certainly, implementation of further risk factor such as spine BMD, cortisone dosage, falls, biochemical markers, etc. would be desirable. However, one should be aware that these factors have not been included into the algorithm simply because the data used for FRAX® development did not allow calculation of the fracture risk of these factors.

The subsequent discussion revealed that nearly 50% of the summit’s participants are interested in the use of FRAX® and would appreciate the incorporation of FRAX® in their local guidelines for the diagnosis and treatment of osteoporosis. The discussions at the “2nd Summit on Osteoporosis-CEE” in 2008, however, disclosed that in most of the CEE countries, implementation of FRAX® was thwarted by the lack of reliable local fracture data for the country-specific adjustment of the model. At the present summit, numerous remarks from the audience made clear that the situation has not considerably changed yet. In this regard, Prof. A. Dimic from Serbia reported that physicians in his country are well aware of FRAX®’s value but that reference data from countries with comparable fracture risk rates have still to be used—a situation unfortunately true for several other CEE countries also in 2009.

Several participants from other countries gave accounts of their experiences with FRAX®. Italy reported that FRAX® is still not widely used particularly because users would prefer to have access to the FRAX® algorithm and to be allowed to immediately enter new local data into the FRAX® system. Through this, the outcome of FRAX® would constantly improve in terms of local adaptation. Approaching this need, software is now offered free of charge in Italy, which facilitates the input of local data directly into the Italian FRAX® algorithm. A participant from Poland reported that prediction data calculated by FRAX® 10 years ago was just recently confirmed with a high significance by real data [9]. In Ukraine, FRAX® is starting to be used in larger medical centres. Turkey attempted to enter local fracture data into the FRAX® algorithm. Compared to fracture rates in other countries, however, their rates are extremely low and, therefore, these epidemiology data are suspected to be unreliable. Germany shared the observation that fracture rates vary substantially between individual federal states. In this regard, several participants from different countries called attention to their concern that one reference data set per country might not be sufficient because regional differences in culture, lifestyle, nutrition, health awareness, health care standards, etc. may produce regionally different fracture risks within one country.

In conclusion, the interest in FRAX® is high but its implementation, both in the clinical routine and in local guidelines, is still delayed by the lack of reliable local fracture data in most CEE countries. Therefore, assessment of country-specific fracture data from trustworthy databases is highly recommended. As reports on practical experiences from several countries demonstrated, the understanding of the benefits to limitations of FRAX® is essential for its optimal use. In addition, it was generally agreed that the predictive value of FRAX® for fracture risk outranks that of exclusive BMD measurement, but that FRAX® will never replace T-scores for the diagnosis of osteoporosis. And, most importantly, good clinical judgement should ultimately determine who should be treated and in which way.

Causes of SOP as a FRAX® risk factor

SOP is defined as bone loss and increased fracture risk caused by a specific disease or medication. Approximately
20% of all osteoporotic postmenopausal women suffer from SOP, 50% of premenopausal osteoporotic women and 75% of osteoporotic men [10]. Jan Stepan (Prague, Czech Republic) and Edward Czerwinski (Krakow, Poland) commented in their speeches on the pros (J. Stepan) and cons (E. Czerwinski) of whether FRAX® should be applied in patients suffering from SOP and how causes of SOP do qualify as risk factors for fracture risk evaluation by FRAX®.

Jan Stepan started with a critical comment: “In 40–65% of the patients evaluated by FRAX® secondary causes of osteoporosis are diagnosed. However, why there are only four secondary causes of osteoporosis (glucocorticoid use, rheumatoid arthritis, current smoking and excessive alcohol use) explicitly mentioned in the FRAX® tool?” His response was that these are the four causes that carry a fracture risk not related to BMD. That means, FRAX® evaluates patients with one of these risk factors as at risk for fracture independent of their BMD.

