



The yield of routine laboratory examination in osteoporosis evaluation in primary care

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Abstract

Summary This study evaluated the yield of routine laboratory examination in a large population of older women in primary care. The prevalence of laboratory abnormalities was low and the clinical consequences in follow-up were limited. There was a weak association of laboratory abnormalities with osteoporosis but no association with vertebral fractures and recent fractures.

Purpose Most osteoporosis guidelines advice routine laboratory examination. We have investigated the yield of laboratory examinations in fracture risk evaluation of elderly women in primary care.

Methods We assessed the prevalence of laboratory abnormalities and their association with risk factors for fractures, recent fractures, low bone mineral density (BMD), and prevalent vertebral fracture in 8996 women ≥ 65 years of age participating in a primary care fracture risk screening study. In a sample of 2208 of these participants, we also evaluated the medical consequences in the medical records during a follow-up period of ≥ 1 year.

Results Vitamin D deficiency (< 30 nmol/L) was present in 13% and insufficiency (< 50 nmol/L) in 43% of the study sample. The prevalence of other laboratory abnormalities (ESR, calcium, creatinine, FT4) was 4.6% in women with risk factors for fractures, 6.1% in women with low BMD (T-score ≤ -2.5), 6.0% after a prevalent vertebral fracture, 5.2% after a recent fracture and 2.6% in the absence of important risk factors for fractures. Laboratory abnormalities other than vitamin D were associated with low BMD (OR 1.4, 95%CI 1.1–1.8) but not with prevalent vertebral fractures nor recent fractures. Low BMD was associated with renal failure (OR 2.0, 95%CI 1.3–3.4), vitamin D insufficiency (OR 1.2, 95%CI 1.0–1.3) and deficiency (OR 1.3, 95%CI 1.1–1.5). In the follow-up period, 82% of the laboratory abnormalities did not result in a new diagnosis or treatment reported in the medical records.

Conclusions We identified a low prevalence of laboratory abnormalities in a primary care population of older women and the majority of these findings had no medical consequences.

Keywords Bone density · Clinical chemistry tests · Fractures · Osteoporosis · Primary health care · Vitamin D deficiency

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Introduction

Osteoporosis is defined as a combination of low bone mineral density (BMD) and loss of microarchitecture. It is an important risk factor for fractures and leads to substantial morbidity and mortality [1, 2]. Most people with osteoporosis have so-called primary osteoporosis, deterioration of the bone caused by multifactorial causes: sex, familial predisposition, life style and aging. Secondary osteoporosis is defined as osteoporosis that is accompanied by a disease or medication that is known to cause decline of BMD and microarchitecture. Some of the causes of secondary osteoporosis can be detected with medical history taking (e.g. corticosteroid use, excessive alcohol use, earlier menopause, rheumatoid arthritis), others can be detected by laboratory examination (e.g. hyperthyroidism, hyperparathyroidism, vitamin D deficiency, renal disease).

Most guidelines advise routine laboratory examination in patients with osteoporosis or in older people with recent fractures [3–6]. This advice is based on high prevalence of laboratory abnormalities in mainly secondary care studies. A review of these studies shows a prevalence of secondary osteoporosis in 5–48% of the evaluated patients with osteoporosis and in 26–51% after a new fracture [7]. This large distribution in prevalence is caused by several factors: the selection of the population, the inclusion of anamnestic data, the number of performed laboratory examinations and the chosen laboratory thresholds. Secondly, the inclusion of vitamin D deficiency makes a large difference. When vitamin D deficiency was included as abnormality, this percentage is even higher up to 68%. There is a lack of data about the situation in primary care; until now, most data are collected in fracture liaisons and secondary care settings. In addition, in the studies that did evaluate subjects that were referred from primary care, the preselection is unclear leaving room for selection bias [8–10]. Beside causes of secondary osteoporosis, there are laboratory results that can influence treatment. Severe kidney failure is a contraindication for bisphosphonate treatment, and vitamin D deficiency can cause osteomalacia and needs primarily supplementation of vitamin D. Also, hypocalcaemia should be corrected before potent anti-osteoporotic treatment is started. Data about the yield of routine laboratory examination in a primary care population is desirable since there is evidence that screening programs in elderly women reduce hip fracture risk which led to the recommendation of the implementation of fracture risk screening in primary care [11–13]. Beside assessing the prevalence of abnormal laboratory results, it is important to know if these findings are associated with low BMD and fractures. One should question the indication for routine laboratory examination if this association is weak or absent.

