A prospective, single-cohort, multicentre clinical investigation to evaluate the performance of POROUS R3C ultrasound device for fracture risk prediction in middle-aged and elderly men and women

Published: 21-02-2025
Last updated: 07-03-2025

Primary objectivesPart 1:• To establish a corrected standardized gradient of fracture risk using the POROUS R3C ultrasound device based on prevalent fractures.Part 2:• To establish a corrected standardized gradient of fracture risk using the POROUS...

Ethical review	Approved WMO
Status	Pending
Health condition type	Bone, calcium, magnesium and phosphorus metabolism disorders
Study type	Interventional

Summary

ID

NL-OMON57319

Source
ToetsingOnline

Brief title
Short: POROUS Fracture Risk Prediction
Acronym: POROUS-preFX

Condition

- Bone, calcium, magnesium and phosphorus metabolism disorders
- Fractures

Synonym
Bone loss, Osteoporosis

Research involving
Human

Sponsors and support

Primary sponsor: Porous GmbH
Source(s) of monetary or material Support: partly funded by the European Innovation Council (EIC)

Intervention

Keyword: bone microstructure, fracture risk, osteoporosis, POROUS

Outcome measures

Primary outcome

Clinical endpoints

Part 1:

Prevalent fractures are the focus of the analysis in Part 1, i.e., fractures

that occurred prior to the Baseline visit. This is reflected in establishing

corrected standardized odds ratio (sOR) for the POROUS R3C ultrasound

device-derived POROUS-ScorePrev. Statistically significant discriminative power

of the sOR will be achieved if the lower limit of the 95% confidence interval

of the sOR is greater than 1. The POROUS-ScorePrev will be evaluated to

demonstrate the discriminative performance of the POROUS R3C ultrasound device

for prevalent fractures.

Part 2:

Incident fractures are the focus of the analysis in Part 2, i.e., fractures

that occur after the Baseline visit until the EoS. This is reflected in

establishing corrected standardized relative risk (sRR) for the POROUS R3C ultrasound device-derived POROUS-Score. Statistically significant prediction power of the sRR will be achieved if the lower limit of the 95% confidence interval of the sRR is greater than 1. The POROUS-Score will be evaluated to demonstrate the predictive performance of the POROUS R3C ultrasound device for incident fractures.

The following fractures, which are associated with cortical bone and/or increasing age, will be considered for collecting information on both prevalent and incident fractures. Any incident fractures caused by high-energy external forces will be excluded (censored) from the analysis.

Proximal humerus, Shaft of humerus, Distal humerus , Proximal ulna, Shaft of ulna, Proximal radius, Shaft of radius, Distal radius, Thoracic spine , Lumbar spine, Rib, Multiple ribs, Pelvic ring, Acetabulum, Femur subtrochanteric, Femur femoral neck, Femur pertrochanteric, Shaft of femur, Distal femur, Proximal tibia, Shaft of tibia, Distal tibia, Fibula/lateral malleolus

Fracture risk prediction model

The diagnostic value of physical biomarkers, which are derived from Baseline measurements with the POROUS R3C ultrasound device, will be assessed, and selected physical biomarkers will be integrated into a model, resulting in a composite POROUS-Score, for fracture risk prediction. In Part 1, the model will be developed using data on prevalent fractures, while in Part 2, the model will

be developed using data on incident fractures. The resulting POROUS-Scores are, therefore, different in Part 1 and Part 2. In Part 1, it is termed POROUS-ScorePrev, whereas in Part 2, it is termed POROUS-Score. Additionally, anthropometric data (age, sex, and BMI) will be evaluated and selected for adding predictive strength to the prediction model.

Part 1:

Prevalent fractures will be recorded, and all relevant variables, including ultrasound parameter values and anthropometric information, will be used to perform partial least squares - discriminant analysis (PLS-DA) followed by subwindow permutation analysis using a Monte-Carlo approach. Only variables that have statistically significant discriminative power will be used in the next step, where a new fracture discrimination model will be created using PLS-DA analysis. Thereafter, the performance of the model will be investigated using receiver operating characteristics (ROC) analysis.