Another ten causes of SOP have been implemented into the FRAX® algorithm by subsuming them in the point “Secondary osteoporosis” [type I (insulin-dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease; www.shef.ac.uk/FRAX/]. However, since these factors affect BMD, evaluation of the fracture risk by FRAX® in patients exhibiting one of these factors is solely based on BMD values. Only when BMD is not entered does FRAX® evaluate the fracture risk related to these ten factors. Besides these, several other causes of SOP are known. Whether these factors affect BMD or not is not entirely clear because data are still sparse. Therefore, they have not been implemented in the FRAX® algorithm yet. Prospectively, these disorders should be incorporated into risk assessment algorithms when they are more adequately characterised.

Finally, Jan Stepan approached two issues that might be raised by critical FRAX® users. Fracture risk increases with the number and severity of previous fractures [11]. Why does FRAX® calculate only an average fracture risk independent of number and severity of prevalent fractures? Similarly, bone architecture is an important parameter of bone quality and, hence, fracture risk [12]. Why have such data not been entered into the FRAX® tool? The rationale for this approach in the FRAX® algorithm is supported by data from a recent study [13]. There, it was shown that independent of whether you enter spine fracture data (FRAX®, only hip data), number and severity of previous vertebral fractures and spine deformity index to the standard risk factors as they are used in FRAX®, the general fracture risk does not change. Similarly, in the FRAX® tool, low body mass index (BMI), a well-recognised risk for fracture, does not contribute to risk if BMD is known because association of thinness with fracture is largely through BMD. Fracture risk in patients with known BMD paradoxically decreases as BMI decreases, apparently because of increased mortality associated with low BMI.

From the presented facts, Jan Stepan concluded that only well-recognised and relevant causes of SOP (BMD-affecting and BMD-not affecting) have been included into the FRAX® algorithm. The approach to SOP is explained by BMD subsuming the risk in the model’s prediction equation. Therefore, FRAX® is suitable for fracture risk evaluation in patients suffering from SOP.

In contrast, Edward Czerwinski’s critical statements did not support the use of FRAX® for fracture evaluation in patients suffering from SOP. He criticised that in the FRAX® tool, only 14 causes of SOP are mentioned, whilst there are actually 71 as listed in the “Report of the Surgeon General, US, 2004” [14] despite the more than 100 drugs which also affect bone mass. In addition, fracture risk coefficients of these causes of SOP vary considerably (e.g. smoking, 1.8 [15]; diabetes mellitus I (insulin-dependent), 6.3 [10]; plasmocytoma, 9.0 [10]), and these differences are not considered in FRAX®. Furthermore, in rheumatoid arthritis and glucocorticoid-treated patients, T-scores from the spine are much more relevant for fracture risk assessment than hip data. On the other hand, with regard to secondary osteoporosis, the FRAX® site states: “Enter yes if the patient has a disorder strongly associated with osteoporosis. These include type I (insulin-dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease”.

Another critical comment concerned the fact that after 10 months of glucocorticoid therapy, BMD decreases by 8% [16]. FRAX® is not able to consider such a rapid bone loss because it evaluates only the 10-year probability of fracture. Also, dose and time of glucocorticoid therapy positively correlate with bone loss [16], a fact also not taken into account in the FRAX® algorithm. Finally, FRAX® ignores the risk of falls, the most important risk factor for non-spinal fractures (90–100%). Risk of falls, however, is often increased in SOP, e.g. caused by rheumatoid arthritis, due to joint impairment [17]. Therefore, according to Edward Czerwinski’s estimation, FRAX® is not an appropriate tool for the management of SOP because too many aspects relevant for fracture risk evaluation in such patients are not or only insufficiently covered.

The subsequent discussion revealed that 76% of the audience would not use FRAX® for fracture risk evaluation
in patients with SOP. Points of criticism were that fracture risks for causes of SOP (e.g. glucocorticoids) as calculated by FRAX® are too low; dose and time of a glucocorticoid treatment are not taken into account in the algorithm, as well as numerous drugs and conditions affecting bone mass and risk of falls; spine data are highly relevant but are missing; and despite for rheumatoid arthritis only insufficient epidemiologic data on the fracture risk of other causes of SOP are available, fracture risk evaluation by FRAX® is suitable only for patients suffering from SOP because of rheumatoid arthritis.

