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Osteodensitometry in primary and secondary osteoporosis¹

Executive Summary

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Research question

The main goal of the present research was the assessment of the patient benefit of osteodensitometry for the prevention of osteoporotic fractures in persons without pre-existing fractures and of potential disease-related complications.

This goal implies various sub-goals:

- Firstly, the benefit assessment can be performed by means of different types of evidence (assessment of the use of osteodensitometry as an intervention [sub-goal 1a] or assessment of the consequences resulting from the use of osteodensitometry [sub-goal 1b]).
- Secondly, 2 principally different situations of use can be distinguished (measurement to determine osteoporosis or measurement within the framework of therapy monitoring [sub-goal 2]).
- Thirdly, in addition to dual-energy X-ray absorptiometry (DXA) (measurement site: hip and/or lumbar spine), which is regarded as the gold standard, other technical methods or clinical scores to determine low bone mineral density (BMD) are to be assessed as potential alternatives (sub-goal 3).
- Fourthly, in addition to primary osteoporosis in women, a condition for which the state of knowledge is comparatively high, primary osteoporosis in men and secondary types of osteoporosis are to be examined (sub-goal 4).

The benefit assessment of osteodensitometry in persons with current osteoporotic fractures or a history of such fractures was explicitly excluded from the present evaluation. The use of osteodensitometry in these patients is already included in the benefits catalogue of the German statutory health insurance.

Methods

Sub-goal 1 (osteodensitometry to determine osteoporosis)

For sub-goal 1a, studies were considered investigating male and female adult patients without pre-existing osteoporotic fractures. In this context, the effectiveness of health care strategies containing osteodensitometry (osteodensitometry + subsequent diagnosis-dependent treatment) was to be compared with the effectiveness of health care strategies without osteodensitometry in respect of the incidence of clinically evident fractures and disease-related complications. Randomized controlled trials (RCTs) were considered for this purpose. If no RCTs were identified, clearly prospectively planned non-randomized controlled

(intervention) trials (CCTs) would have been examined, if applicable, providing they gave adequate consideration to the problem of potential structural inequality (unfair comparison).

For sub-goal 1b, studies with the same population as for sub-goal 1a were included. In these persons, the decision to initiate treatment should largely be based on evidence of reduced BMD, i.e. the population included was defined as persons who, among other things, had a low BMD measurement. For proof of benefit by means of a consequence resulting from the application of a diagnostic measurement method, studies were considered that provided proof of the efficacy of causal therapy principles with regard to the incidence of clinically evident fractures and disease-related complications (causal therapy principles = treatments targeted towards influencing BMD). For this purpose, consideration was given to RCTs that used placebo or sham treatment or no treatment as the comparator intervention.

A precondition for inclusion of the (intervention) studies was a minimum study duration of 2 years. According to the European Medicines Agency's (EMA) "Guideline on the evaluation of medical products in the treatment of primary osteoporosis" (2006), in postmenopausal women, this is an appropriate time-frame for collecting data with regard to fractures and safety parameters [1].

Sub-goal 2 (therapy monitoring)

To demonstrate proof of benefit from therapy monitoring by means of osteodensitometry, the population already described was to be investigated. Studies were to be considered that compared the following 2 strategies:

- a) a strategy in which the continuation, adaptation or discontinuation of a treatment to increase BMD (vs. placebo or no treatment or sham treatment) depended on the results of the BMD monitoring;
- b) a strategy in which no monitoring was performed or in which the results of monitoring had no influence on the decision to continue treatment.

Both RCTs and CCTs (see sub-goal 1a for preconditions) were to be examined, as well as the outcomes already described under sub-goals 1a and 1b.

A minimum study duration of at least 2 years (see sub-goal 1) was also a precondition for inclusion here.

Sub-goal 3 (diagnostic accuracy)

For this sub-goal, studies were included that investigated adult patients with a clinical suspicion of osteoporosis. The fracture status at the start of the study was not relevant. The gold standard DXA was the reference standard for determining osteoporosis. The diagnostic

accuracy of DXA (diagnosis of “osteopenia” or “osteoporosis”) was compared to that of the other technical procedures (QCT,² peripheral DXA procedures, DXL,³ DXR,⁴ and ultrasound) as well as to clinical scoring systems. If in sub-goal 1 a benefit could have been inferred from a different procedure than the gold standard, this procedure would also have been used as a reference method.