The PLS-DA yields the final composite POROUS-ScorePrev (generated from the internally validated model). Then, standardized odds ratios (sOR) will be calculated, for the final composite POROUS-ScorePrev (generated from the internally validated model), i.e., the fold-increase of the relative fracture risk per standard deviation decrease of the respective score. Similarly, the sOR will be calculated for the DXA T-scores. Since the comparative data are not from randomized groups, confounders will be analyzed (e.g. clinical risk factors, age, sex, and anthropometric data) in the association between the DXA

T-score and prevalent fractures. The model shall be adjusted if the confounders* effect is different from the effects reported in the literature. Finally, the POROUS sOR will be corrected based on a formula for the assessment of peripheral bone densitometry devices, officially published by The International Society for Clinical Densitometry (ISCD):

ln(sORcor) = ln(sORstudy(POROUS)) x ln(sORref (DXA)) / ln(sORstudy (DXA))

The sORs in this study are sORstudy(POROUS) and sORstudy(DXA); sORref(DXA) is obtained from published meta-analyses. The sORcor correction is needed to (i) normalize the sOR against the gold standard DXA and (ii) account for the potential effects on sOR caused by the study population. The discriminative ability of the POROUS model for prevalent fractures is demonstrated if the lower limit of the 95% confidence interval of the corrected sOR is higher than 1.

Part 2:

Incident fractures will be recorded, and all relevant variables, including ultrasoundparameter values and anthropometric information, will be used to perform PLSDA followed by sub-window permutation analysis using a Monte-Carlo approach.Only variables that have statistically significant predictive power will be used in the next step, where a multivariate Cox-proportional Hazard

model will be performed to calculate the hazard ratio (HR). Then, the model performance will be investigated using ROC analysis. Internal validation of the model will be done by running cross-validation followed by Bootstrap analysis.

The sRR will be calculated, i.e., the fold-increase of the relative fracture risk per standard deviation
decrease of the respective score. Similarly, the sRR will be calculated for the DXA T-scores. Since the comparative data are not from randomized groups, confounders (e.g. clinical risk factors, age, sex, and anthropometric data) will be analyzed in the association between the DXA T-score and incident fractures. The model shall be adjusted if confounders* effect is different from the effects reported
in the literature. Finally, the POROUS sRR will also be corrected based on a formula for the assessment of bone peripheral densitometry devices, officially published by the ISCD:

ln(sRRcor) = ln(sRRstudy(POROUS)) x ln(sRRref (DXA)) /
ln(sRRstudy (DXA))

The sRRs in this study are sRRstudy(POROUS) and sRRstudy(DXA); sRRref(DXA) is obtained from published meta-analyses. The sRRcor correction is needed to (i) normalize the sRR against the gold standard DXA and (ii) account for the potential effects on sRR caused by the study population. The predictive ability of the POROUS model for incident fractures is demonstrated if the lower limit

of the 95% confidence interval of the corrected sRR is higher than 1.

Secondary outcome

Safety endpoints

In order to establish that the POROUS R3C ultrasound device is safe with a minimal number of adverse events affecting the participants or the healthcare professionals using the device, the following safety endpoints are investigated:

• Incidence of procedural/device-related adverse events, caused by the

o Absorbed energy

o Probe/transducer heating

o Irritation by ultrasound gel

o Release of substances

o Inappropriate hygiene measures.

• Other (serious) adverse events.

Performance endpoints

The discriminative and predictive performance of the POROUS R3C ultrasound device will be analysed for prevalent and incident fractures, respectively.

Part 1:

Establish discriminative performance of the POROUS R3C ultrasound device in comparison with DXA based on prevalent fractures. sOR values for both POROUS-ScorePrev and DXA T-Score will be compared by applying ROC analysis.

Part 2:

Establish predictive performance of the POROUS R3C ultrasound device in comparison with DXA based on incident fractures. Standardized hazard ratio (sHR) values for both POROUS-Score and DXA T-Score will be compared by applying Cox-proportional hazard modelling.

Exploratory endpoints

Performance endpoints

Part 1:

• Establish associations of various ultrasound parameters measured by the POROUS R3C ultrasound device with specific clinical risk factors/indicators for vertebral and hip fractures (as outlined by the DVO), including BMD, age, sex, BMI, and prevalent fractures.

• Establish corrected sOR for prevalent fractures (e.g. hip, vertebral, and major osteoporotic fractures) and demonstrate significant performance.

• Establish reference data for developing age-matched POROUS Z-scores using the POROUS R3C ultrasound device based on prevalent fractures.

Part 2:

• Establish associations of various ultrasound parameters measured by the POROUS R3C ultrasound device with specific clinical risk factors/indicators for vertebral and hip fractures (as outlined by the DVO), including BMD, age, sex, BMI, and incident fractures.