Members from the summit’s board commented that most of these issues arise from the fact that risk rates per factor have been developed on the basis of one specific study population. Consequently, therapies/disorders not or hardly represented in this population could not be identified as risk factors just because of the lack of data. As soon as more comprehensive epidemiological data on these causes of SOP and their fracture risk are available from comprehensive prospective studies, the FRAX® algorithm can be updated. In addition, the board members warned that FRAX® is only meant for the determination of fracture risk and not as treatment rationale or to decide on the type of treatment. In fact, FRAX® should be only one component of the decision process in addition to a comprehensive consideration of other clinical and patient-related parameters.

To summarise the outcome of this session, FRAX® should be applied with caution in SOP patients (with the exception of rheumatoid arthritis) because currently, only insufficient epidemiologic data on the fracture risk of most causes of SOP (except rheumatoid arthritis) are available. As soon as fracture risk data of these causes of SOP are available from comprehensive prospective studies, they might be implemented in the algorithm. In general, in diseases causing increased fracture risk primarily through low BMD, FRAX® can be used, whereas in conditions not primarily acting through BMD, FRAX® may not be applicable. Above all, 10-year fracture risk as estimated by FRAX® should not be used as a pharmacological treatment threshold, but treatment thresholds should be tailored individually.

BTMs to estimate bone loss, fracture risk, or monitor therapies

BTMs are used for the biochemical monitoring of bone metabolism. By measuring enzymes and proteins produced during bone formation and of degradation products released during bone resorption, a sensitive assessment of the rate of bone formation and resorption is facilitated. Vladimir Palicka (Hradec Králové, Czech Republic) outlined where and how BTMs can be useful in the diagnosis and management of osteoporosis (pro), whilst István Takács (Budapest, Hungary) spoke about their drawbacks (contra).

In the beginning, Vladimir Palicka made clear that BTMs on their own are not suited for the diagnosis of osteoporosis. However, in the context of differential diagnostics, they are very useful. In addition, they could help detect prevalent bone loss or, in some cases, even predict rapid bone loss in the near future—information that cannot be given by any other marker. Some studies described that women with BTM values above the premenopausal range have an increased fracture risk independent of age and BMD. Hence, BTMs seem also to have some predictive value regarding fracture risk [18].

BTMs are of proven significance in monitoring the effect of antiresorptive agents on the bone metabolism of osteoporotic patients. To some extent, BTMs can even predict the efficacy of such treatments: The greater the effect on BTMs at the beginning of an antiresorptive therapy, the greater the treatment response in terms of BMD changes will be [19, 20]. Such information may be used by physicians to enhance the compliance of their patients: Lack of changes in BMD in the beginning of a therapy can hamper the patient’s motivation; telling them that BTMs already improved in response to the treatment could convince them to continue taking their drugs. However, there is no evidence-based study supporting this hypothesis. Another advantage of BTMs is that they deliver the quickest response when compared to any other treatment efficacy marker (e.g. BMD) [21]. In addition, measuring BTMs is the only way to distinguish between the effect of a certain therapy on bone ana- or catabolism and, hence, to estimate the therapeutic window. BTMs could also be of some help in drug selection. Vladimir Palicka stated that based on plenty of study data, the general opinion is that antiresorptive therapies should be given to patients with very high bone turnover whilst osteoanabolic therapies to patients with very low bone turnover. He summarised that all these features make BTMs indispensable tools for the management of osteoporosis.

Finally, Vladimir Palicka mentioned new biochemical markers such as osteoprotegerin (OPG), receptor activator of NF-κB ligand (RANKL) and cathepsin K, and one genetic marker, the vitamin D receptor (VDR) genotype. Levels of OPG and RANKL change under bisphosphonate therapy, and the effect on OPG positively correlates with changes in BMD. Expression of cathepsin K significantly correlates with fracture risk [22]. Polymorphism in the VDR genotype influences the efficacy of various anti-resorptive drugs [23]. Overall, data are promising, but final confirmation of the validity of these new indices of skeletal metabolism has still to be provided.