The first aim of our study was to assess the prevalence of relevant laboratory abnormalities that are detectable with simple laboratory examination in a population of older women in primary care.

Secondly, we wanted to study the association of the detected laboratory abnormalities with risk factors for fractures, low BMD, prevalent vertebral fractures and recent fractures.

And thirdly, we wanted to quantify the effect of routine laboratory examination on diagnosis and treatment during a 1-year follow-up.

Methods

Participants

We analysed the data of women that participated in the Salt Osteoporosis Study (SOS). SOS is a pragmatic randomized clinical trial to study the effect of screening women ≥ 65 years in primary care for high fracture risk [14, 15]. In this study, all women in the intervention group with at least one risk factor for fractures were invited for bone densitometry. The exclusion criteria were a short-life expectancy according to the GP, current use of anti-osteoporotic medication or in the preceding 5 years, recent bone densitometry (< 2 years), terminal illness, body weight > 135 kg or current corticosteroid use ≥ 7.5 mg prednisone equivalent per day. In this study, 47.1% of all older women responded and of these women 42.3% with at least one risk factor were invited for bone densitometry. All women that had bone densitometry and laboratory examination (68.0%) were included in the study. Besides the women participating in the SOS trial, a random sample (15%) of the source population without important risk factors were asked to undergo the same examinations.

Measurements

Participants fulfilled a questionnaire that included questions about risk factors for fractures. Measurement of weight, length, bone densitometry of the femoral neck and the lumbar spine, vertebral fracture assessment (Hologic Discovery SL) and laboratory examinations were performed. Low BMD was defined as a T-score ≤ -2.5 in the femoral neck or lumbar spine. Prevalent vertebral fractures were defined as a reduction in vertebral height of $\geq 20\%$ in the lumbar spine or $\geq 25\%$ in the thoracic spine on the vertebral fracture assessment [16]. A recent fracture was defined as any fracture < 1 year before examination (fractures of fingers, toes and skull excluded).

The serum laboratory examinations were as follows: calcium, albumin, thyroid-stimulating hormone (TSH),

free tetraiodothyronine (FT4), creatinine (Cobas, Roche), erythrocyte sedimentation rate (ESR) (Vesmatic Cube 200, Menarini), 25(OH) vitamin D3 (Diasorin, Stillwater, USA). All test were performed in the same laboratory (SALT, Koog aan de Zaan, ISO certified), except for the 25(OH) vitamin D3 (AML, Antwerpen). The thresholds for the laboratory abnormalities were as follows: ESR > 50 mm/h, calcium corrected for albumin > 2.60 mmol/L, TSH < 0.30 mU/L with FT4 > 21 pmol/L, cockcroft clearance < 30 ml/min, vitamin D deficiency 25(OH)D3 < 30 nmol/L, vitamin D insufficiency 25(OH) D3 < 50 nmol/L.

We have chosen the cut off for severe renal failure (< 30 ml/min), because this has consequences for the prescription of medication. The other thresholds were the regular thresholds of our laboratory.

The questionnaires, biometrics, bone densitometry measurement, vertebral fracture assessment and laboratory measurements have been extensively described previously [14].

Medical files

We analysed the GP medical files of all participants with at least one laboratory abnormality during screening in the period between February 2010 and May 2012. The medical file of the GP was analysed by either a GP or a GP supervised medical doctor in training to become a GP. This was done after at least 1 year had elapsed between the moment the abnormal laboratory examination was reported to the GP. We studied whether the abnormal

laboratory examination was previously registered in the medical file. Secondly, we looked for notes in the medical file whether the observed abnormality had led to a new diagnosis or had influenced treatment. The evaluation of the medical files and definitions are shown in Table 1.