• Establish corrected sRR for incident fractures (e.g. hip, vertebral, and major osteoporotic fractures) and demonstrate significant performance.

• Establish reference data for developing age-matched POROUS Z-scores using the POROUS R3C ultrasound device based on incident fractures.

Treatment effect endpoints

• Treatment effect of anti-osteoporotic (anti-resorptive/anabolic) medication on DXA T-Scores and POROUS-Scores with respect to fracture incidence.

• Treatment effect of drugs known to influence bone metabolism on DXA T-Scores and POROUS-Scores (oral glucocorticoid of >= 2.5 mg/day prednisone equivalent for > 3 months, proton pump inhibitors, aromatase inhibitors, hormone ablation therapy/antiandrogens in male participants).

Study description

Background summary

Brief description of the investigational device

The POROUS R3C is an ultrasound device for measuring and quantifying microstructural, acoustic, and viscoelastic properties in cortical bone (e.g., in the tibia of the lower limb). The purpose of the device is to analyse the microstructural, acoustic, and viscoelastic properties of human cortical bone, to discriminate prevalent fractures, and to predict fracture risk in an aging population. The accompanying software generates B-mode images for guidance and stores pre-beamformed data for further analysis. These performance abilities are based on data obtained by ultrasound imaging and measurement of cortical bone properties. The output parameter values can be used to assess bone state and quality and determine physical biomarkers in cortical bone. The standardized risk ratios are obtained from measurements at the midshaft tibia and estimate the risk for fractures at various bone sites (e.g., spine and hip) in an aging population.

Clinical investigation purpose and background

Currently, osteoporosis and fracture risk are indirectly evaluated via the assessment of risk factors and bone mineral density (BMD) measurement. Although BMD is currently the most important indicator for osteoporosis associated bone fractures, most of those fractures occur in persons who do not show pathologically reduced BMD value. Therefore, osteoporosis is one of the most frequently underdiagnosed common diseases. Established guidelines for the diagnosis of osteoporosis recommend the assessment of fracture risk factors and the T-Score, which is derived from the measurement of areal bone mineral density (aBMD) by means of DXA at major fracture sites, i.e. spine and proximal femur. DXA is regarded as the *gold standard* well-established methodology to determine aBMD for diagnostic purpose.

Epidemiological data emphasise the urgency of developing diagnostic tools that can improve fracture risk prediction so that patients can be treated with the appropriate anti-osteoporotic therapies. Current guidelines for diagnosis and treatment lead to treatment gaps. It is estimated that at least 80% of males and 77% of females who would benefit from osteoporosis treatment are neither diagnosed nor treated in Germany. The POROUS R3C ultrasound device enables a non-invasive, non-ionising quantitative detection of microstructural bone changes. As opposed to diagnosis based on a combination of clinical risk factors and a relative decrease of BMD, the novel device enables detecting pathological changes of bone microstructure at an earlier timepoint as well as monitoring such changes in a longitudinal manner. In the course of this clinical investigation, data will be collected to establish relevant ultrasound-based physical biomarkers for the prediction of fracture risk.

Study objective

Primary objectives
Part 1:
• To establish a corrected standardized gradient of fracture risk using the POROUS R3C ultrasound device based on prevalent fractures.
Part 2:
• To establish a corrected standardized gradient of fracture risk using the POROUS R3C ultrasound device based on incident fractures and to demonstrate the predictive performance of the derived fracture risk,

Secondary objectives
Part 1:
• To compare the discriminative performance of the POROUS R3C ultrasound device and standard-of-care DXA based on prevalent fractures.
Part 2:
• To assess the safety of the POROUS R3C ultrasound device by monitoring adverse events affecting participants or the healthcare professionals using the device.

• To compare the predictive performance of the POROUS R3C ultrasound device and standard-of-care DXA based on incident fractures.

Exploratory objectives
Part 1:
• To assess the association of various ultrasound parameters measured by the POROUS R3C ultrasound device with specific clinical risk factors/indicators for vertebral and hip fractures (as outlined by the DVO) and prevalent fractures.
• To demonstrate the discriminative performance of the POROUS R3C ultrasound device based on subgroups of prevalent fractures, e.g., hip, vertebral, and major osteoporotic fractures.
• To establish reference data for developing age-matched POROUS Z-scores using the POROUS R3C ultrasound device based on prevalent fractures.