These positive statements on the significance of BTMs in the diagnosis and management of osteoporosis were
opposed by the critical remarks by István Takács. Basically, there are three issues associated with the use of BTMs: theoretical problems, practical difficulties, and questionable results. One theoretical problem is that BTMs are not as "exact" as we expect them to be. For example, the expression of serum type I procollagen is not absolutely bone-specific, or osteocalcin, actually used as a bone formation marker, is also released from bone during the resorption process. Another problem is that BTMs can reflect the general process of bone turnover only when the bone is in a steady state, e.g. during senile osteoporosis, because BTMs show only the acute situation. As soon as bone processing changes, BTMs are no longer predictive regarding bone loss/bone formation.

Practical difficulties involve within-patient variability generated by uncontrollable and controllable factors. Uncontrollable factors, like age, gender, menopausal status, recent fracture as well as comorbidities and concomitant medication, have to be taken into account when interpreting BTM levels. Frequently, however, no appropriate reference ranges are available for these factors (e.g. age) or variability is rather high (e.g. comorbidities, concomitant medication). Controllable factors such as circadian rhythm, fasting, seasonal changes, menstrual cycle, exercise or quality of sample storage can also have a strong impact on BTM levels measured. Quite often, however, they are difficult to control and therefore can further hamper the validity of BTM results. Another practical aspect that is particularly problematic is diagnostics of BTM: For one BTM, several different test assays are used, within-laboratory variations are considerable, and literally no standardisation exists. Altogether, this results in BTM data not comparable to each other [24, 25].

Finally, although the interrelation of BTM levels and fracture rates or treatment outcome has been confirmed in many studies, there are still several open questions. What is the proportion of the anti-fracture effect explained by the fall in the BTM level? Are BTMs equally predictive of vertebral and non-vertebral fractures? How should we interpret the observations that some antiresorptive drugs have similar effects on bone turnover regardless of pretreatment BTM rates or that fracture risk reduction of two drugs is comparable although they affected BTM levels to different extents? Summarising his presentation, István Takács asked for better markers, reduction of the pre-analytical and analytical variability and more data from clinical studies before BTMs can safely be used in clinical practice.

Based on this comprehensive information on the pro and cons of BTMs, the audience and the expert panel agreed that BTMs may be useful in monitoring the effect of an osteoporosis therapy and that they can be helpful in increasing the compliance of the patients. In combination with BMD and other patient-related factors, BTMs can improve the assessment of fracture risk and, hence, assist clinical decision making. However, BTMs are not suited for the diagnosis of osteoporosis and selection of the appropriate treatment. To further increase the value of BTMs, standardisation of analytical methods is urgently required.

Role of QUS in osteoporosis management

Currently, measurement of BMD via dual-energy X-ray absorptiometry (DXA) is the method of choice for the diagnosis of osteoporosis and fracture risk estimation. Recently, QUS came up as a potential alternative. The significance of QUS in the detection and management of osteoporosis, however, is still a matter in dispute. Didier Hans, Lausanne, Switzerland, and Ádám Balogh, Debrecen, Hungary, approached this issue and highlighted the pros (Didier Hans) and cons (Ádám Balogh) of the use of QUS in osteoporosis management.

Didier Hans started with the observation that QUS for osteoporosis management seems not to be acknowledged much in the clinical practice. In his opinion, this is mainly due to the lack of information on several aspects important for the use of QUS in this area. Hence, the aim of his talk was to provide this missing information, thereby increasing the awareness for the value of QUS in osteoporosis management.

The only validated skeletal site for the clinical use of QUS in osteoporosis management is the heel. There are numerous ultrasound devices for heel measurements on the market. They, however, differ substantially with respect to the algorithm used, the parameters they measure, the strength of empirical evidence supporting their use, and validation. Consequently, QUS measurements from technologically different devices cannot be directly compared. Rather, appliances should be independently validated for fracture risk prediction by prospective trials or by demonstration of equivalence to a clinically validated device. Hence, for a successful QUS evaluation in the clinical practice, measurements should be performed only at the heel and only with properly validated devices.