Statistical analysis

We assessed the prevalence of laboratory abnormalities and performed univariate logistic regression, to calculate the odds ratios (OR) for all individual laboratory abnormalities and at least one laboratory abnormality in the presence a recent fracture, low BMD or prevalent vertebral fracture. Additionally, we performed a multivariate logistic regression analysis to evaluate possible confounding effect of age and body mass index. We defined a confounding effect as a more than 10% change in regression coefficient of the determinant. In this regression analysis, we made a distinction between either vitamin D deficiency and insufficiency or any other laboratory abnormality combined, because there is a considerably lower prevalence of laboratory abnormalities other than 25(OH) vitamin D, and we wanted to avoid low vitamin D to dominate the other results.

In the patients of whom the medical files were examined, we evaluated the number of new diagnoses/treatments for all participants with one or more per laboratory abnormalities.

Table 1 Information from the medical files

Definitions of laboratory abnormalities and searches GP medical file*	
Previously documented abnormality	The laboratory abnormality was noted previously in the medical file in journal, laboratory register or episode list
New laboratory abnormality	The laboratory abnormality was not previously noted in the medical file (journal, laboratory register or episode list) or there was a clinical relevant change in a known abnormality compared with the last measurement (e.g. elevated FT4 in a participant with supplementation for hypothyroidism or deterioration of known kidney failure)
Follow-up in medical file ≥ 1 year	
Medical consequence/diagnosis	The new laboratory abnormality was reported in the journal or in the laboratory registry and induced evaluation or further examination by the GP or medical specialist and resulted in a new diagnosis or treatment (in journal, episode list or specialist letter)
False positives	The new laboratory abnormality was reported in the journal or in the laboratory registry and induced laboratory follow-up or further examination by the GP or medical specialist but did not result in a new diagnosis or treatment (in journal, episode list or specialist letter)
No further examination	The new laboratory abnormality was reported in the journal or in the laboratory registry but had not induced further examination (e.g. the GP and/or the participant decided to do no further examination or there was no note in the medical file)

*In the Netherlands, several software providers that offer electronic medical file systems for the general practice. All systems use the same standardized structure. Information is reported according the so-called SOEP method. This implies the option to store free text in four lines of information: Subjective, Objective, Evaluation, Plan. To the 'Evaluation' line an ICPC (international classification primary care) code for the reason of encounter is added as evaluated by the health professional [17]. Decisions and actions are noted in 'Plan'. Laboratory measurements are noted in a laboratory registry. Furthermore, there are lists of medical episodes (also using the ICPC coding system) and prescribed medication and received specialist letters are stored as well. The letters are mostly integrated in the digital medical file, but in some practices, these are still stored in a separate database or as paper file

Results

Of 8996 women with risk factors for fractures, 2536 had a low BMD, 1044 had a prevalent vertebral fracture and 334 had a new fracture. The prevalence of vitamin D insufficiency in participants with risk factors was 43.0% and vitamin D deficiency was 13.2%. The prevalence of any other abnormality was 4.6% in participant with risk factors for fracture, in participants with low BMD 6.1%, in participants with prevalent vertebral fracture 6.0%, in participants with a recent fracture 5.2% and in the group without risk factors 2.6% (Table 2).

Because of a confounding effect for age but not for BMI, we present the multivariate odds ratios corrected for age.

The presence of risk factors for fractures was associated with any laboratory abnormality other than low 25(OH)D

(OR 1.8, 95% CI 1.3–2.5). Also, low BMD was associated with any laboratory abnormality other than low 25(OH)D (OR 1.4, 95% CI 1.1–1.8). There was no significant association of prevalent vertebral fractures (OR 1.1, 95% CI 0.8–1.6) nor with recent fractures (OR 1.1, 95% CI 0.7–1.9) and any laboratory abnormality other than low 25(OH)D. In the analysis of the individual laboratory abnormalities, an association was found of low BMD with creatinine clearance < 30 ml/min (OR 2.0, 95% CI 1.3–3.4), vitamin D insufficiency (OR 1.2, 95% CI 1.0–1.3) and vitamin D deficiency (OR 1.3, 95% CI 1.1–1.5). Low BMD had an inversed correlation with FT4 (OR 0.5, 95% CI 0.3–0.8) (Table 3).