Part 2:
• To assess the association of various ultrasound parameters measured by the POROUS R3C ultrasound device with specific clinical risk factors/indicators for vertebral and hip fractures (as outlined by the DVO) and incident fractures.
• To demonstrate the predictive performance of the POROUS R3C ultrasound device based on subgroups of incident fractures, e.g., hip, vertebral, and major osteoporotic fractures.
• To establish reference data for developing age-matched POROUS Z-scores using the POROUS R3C ultrasound device based on incident fractures.
• To explore the treatment effect of anti-osteoporotic medication
• To explore the treatment effect of drugs known to influence bone metabolism.

Study design

This is a single-cohort, multicentre, prospective, age- and sex-stratified study in participants > 55 years of age. In this study, Baseline data will be collected to establish a corrected standardized gradient of fracture risk using the POROUS R3C ultrasound device and test its performance in predicting fracture risk. Further, the performance of the POROUS R3C ultrasound device in the analysis of cortical bone properties and discrimination of prevalent fractures will be assessed. Participants will be enrolled into different groups based on their age (consisting of five-year bands), sex (males and females), and risk status for hip and vertebral fractures (i.e., high risk of >= 2-fold and low risk of < 2-fold increased risk compared to the general population of the same age and sex).

Two measurements with each device: investigational device (POROUS R3C ultrasound device at the midshaft tibia), and comparator (DXA of the lumbar spine and proximal femur), are scheduled per participant:
• Measurement 1: At Baseline
• Measurement 2: At the End-of-Study (EoS) visit.

Part 1:

In Part 1, information on prevalent fractures will be used to establish a corrected standardized gradient of fracture risk using the POROUS R3C ultrasound device. In other words, Part 1 aims to establish the discriminative performance and a standardized gradient of fracture risk based on prevalent fractures. In addition, the discriminative performance of the POROUS R3C ultrasound device and standardof-care DXA will be compared based on prevalent fractures.

Part 2:
In Part 2, information on incident fractures will be used to establish a corrected standardized gradient of fracture risk using the POROUS R3C ultrasound device. It will be developed to demonstrate the predictive performance of the derived fracture risk. In other words, Part 2 aims to establish a standardized gradient of fracture risk based on incident fractures. In addition, the predictive performance of the POROUS R3C ultrasound device and standard-of-care DXA will be compared based on incident fractures. The collection of data obtained by DXA and the POROUS R3C device at the EoS visit is used to monitor changes in the bone state in comparison to the respective data obtained at Baseline. However, only measurement data obtained by the POROUS R3C device at Baseline is used to develop the POROUS-Score model and the standardized gradient of fracture risk (for Part 1 and Part 2).

Intervention

Intervention 1
Measurement with POROUS R3C ultrasound device at midshaft tibia
Measurements are to be performed at the central antero-medial tibia region. The tibia length is assessed as the distance between the medial knee joint cleft and the medial malleolus. The ultrasound transducer is coupled to the skin at this position using an ultrasound coupling pad. Then transducer must be positioned about 1cm above the surface of the skin using a gel pad. Conventional B-mode images are used to position the probe. The probe has then to be manually tilted until the bone surface is approximately normal to the sound beam direction and the focus position is adjusted to be approximately aligned with the periosteal bone surface. Scans of the bone using the CortBS (x2) and Multifocus (x2) methods must be performed. The 3D acquisition minimises the operator dependence of the measurement. This is done manually using the probe applicator and sweep module. Beamsteering sequences must be used to send focused beams at multiple inclination angles to the cortical bone surface.

Intervention 2
Radiation:DXA measurement , lumbar spine and prox. femur
The aBMD of the lumbar spine and the proximal femur at Baseline and at the EndofStudy visit after 36 months are assessed via DXA. The following DXA measurements are to be performed:

Spine L1-4
Hip left (alternatively Hip right, if a valid measurement of the left hip is not possible)

Intervention 3
Radiation: DXA-based VFA. Alternatively, VFA may be replaced by projectional radiography
DXA-based Vertebral Fracture Assessment (VFA) of thoracic and lumbar spine from T4 to L5 (Alternatively, VFA may be replaced by projectional radiography of thoracic spine T4-T12 and lumbar spine L1-L5 if DXA-based VFA is not available.