The question of the diagnostic accuracy of alternative technical procedures for measuring BMD and of clinical scores (compared with DXA) was answered by means of cross-sectional studies in which all participants were examined both with the method to be assessed as well as with the reference method (phase 3 studies according to [2]).

Sub-goal 4 (association between BMD and osteoporotic fractures/disease-related complications in men with a suspected diagnosis of primary osteoporosis or in mixed-gender populations with a suspected diagnosis of secondary osteoporosis)

With regard to primary osteoporosis, the question in sub-goal 4, i.e. the association between BMD and patient-relevant outcomes (see also sub-goals 1 and 2), was only investigated in men. With regard to secondary osteoporosis, both men and women were investigated. Results from prospective cohort studies and nested case-control studies were primarily considered. In this context, the osteodensitometry test at the start of the study had to have been performed with the gold standard DXA. If in sub-goal 1 it had been shown for another measurement method that persons identified with this method could benefit from treatment, studies that had applied this method as a reference standard would also have been included.

A minimum study duration of one year was a precondition for study inclusion. The EMA guideline (see above) recommends this time-frame for men with osteoporosis in the investigation of drug interventions that have already been approved in postmenopausal women.

For all research questions to be investigated, studies were considered that included Caucasian populations.

In addition, for all sub-goals, vertebral body fractures diagnosed by X-ray were exclusively presented descriptively.

Linked evidence

If no intervention studies were available for the procedure to be tested (index test), in the present report it was to be attempted to infer potential statements on the benefit of the index test via the linking of results from therapy and diagnosis studies (“linked evidence”). The preconditions for this were, firstly, that therapy studies displaying certainty of results (sub-

² *quantitative computed tomography*

³ *dual X-ray laser absorptiometry*

⁴ *digital X-ray radiogrammetry*

goal 1b) showed a benefit for patient-relevant outcomes in patients identified by means of the reference method (under the assumption that there was no benefit in test-negative persons and that in test-positive persons the harm caused by non-treatment did not outweigh the potential benefit of osteodensitometry), and, secondly, that diagnostic cross-sectional studies show that the index test largely identifies the same persons as the reference test (sub-goal 3). If in this case the persons identified as test positive in the cross-sectional studies are comparable to the population of therapy studies, it can be assumed that persons identified by means of the index test will also very probably benefit from treatment.

Literature search

The systematic literature search was conducted in the databases MEDLINE, EMBASE und CENTRAL. Due to the comprehensive nature of the research question, additional databases were searched, depending on the sub-goal investigated. The period between 1990 and December 2009 was covered. In addition, reference lists of relevant secondary publications (systematic reviews, health technology assessment [HTA] reports) were screened.

Results

Sub-goal 1 (osteodensitometry to determine osteoporosis)

For sub-goal 1a, 2 studies were identified that compared

- a) a health care strategy containing a procedure (osteodensitometry) for determining osteoporosis and estimating fracture risk (including the resulting treatment consequences) with
- b) a strategy without such an intervention.

One of these studies investigated the use of central DXA with a subsequent recommendation for the prescription of hormone replacement therapy (HRT) in the case of a positive result. The other study investigated a health care strategy with quantitative ultrasound (QUS) and/or risk factor analysis with a subsequent recommendation for the prescription of calcium and Vitamin D supplements in the case of a positive result.

A total of 7315 women were randomized who were between 45 and 54 years old (mean age at baseline not provided) or who were on average 77 years old. Both studies showed a high risk of bias of results.

- In summary, for persons without pre-existing osteoporotic fractures, neither an indication nor proof of benefit or harm can be inferred from these 2 studies with regard to the use of a procedure for diagnosing osteoporosis and estimating fracture risk as an intervention. This applies to the prevention of clinically evident fractures, the improvement in quality of life (QoL), as well as to the premature discontinuation of such a health care strategy.

- In the studies included, no data were reported on fracture-related functional limitations and pain, fracture-related mortality, or adverse events.