The follow-up group compromised 24.5% of all participants of which 109 (4.5%) had a laboratory abnormality. In 55/109 (50.5%), the same abnormality had also previously been noted in the medical file indicating that the abnormality was no new observation. In one third ($n = 16$) of the other

Table 2 Participant characteristics

	≥ 1 Risk factors for fractures	Low BMD (T-score ≤ -2.5)	Prevalent vertebral fracture	Recent fracture	No important risk factors
<i>N</i>	7509	2173	936	334	1487
Age, years (SD)	74.8(6.1)	76.1(6.4)	77.3 (6.6)	74.8 (5.8)	74.9 (4.4)
BMI, kg/m ² (SD)	27.9 (5.2)	26.2(4.8)	27.4 (4.6)	27.8 (5.1)	27.4 (4.6)
Fracture > age 50 years	54.5%	49.4%	57.9%	100%	0%
Recent fracture < 1 year	4.4%	5.3%	6.4%	100%	0%
Recent MOF	2.3%	3.0%	3.8%	50.4%	0%
Recent hip fracture	0.5%	1.1%	0.7%	10.0%	0%
Parental hip fracture	27.0%	25.0%	23.3%	12.0%	0%
Smoking	10.2%	11.2%	10.7%	9.4%	7.2%
Alcohol ≥ 3EH/day	6.3%	5.5%	5.9%	5.3%	4.7%
Impaired mobility	22.3%	24.1%	25.4%	15.8%	0%
Walking aid	27.5%	31.7%	34.5%	24.3%	0%
Falls ≥ 1/year	31.1%	32.7%	34.1%	22.3%	21.4%
T-score hip	-1.54	-2.6	-2.0	-1.48	-1.37
T-score LWK	-0.89	-2.1	-1.3	-0.85	-0.85
Prevalent vertebral fracture	12.9%	19.5%	100%	18.2%	7.4%
FRAX 10-years fracture risk	17.2%	24.4%	23.5%	15.7%	11.0%
FRAX 10-year hip fracture risk	6.3%	11.9%	10.3%	5.4%	2.8%
25(OH)D < 50 nmol/L	43.0%	46.3%	41.7%	47.1%	31.6%
25 (OH)D < 30 nmol/L	13.2%	16.3%	13.9%	14.2%	8.4%
ESR > 50 mm/h	1.9%	2.5%	2.2%	1.8%	0.9%
Calcium (corrected) > 2.60mmol/L	1.9%	2.0%	1.8%	2.7%	1.4%
Calcium (corrected) < 2.10mmol/L	1.3%	1.2%	1.2%	0.6%	0.7%
Creatinine clearance < 30ml/min	0.9%	1.8%	2.1%	0.9%	0.4%
Creatinine clearance < 45ml/min	8.3%	13.3%	14.7%	9.1%	5.8%
TSH < 0.3 mU/L	2.6%	2.1%	2.5%	3.7%	2.4%
FT4 > 21 pmol/L	1.2%	0.7%	1.3%	1.8%	0.9%
Other laboratory abnormality than low 25(OH)D	4.6%	6.1%	6.0%	5.2%	2.6%

Table 3 Odds ratio and 95% confidence interval for laboratory abnormalities in the presence of risk factors for fractures, recent fractures, low BMD or prevalent vertebral fractures in women > 65 year ($n = 8996$), odds ratios adjusted for age