In which areas of osteoporosis management might QUS be applicable? Using validated heel QUS devices, there is satisfactory evidence (>80 cross-sectional and/or prospective studies) that QUS can predict fracture risk of postmenopausal women (hip, vertebral and global fracture risk) and men over the age of 65 (hip and all non-vertebral fractures) equally as well as DXA and independent of central DXA BMD. In contrast, employing QUS for the diagnosis of osteoporosis is somehow problematic. The reason for this is that the WHO diagnostic classification applied to DXA T-scores cannot be used for QUS because QUS T-scores are not equivalent to T-scores derived by
DXA [26]. Approaches to overcome this dilemma require appropriate conversion equations and predefined, device-specific diagnostic thresholds; these, however, are still in development.

Whilst the initiation of an osteoporosis therapy should not be based exclusively on QUS measurements, Didier Hans suggested that heel QUS in conjunction with clinical risk factors combined into a probability model involving device-specific thresholds can be used to “pre-screen” a population: Individuals identified with a very low fracture probability might not require further diagnostic evaluation; in case of higher fracture probability, the patient can be referred to a DXA centre. In other words, QUS data might be seen as an additional clinical risk factor that supports decision making regarding the initiation of an osteoporosis therapy. Such an approach seems to be of particular importance because currently, 80% of the European population at risk have never been diagnosed or even been tested for fracture risk because they have no access to DXA. Finally, QUS can currently not be recommended for monitoring the treatment response in patients with osteoporosis due to the lack of supportive large-scale clinical trials.

Ádám Balogh started with the features of an appropriate diagnostic tool for osteoporosis. Besides a conceptually sound and transparent technology, it should be suitable for the diagnosis of osteoporosis and able to predict fracture risk at relevant fracture sites, easy to use and precise, deliver results that are comparable to those of other devices, free of environmental influences such as temperature or contact media, without harm for individuals or the environment and reimbursed by health insurance systems.

DXA is affected by the environmental temperature and is based on radiation. Other than having these limitations, it fulfils all of the above expectations. Furthermore, it has an extra advantage of being able to detect prevalent vertebral fractures with acceptable precession using the Vertebral Fracture Assessment (VFA) software within the session of traditional DXA measurements. VFA is approved by international organisations, e.g. the International Society for Clinical Densitometry. Regarding QUS, this method can predict fracture risk, but its applicability for the diagnosis of osteoporosis, decision making in terms of treatment initiation and monitoring of treatment efficacy is rather limited. Compared to DXA, QUS stands out due to its non-radiation technique, easier application and less costly implementation; costs for this diagnostic procedure, however, are quite often not reimbursed, unlikely to be the case with DXA. Finally, results from different QUS devices are not comparable.

After comparing these two methods, Ádám Balogh concluded that instead of choosing one of the two diagnostic technologies, the paradigm of fracture prediction will change with the use of the more complex approach of FRAX® which integrates data of DXA (and QUS) and validated clinical risk factors to achieve a more efficient management of osteoporotic patients.

To summarise the outcome of this session, the most validated skeletal site for the clinical use of QUS in osteoporosis management is the heel. QUS measurements from technologically different devices cannot be directly compared and many available devices have not yet been validated. Validated heel QUS devices, however, can predict fragility fracture risk in postmenopausal women and men over the age of 65 independently of central DXA BMD. QUS is not suitable for the diagnosis of osteoporosis since the WHO diagnostic classification is based on DXA T-scores which are different from QUS T-scores. QUS cannot be used to monitor the skeletal effects of an osteoporosis treatment. The future perspective of QUS in osteoporosis management might involve the measurement of heel QUS in conjunction with clinical risk factors to pre-screen a larger population for potential fracture risk that might then be confirmed by DXA. Here, DXA has the extra advantage of being able to detect prevalent vertebral fractures with superior precession (VFA software). The experts and the audience agreed that in the future, the FRAX® system should be used for fracture risk assessment with inclusion of DXA and QUS data.