Fifteen intervention studies were identified for sub-goal 1b. Of the 14 identified studies investigating primary osteoporosis, 11 studies investigated a drug vs. placebo intervention, 2 a nutritional supplement vs. placebo intervention, and one an exercise-related intervention vs. no treatment. A further study investigated patients with cystic fibrosis who suffered from secondary osteoporosis. In 13 of 15 studies, central DXA measurements were performed as the basis for a decision on the further course of action; in one study each, dual-photon absorptiometry (DPA) or single-photon absorptiometry (SPA) was applied. From the 11 studies on the use of drugs in primary osteoporosis, aggregated data of a total of 25 636 men and women were included in the present assessment. The studies on nutritional supplements investigated 914 women, the study on exercise-related interventions 160 women, and the study on the use of a drug in secondary osteoporosis 22 men and women.

- In summary, the data provide an indication of a benefit of treatment for postmenopausal women without pre-existing fractures who had a BMD of $T < -2.5$ measured with central DXA. This applies to “clinically evident fractures” (excluding skull, facial and vertebral body fractures), as well as to hip fractures and clinically evident vertebral body fractures. In addition, with the exception of clinically evident vertebral body fractures, an interaction between BMD and therapy effect was shown.
- Regarding wrist fractures, the data provide neither an indication nor proof of a benefit of treatment for women with low BMD and without pre-existing fractures.
- Regarding fracture-related functional limitations and pain, neither an indication nor proof of a benefit of treatment can be inferred, as no informative data were found on the population to be investigated for the present report.
- Regarding fracture-related mortality, no data on the population to be investigated in this report were reported in the studies.
- Regarding changes in health-related QoL during and after fractures, neither an indication nor proof of a benefit from treatment can be inferred, as no informative data were found on the population to be studied in this report.
- In the assessment of adverse events, an indication of a disadvantage of the selective oestrogen receptor modulators (SERMs) raloxifene and bazedoxifene was shown (higher rates of thromboembolic events, leg cramps, and hot flushes).
- The data provide an indication that the intake of strontium ranelate leads to higher rates of nausea, diarrhoea, headache, skin infections or eczema than placebo. They also provide an indication that women taking strontium ranelate discontinue treatment more frequently due to adverse events than those taking placebo.

Besides the gold standard, it was not demonstrated for any other procedure that persons identified with this procedure can benefit from treatment targeted towards influencing BMD.

Sub-goal 2 (therapy monitoring)

No studies investigating the research question in sub-goal 2 were available. No statement is therefore possible concerning the use of osteodensitometry to decide upon the continuation, adaptation or discontinuation of treatment influencing BMD; the benefit and harm of therapy monitoring remain unclear.

Sub-goal 3 (diagnostic accuracy)

For sub-goal 1a or b, no other procedure than central DXA was identified for which a benefit with regard to patient-relevant outcomes could have been inferred. For this reason, for sub-goal 3, studies were exclusively considered that applied central DXA as a reference procedure.

A total of 85 studies were identified for the investigation of test accuracy. In comparison to the gold standard (central DXA), as index procedures these studies investigated QUS, risk scores, and individual procedures summarized as “other procedures” in the following text (see below). In the present report, the studies are arranged according to the (index) procedures investigated and described according to this arrangement. Some of the studies investigated more than one index text, so that studies may be mentioned more than once in the following text.

A total of 39 studies investigated QUS procedures, 36 investigated 23 different risk scores, and 21 investigated “other procedures”. Procedures subsumed under “other procedures” were those for which a maximum of 5 studies per index procedure were identified. These included: peripheral DXA procedures, radiographic absorptiometry (RA), single-energy X-ray absorptiometry (SXA), DXL, DXR, as well as combinations of technical procedures and clinical scores (ultrasound + simple calculated of osteoporosis risk estimation [SCORE], ultrasound + body mass index [BMI], RA of the jaw + osteoporosis index of risk [OSIRIS], RA + age). For each of the index groups, the studies were very heterogeneous. This heterogeneity was mainly due to the following factors: different study populations, different selection criteria, varying detailedness of the description of baseline data (particularly on BMD), the use of different reference populations for inferring T-scores, as well as the use of different measurement sites/parameters and cut-off values for both the index and the reference test.

A high risk of bias of results was inferred for most studies. None of the index procedures investigated fulfilled the minimum requirements for an index text as defined for the present report. This referred to the lower limits of the one-sided confidence interval for sensitivity and specificity, which in each case had to reach a value of at least 85%. As the minimum requirement was not fulfilled for any of the index procedures investigated, it cannot be

assumed that any of the index test procedures investigated are sufficiently well-suited to identify the same persons as the gold standard DXA.