Lab abnormalities	≥ 1 Risk factors for fractures	Recent fracture	Low BMD (T-score ≤ -2.5)	Prevalent vertebral fracture
25(OH)D < 50 nmol/L	1.6 (1.5–1.9)	1.3 (1.0–1.6)	1.2 (1.1–1.3)	0.9 (0.8–1.0)
25 (OH)D < 30 nmol/L	1.6 (1.3–2.0)	1.2 (0.8–1.6)	1.3 (1.1–1.5)	1.0 (0.8–1.2)
ESR > 50 mm/h	2.0 (1.2–3.5)	1.0 (0.4–2.3)	1.5 (1.0–2.0)	1.0 (0.6–1.6)
Calcium cor. > 2.60 mmol/L	1.3 (0.8–2.1)	1.6 (0.8–3.1)	1.1 (0.8–1.5)	0.9 (0.6–1.6)
Creatinine clearance < 30 ml/min	1.7 (0.7–3.9)	0.9 (0.3–3.1)	2.1 (1.3–3.4)	1.5 (0.9–2.5)
FT4 > 21 pmol/L	1.4 (0.8–2.5)	1.6 (0.7–3.7)	0.6 (0.3–0.9)	1.3 (0.7–2.2)
Other laboratory abnormality than low vitamin D	1.8 (1.3–2.5)	1.2 (0.7–2.0)	1.4 (1.1–1.7)	1.1 (0.8–1.5)

54 participants, no note of follow-up was found regarding the abnormality. In a third ($n = 18$), a follow-up measurement was normal indicating that the initial measurement had normalised or had been false positive. In about one third ($n = 20$) of the participants, a new diagnosis was made or the abnormal laboratory finding had led to a medical consequence (Table 4). The diagnoses are displayed in Fig. 1.

Discussion

Principal findings

This is the first study in a large primary population of older women with increased fracture risk that has quantified the prevalence of abnormalities during routine laboratory examination and the associations of these abnormalities with risk factors for fractures, recent fractures, low BMD and prevalent vertebral fractures. While the prevalence of low vitamin D is high, the prevalence of other laboratory abnormalities is low. Although we have observed an association between all laboratory abnormalities and the presence of both clinical risk factors and low BMD, we have to conclude that the associations are weak. The only exception is the association with severe renal failure. In this population, recent fractures and prevalent vertebral fractures do not increase the probability of finding laboratory abnormalities. About half of the laboratory abnormalities were previously reported

in the medical file. Furthermore, 82% the new laboratory abnormalities did not lead to a new diagnosis or treatment. New diagnoses were as often found in participants with or without low BMD, recent fractures and prevalent vertebral fractures.