Compliance and economical aspects of osteoporosis

As a chronic disease often associated with limiting complications and consequences, osteoporosis is not only a treatment- but also a very cost-intensive condition. Therefore, decision making on diagnostic and therapeutic measures to prevent or treat osteoporosis has to also involve economic considerations. Gerold Holzer, Vienna, Austria, approached this economical aspect of osteoporosis management by putting a special focus on the impact of patient compliance on cost effectiveness.

Cost effectiveness analyses compare the costs and health effects of an intervention to assess whether it is reasonable from an economic point of view. A study by Kanis et al. [27] demonstrated that alendronate is cost-effective when used for the prevention and treatment of osteoporotic fractures in postmenopausal women with clinical risk factors (assumed price of alendronate, £90/year). Needless to say, fracture probabilities at which individual treatments become cost-effective are directly correlated to the drugs’ price and, therefore, vary considerably. For example, in a 70-year-old patient, risedronate is cost-effective when the patients has a 10-year fracture risk of 16% (evaluated by FRAX®), whilst the less expensive alendronate already becomes cost-effective at a fracture risk of 8% [28].

Using costs of osteoporosis therapy in Austria, Holzer contrasted direct costs (acute care and rehabilitation) of hip fracture treatment to expenses for osteoporosis management. The former added up to 133 million euros per year, the latter to
comparably low 42.5 million euros per year. In CEE countries [29], annual costs for hip fracture management range from a minimum of 584.00 euros (Slovakia) to a maximum of 6,000.00 euros (Hungary), whilst differences in cost of, e.g. annual alendronate (min, 230.00 euros; max, 354.53 euros) or teriparatide (min, 3,500.00 euros; max, 6,469.62 euros), are more comparable. Still, in all evaluated CEE countries, expenses for fracture treatment exceed those for osteoporosis therapy. Obviously, for a precise calculation, number needed to treat values should be taken into consideration.

As a chronic disease that is asymptomatic until a fracture occurs, osteoporosis is quite often associated with rather low compliance rates [30–32]. Besides price and efficacy of a drug, this can also have a significant impact on the cost effectiveness of an osteoporosis treatment. This was shown by Ström et al. [33] who pointed out that in addition to fracture risk, anti-fracture drug effect and drug price also reduced drug effectiveness due to poor compliance and offset time as potentially important drivers of cost effectiveness. Optimal adherence was associated with fewer osteoporotic fractures, which is likely to be considered added value for health care systems [33]. As a possible approach to increase the patients’ awareness and, thereby, compliance, the audience suggested consistent monitoring of compliance rates preferably by combined DXA, BTM and self-evaluation. Further improvement might be achieved with new drugs that are better received by the patients because of, e.g. fewer side effects or less frequent dosing.

During the discussion, the audience remarked that cost effectiveness analyses should definitely include compliance data. In addition, besides direct costs, also indirect costs such as loss of income because of sick leave should be taken into account. Data on these very country-specific expenses, however, are currently rarely available. Therefore, as already claimed during the “2nd Summit on Osteoporosis—CEE” in 2008, further investigations should focus on country-specific cost effectiveness models to facilitate the calculation of regional therapy costs. This information is crucial not only to identify cost-effective therapeutic approaches but also when claiming reimbursement. The ongoing ICUROS Study is approaching this issue in several EU countries and Russia. Whilst Russia already started to evaluate local costs, other CEE countries have not yet started.

Thereupon, members of the summit’s board approach this still not satisfactorily resolved issue by suggesting a collaborative approach to collect such data in a standardised way. Gerold Holzer was asked to put together a simple questionnaire for the evaluation of costs for hip fracture surgery, including direct (treatment, rehabilitation, etc.) and indirect (nursing homes, log-term disability, etc.) costs that will then be sent to all participants by e-mail. The audience was delighted by this idea and 90% agreed to participant in this collaborative study.