Sub-goal 4 (association between BMD and osteoporotic fractures/disease-related complications)

For sub-goal 4, too, only those studies were considered that used the gold standard DXA as a reference standard (see sub-goal 3 above).

A total of 14 studies investigating the association between BMD and fractures were identified. Eight of these studies investigated patient-relevant outcomes and 6 studies exclusively investigated radiologically verifiable vertebral body fractures. Four of the studies on patient-relevant outcomes investigated men with suspected primary osteoporosis and 4 studies referred to mixed-gender populations with suspected secondary osteoporosis.

Four studies including men with suspected primary osteoporosis investigated the association between BMD and clinically evident fractures, as well as mortality. None of the studies described the blinding of participants with regard to their test result. The 4 studies investigated between 257 and 5995 men who lived independently (mean age from approx. 68 to 79 years). Two further studies exclusively reported data on the risk of radiologically verified vertebral body fractures. In summary, the following results for patient-relevant outcomes were shown in elderly men:

- The data provide proof of a statistical association between low BMD and an increased hip fracture risk if BMD was measured at the site of the femoral neck by means of the gold standard DXA. The data provide an indication of such an association if BMD was measured at the site of the lumbar spine or whole hip.
- The data provide an indication of a statistical association between low BMD and an increased risk of clinically evident fractures if bone density was measured by means of DXA at one of the central measurement sites.

Four studies included men and women after lung and heart transplantation, as well as patients undergoing haemodialysis, and investigated patient-relevant outcomes. The sample sizes were rather small (between 14 and 106 men and women). All studies had a high risk of bias of results. Four further studies merely investigated the association between BMD and radiologically verified vertebral body fractures.

Regarding risk groups for secondary osteoporosis, the data provide neither an indication nor proof of a statistical association between low BMD and an increased risk of clinically evident fractures or overall mortality.

In the studies included, no data on the following outcomes were found for men with suspected primary osteoporosis or for men or women with suspected secondary osteoporosis: fracture-

related functional limitations, fracture-related pain, fracture-related mortality, as well as changes in health-related QoL during and after fractures.

Linked evidence

From the therapy studies, an indication of a benefit of a drug intervention targeted towards influencing BMD could be inferred in persons without pre-existing fractures. However, it was not demonstrated for any index test that it was good enough to identify the same patients as the gold standard DXA. It was therefore not possible to link the results from therapy studies and diagnostic cross-sectional studies, and to infer a statement on one of the (index) procedures to be investigated.

Conclusions

The key question of the present report was whether women or men with primary or secondary osteoporosis (but without pre-existing osteoporotic fractures) benefit from a health care strategy containing a diagnostic procedure (osteodensitometry) for determining low BMD and an increased fracture risk, as well as containing subsequent treatment, compared to a strategy without such an intervention. Due to the lack of studies with certainty of results, no direct statement on the benefit or harm of a health care strategy containing osteodensitometry can be inferred.

However, the data provide an indication of a benefit of osteodensitometry in post-menopausal women without pre-existing osteoporotic fractures in whom BMD is measured by means of central DXA measurement. This indication is inferred from evidence of an interaction between BMD and therapy effects. This evidence is largely based on the results of one study.

For individual therapy options in the treatment of osteoporosis without clinically evident fractures, the data provide indications of harm caused by adverse events. However, the results on adverse events are based on analyses that also included women with pre-existing fractures.

Due to the lack of studies, both the benefit and the harm from therapy monitoring by means of osteodensitometry are unclear and therefore not proven.

No equivalent alternative for determining BMD and fracture risk was found that could be applied as a replacement for measurement by means of central DXA.

For elderly men with suspected primary osteoporosis, the data provide proof of a statistical association between low BMD and an increased fracture risk. Regarding risk groups for secondary osteoporosis, the data provide neither an indication nor proof of such an association. It cannot be inferred from this finding that such an association does not exist.

References

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Key words: osteoporosis, osteodensitometry, DXA, QCT, QUS, fractures, systematic review, benefit assessment

The full report (German version) is available on www.iqwig.de