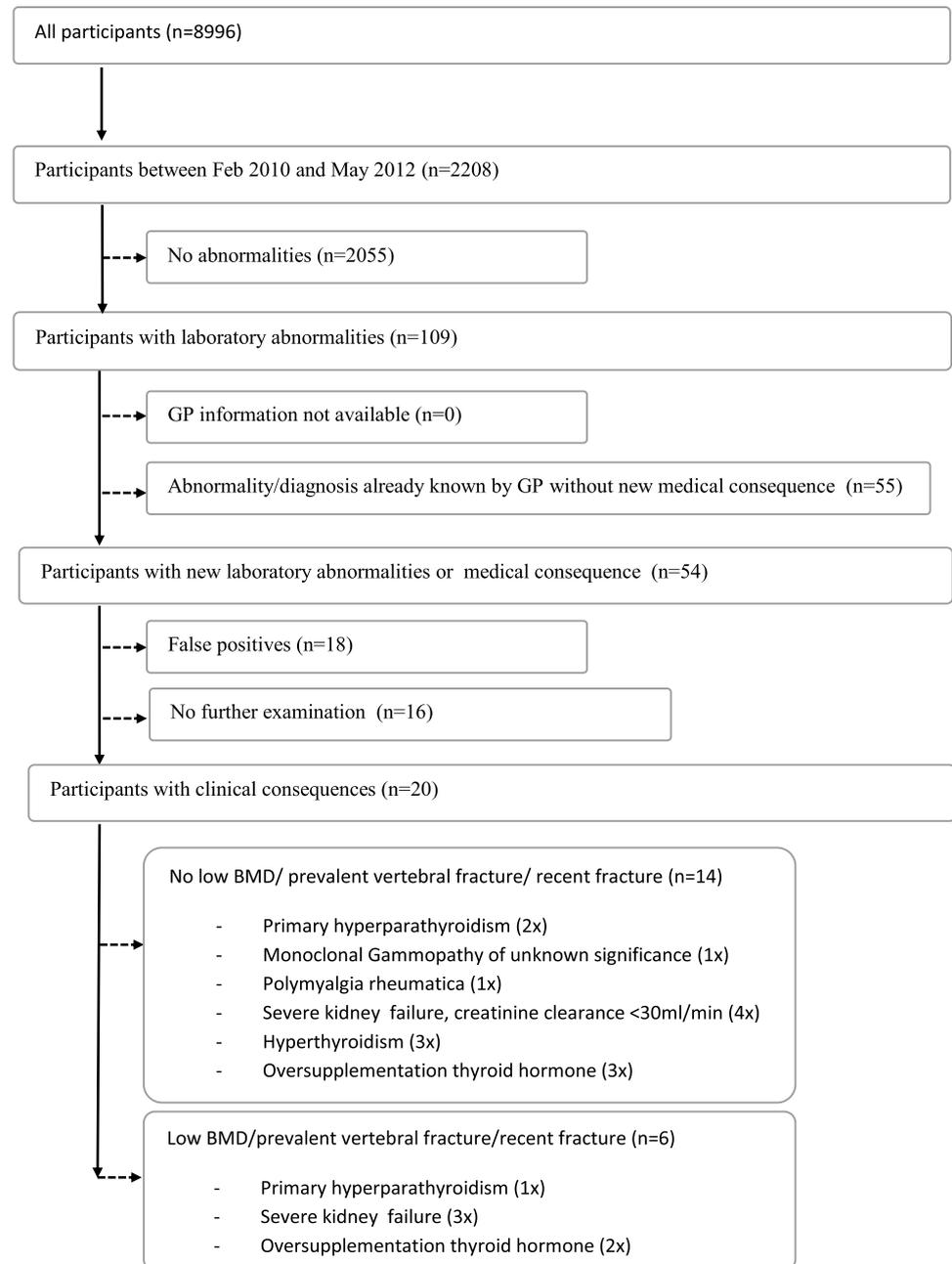
If we weigh this limited yield against the costs, the discomfort of examination and unnecessary further examination in false positives, the conclusion might be that there is not enough ground for a routine laboratory panel in fracture risk assessment or screening in primary care. The only exception might be the assessment of vitamin D and renal function. An alternative solution to the assessment of vitamin D would be to advise vitamin D supplementation in all women at risk for fractures since deficiency is very frequent. This is currently the policy in the Netherlands [18]. Another alternative could be to select those with risk factors for vitamin D deficiency for supplementation or measurement [19]. Since severe chronic kidney failure is a contra indication for bisphosphonates, we suggest that the kidney function is routinely verified or assessed before start of treatment.

Leaving out most of the routine laboratory examinations will sound contra-intuitive to many physicians. When you have a patient with osteoporosis you do not want to miss that one patient with hyperparathyroidism or a malignancy. On the other hand, we have to conclude that low BMD, recent fractures and prevalent vertebral fractures turn out to be no strong signals for these conditions in a primary care population. Primary care seems to have particularly primary

Table 4 Evaluation of all laboratory abnormalities in medical file of the participants between Feb 2010 until March 2012

	All laboratory abnormalities	Previously documented in medical file	No further examination	False positives	Medical consequence/diagnosis
ESR > 50 mm/h	56	32 (57.1%)	13 (23.2%)	9 (16.1%)	2 (3.6%)
Calcium cor. > 2.60 mmol/L	14	2 (14.3%)	3 (21.4%)	6 (42.9%)	3 (21.4%)
Creatinine clearance < 30ml/min	18	10 (55.6%)	0 (0%)	1 (5.6%)	7 (38.9%)
FT4 > 21 pmol/L	21	11 (52.4%)	0 (0%)	2 (9.5%)	8 (38.1%)
Total	109	55 (50.5%)	16 (14.7%)	18 (16.5%)	20 (18.3%)

Fig. 1 Flow diagram of evaluation of the medical file at least one year after routine laboratory examination



osteoporosis. Performing additional laboratory examinations should therefore be performed on clinical indication only.