To summarise, lack of appropriate compliance can impair not only the outcome of an anti-osteoporosis therapy but also its cost effectiveness, particularly because costs for fracture treatment by far exceed costs for osteoporosis management. Therefore, proper actions to identify and prevent non-compliance should be implemented. Knowing its economic impact, it is essential to incorporate compliance data into cost effectiveness analyses. To calculate the cost effectiveness of osteoporosis therapies in individual CEE countries, evaluation of local expenses for osteoporosis and fracture management (direct and indirect) is imperative. A collaborative approach for the standardised collection of such data in CEE countries was suggested; this idea was very much appreciated by the audience.

Osteoporosis and genetics—what the future brings

Osteoporosis is a multifactorial disease: Its development and related fractures are dependent on a variety of factors, including clinical risk factors (BMD, comorbidities, fall risk, etc.), environmental factors (diet, exercise, sunshine, etc.) and, last but not least, genetic factors. Barbara Obermayer-Pietsch, Graz, Austria, focussed in her speech the significance of genetic aspects in diagnostics and therapy of osteoporosis.

In osteoporotic patients, several genes directly and indirectly involved in bone metabolism carry mutations and therefore are considered as candidate genes for osteoporosis management. Genome-wide association studies such as GENOMOS, a large-scale, multicentre prospective meta-analysis in Europe, and GEFOS, a comparable worldwide study, have already identified candidate genes not only for osteoporosis but also for several other diseases. From these genes, Barbara Obermayer-Pietsch chose lactose malabsorption (LM) as an example to demonstrate successful clinical diagnostics based on a genetic approach. Several mutations responsible for LM have been identified and verified, and their detection threshold is sufficiently high to easily identify affected individuals. With this, the most important prerequisites for a reliable genetic analysis that can easily (and also cost effectively) be performed in clinical practice are fulfilled.

Also in osteoporosis, quite a number of candidate genes have been identified involving calciotropic hormones, bone matrix proteins, adhesion molecules and their ligands, cytokines, growth factors and their receptors, several enzymes, gonadal hormones and their receptors, as well as disease-associated genes [33–35]. Despite this large number of potential candidates, final validation of any one of these genes for clinical use is still missing. To demonstrate what can hinder validation, Barbara Obermayer-Pietsch presented data on lipoprotein
Table 1 Conclusions and consensus on the diagnosis and management of osteoporosis developed during the “3rd Summit on Osteoporosis—CEE” in 2009

<table>
<thead>
<tr>
<th>Conclusion/Consensus</th>
<th>Details</th>
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<tr>
<td>Past year experience from FRAX® implementation into local diagnostics algorithms</td>
<td>- FRAX® has been developed as a 10-year calculator based on femoral neck BMD; however, the applicability of the model in CEE countries requires caution because reliable local fracture data are not available. - Prior to implementation of FRAX® into local guidelines, assessment of country-specific fracture data from reliable databases is recommended. - Understanding the benefits and limitations of FRAX® is essential for its optimal use. - Good clinical judgement should ultimately determine who should be treated and how.</td>
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<tr>
<td>Causes of SOP as a FRAX® risk factor</td>
<td>- In secondary osteoporosis (with the exception of rheumatoid arthritis), FRAX® should be applied with caution. - In diseases causing increased fracture risk primarily through low BMD, FRAX® can be used, whereas in conditions not primarily acting through BMD (e.g. Turner sy, antidepressants), FRAX® may not be used. - Ten-year fracture risk as estimated by FRAX® should not be used alone as a pharmacological treatment threshold in individuals. Treatment threshold should be tailored individually.</td>
</tr>
<tr>
<td>BTMs to estimate bone loss, fracture risk, or monitor therapies</td>
<td>- BTMs may be useful in the monitoring of treatment and might increase the compliance. - Within the BTMs, resorption markers are generally of more clinical utility than formation markers. - In combination with BMD, BTMs can improve the assessment of fracture risk and assist clinical decision making. - BTMs cannot help in selecting treatment for osteoporosis. - Further standardisation of the methods for evaluation of BTMs is necessary.</td>
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<tr>
<td>Role of QUS in osteoporosis management</td>
<td>- The most validated skeletal site for the clinical use of QUS in osteoporosis management is the heel. QUS measurements from devices technologically different cannot be directly compared. - Validated heel QUS devices predict fragility fracture in postmenopausal women and men over the age of 65 independently of central DXA BMD. - QUS is not suitable for diagnosis since the WHO diagnostic classification applied to DXA T-scores cannot be used for QUS because QUS T-scores are not equivalent to T-scores derived by DXA. - QUS cannot be used to monitor the skeletal effects of treatments for osteoporosis. - Heel QUS in conjunction with clinical risk factors combined into a probability model can be used to identify a population at very low fracture probability in which no further diagnostic evaluation may be necessary. In case of higher fracture probability, patient should be referred to a DXA centre.</td>
</tr>
<tr>
<td>Compliance and economical aspects of osteoporosis</td>
<td>- Lack of appropriate compliance is harmful for most osteoporotic patients. It should be identified and a proper action should be implemented. - New therapies in osteoporosis are needed. To implement them in the population, their cost effectiveness should be documented in order to get reimbursement. Adherence should be incorporated into such calculations. - Standardized data collection regarding hip fracture (direct and indirect) costs is recommended in the participating countries.</td>
</tr>
<tr>
<td>Osteoporosis and genetics—what the future brings</td>
<td>- In osteoporosis research, the identification of gene variants that are associated with osteoporosis phenotypes or response to therapy may help to individualise the prognosis, treatment and prevention of low energy fracture and its adverse outcomes. - Combination of genomics with classical approaches can be a model of innovative therapeutic approaches in a continuing interaction between clinical science and basic research.</td>
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</table>