Comparison with other studies

Compared to other studies the number of laboratory abnormalities is low in our study. There are several explanations. In the first place, some studies use a more extensive laboratory panel. Secondly, the threshold in our study for abnormal renal function is lower than in some other studies (some studies include renal failure stage 3, 30–45 ml/min). And in the third place, our study population differs from other

studies. The population in studies in a fracture liaison service or secondary care might be a selection of less healthy persons.

Another difference with the previous studies is that of all laboratory abnormalities the proportion of new abnormalities is lower in our population. We think that this is caused by not only collecting information from the participants but also including information from the GP medical file in our study.

Five studies looked at the association between osteoporosis and laboratory abnormalities or newly found secondary osteoporosis, three in a fracture liaison, one in a population

of healthy older women and one in an unselected cohort of older men [20–24]. Only one study in the fracture liaison found an association between osteoporosis and newly found secondary causes of osteoporosis. The weak associations we have found in our study population is in concordance with the inconsistency between the studies.

Strengths and limitations

The primary strength of this study is the strictly primary care setting, since information on the prevalence of laboratory abnormalities in women at risk for fractures in primary care is not available. A second strength of the study is the sample size. This opened the opportunity to identify not only associations between risk factors and the complete laboratory panel, but also with the single measurements. The third strength of this study is the follow-up by checking the medical files at least 1 year later. The benefit of the approach is that we could estimate the yield of the routine laboratory examination and get insight in what are true findings and false positives. We think that this approach is important to support solid recommendations in guidelines. The fourth strength in this study is that not only the association with low BMD was taken into account but also with prevalent vertebral fractures and recent fractures. These are important pillars of fracture risk assessment besides the diagnosis low BMD based on bone densitometry alone.

A limitation in this study is that only about 50% of the people invited to the SOS participated in the trial. Furthermore, all women with recent bone densitometry or earlier use of osteoporosis medication were excluded; this comprised 6.6% of the population. This could have led to selection bias. Indeed, we saw a lower participation in higher age in the SOS, indicating a possible selection of the healthier individuals. In a previous pilot study of SOS women of 50 years or older, which was performed during a clinical improvement program without requesting extensive informed consent of the participants, the risk of selection was smaller with a response rate of 83.4% [14]. In the women of 65 years and older ($n=324$) with risk factors for fractures, the prevalence of vitamin D deficiency was 44.9% and other laboratory abnormalities was 4.1% (unpublished). Since these percentages are similar to our study, this indicates that the effect of selection bias is probably limited.

In our study, we have focused on laboratory examinations that are easily accessible in primary care and which cover most prevalent and relevant secondary causes. Another limitation of this study is, therefore, that we did not measure PTH, resulting in the inability to identify secondary hyperparathyroidism. However, since we have measured vitamin 25(OH)D and creatinine clearance, the main causes of secondary hyperparathyroidism are covered. With our panel, we have probably also missed some rare causes of secondary

osteoporosis, but that is unlikely to have much effect on the results, since the prevalence of the more common causes of secondary osteoporosis are already very low. Furthermore, there are two restrictions regarding generalizability. As this study included only women in primary care, the results cannot be extrapolated to men nor to a fracture liaison or secondary care setting.

Conclusion

In elderly women at risk for fractures in primary care, the prevalence of relevant laboratory abnormalities found in a routine screening is low. Examination of ESR, calcium, creatinine and TSH/FT4 leads to few new diagnoses and clinical consequences. Nevertheless, we found a high prevalence of vitamin D insufficiency and deficiency. There was a weak association between all laboratory abnormalities and low BMD, but in particular severe renal failure was associated with low BMD. We suggest that the routine laboratory examination in primary care in women with low BMD should only imply creatinine measurement and 25(OH) vitamin D, if vitamin D supplementation is not already started. The recommendation in guidelines to add other routine laboratory examinations is not supported by this study.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00198-024-07042-3>.

Declarations

Consent informed Consent was obtained from all individual participants and the study was approved by the Dutch Health Council (OGZ, 2.978.265).

Conflicts of interest None.

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