receptor-related protein 5 (LRP5). Clearly, this protein plays a role in bone metabolism: In the LRP5 gene of patients with pathologically altered BMD, several mutations have been detected [36–38]. Also in osteoporotic patients, LRP5 mutation was associated with decreased BMD and increased fracture risk [39]. The magnitude of the BMD effect associated with these mutations, however, was rather modest (overall variation in BMD, 2.9%). Therefore, LRP5 does not qualify as a diagnostic marker to identify osteoporosis in the clinical practice. Unfortunately, the validation of other candidate genes for osteoporosis management is also hampered by such obstacles, and therefore, a reliably genetic approach to identify or even treat osteoporosis is not available yet.
To summarise, in osteoporosis research, the identification of gene variants that are associated with osteoporosis phenotypes or response to therapy will help individualise the prognosis, treatment and prevention of fracture and its adverse outcomes. In the future, large-scale screening by, e.g. gene arrays as well as analyses at the epigenomic and protein level will further elucidate the complex interplay between several mutated genes, which finally leads to the development of osteoporosis. A combination of genomics with classical approaches can then be a model for innovative therapeutic approaches in a continuing interaction between clinical science and basic research.

Consensus and recommendations for the clinical practice

During the “3rd Summit on Osteoporosis—CEE” in November 2009, the following pivotal aspects of osteoporosis management were comprehensively reviewed and discussed: use and implementation of FRAX® in CEE since the last summit in 2008; significance of FRAX® in SOP; the role of BTMs and QUS for diagnostics of osteoporosis; economic aspects of prophylaxis and therapy of fractures and how they are influenced by the patients’ compliance; and potential genetic approaches for diagnostics and therapy. Besides up-to-date information, the major aim of the meeting was to agree on approaches that allow for the most efficient and cost-effective diagnosis and therapy of osteoporosis in CEE countries in the future. Here, the focus was laid on practical aspects so that the developed recommendations would be particularly helpful in the clinical routine. Consensus and recommendations developed on the topics are summarised in Table 1.

The conference by itself was well received by the participants. Based on up-to-date data of topical interest presented during the conference, animated discussions and an intense mutual exchange of individual experiences took place. A particular plus was that due to the distinct regional provenances of the participants, issues could be approached from different points of view. These circumstances, the strong interest in cross-border cooperation as well as the readiness to learn from each other provided the basis for the establishment of a consensus on key issues in osteoporosis management (Table 1). The “4th Summit on Osteoporosis—CEE” held in Prague, Czech Republic, in December 2010 will reveal whether these recommendations prove of value when implemented in the clinical routine or whether further improvements are still required.

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