Intervention 4
Radiation: Projectional radiography of thoracic spine (alternatively to DXA based VFA, if it is not available).
Projectional radiography of thoracic spine T4-T12 and lumbar spine L1-L5

Study burden and risks

Risks of the clinical trial

POROUS R3C is a device which applies ultrasound energy into the human body where it is resorbed. Like other ultrasound devices, it does not emit ionising radiation. Risks related to the output of acoustic levels are reduced by fulfilment of the applicable standard ISO 60601-2-37. Appliance of ultrasound energy is performed and experienced for a long time, risks arising from this kind of energy can be assumed to be under control.

Safety incidents or adverse effects might be caused by the emitted non-ionising radiation, probe/transducer overheating, the release of substances, and inappropriate hygiene measures.

A too-high output level of the device might cause thermal stress in the measured participant*s body, which can lead to serious injury. Temporary, mild skin irritation as a result of a reaction to the ultrasound gel is not common but possible.

The safety of the gold standard and comparator DXA is well-known. DXA scanning involves exposure to low-dose ionising radiation. In this clinical investigation, a single DXA scan for assessing BMD values and T-Score reaches a maximum radiation dose of ~0.08 mSv. Even if the Vertebral Fracture Assessment is done with conventional X-Ray (alternativly to DXA) a maximum radiation dose of ~0.22 mS. For comparison, the total worldwide average effective dose from naturally occurring background radiation is approximately 2.4 mSv per year.

The overall risks for the study participants associated with the use of the investigational device and the use of other techniques in the clinical investigation are acceptable from the sponsor's point of view.

Benefits of the clinical trial

Participation in the clinical trial may result in an indirect benefit for participants if a diagnosis of osteoporosis is made as a result of the DXA examination and early treatment can be initiated (independently of the investigation).

The aim of the study is to evaluate the performance of the POROUS R3C device for fracture risk prediction. This increase in knowledge can form the basis for further studies on the further development of refined models for fracture risk prediction and the diagnosis of osteoporosis. If the POROUS method becomes established, it would have advantages over the current gold standard DXA: The method is based on ultrasound technology, which does not involve the use of ionising radiation. The operating costs are low and the availability of the mobile device could be higher than that of DXA. In addition, the direct measurement of physical parameters makes it possible to derive microstructural, macrostructural and viscoelastic properties of the cortical bone that are associated with the pathogenesis of osteoporosis. This promises an increased gain in knowledge compared to the DXA BMD. By reconstructing a 3D image of the cortical bone, the microarchitecture of the bone, including osteoporotic pores, can be analysed. Patients benefit from the improved ability to predict fracture risk and, if necessary, to initiate therapeutic measures at an early stage.

Conclusion of the risk analysis

By analysing the risks the Sponsor comes to the conclusion that the probability that participants in the clinical investigation will experience a benefit (due to the incidental finding of osteoporosis with DXA) or will not be harmed by the examinations outweighs the probability of harm due to a residual risk of the procedures used. All residual risks are considered acceptable mostly because of low occurrence probability. In addition, there is the great general benefit of the POROUS application, provided that the method whose benefits are to be demonstrated here becomes established. The benefit/risk profile is, therefore, determined as acceptable for the clinical investigation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Female or male individuals aged 56 to and including 85 years.
• Written informed consent has been obtained.

[Let op: Klinische risicofactoren die nodig zijn voor het berekenen van het risico op heup- en wervelfracturen (op basis van het risicoberekeningsschema van de DVO-richtlijn osteoporose) worden tijdens de screening verzameld. Dit gebeurt om over- of ondervertegenwoordiging te voorkomen met betrekking tot de vereiste steekproefgrootte van deelnemers met een >= 2-voudig verhoogd leeftijds- en geslachtsgecorrigeerd risico op heup- en wervelfracturen en deelnemers met een < 2-voudig verhoogd leeftijds- en geslachtsgecorrigeerd risico.]

Exclusion criteria

• Presence of diseases that rule out valid measurements with the DXA and/or POROUS R3C devices (e.g., fractures or metal implants in the examined bones, paralysis of the lower extremities, severe bone abnormalities).
• Inability to undergo the investigations required by the Clinical Investigation Plan (CIP) or cognitive limitations that preclude understanding of the Participant Information Sheet and the Informed Consent Document.
• Previous medical procedures involving exposure to a cumulative dose of

ionising radiation deemed by the Investigator to exceed usual limits within standard of care.
• Enrolment in any other interventional clinical study (current or during the last three months)
• Close affiliation with an investigational site, e.g. employed at investigational site, close relative of an investigator, dependent person (e.g. student of the investigational site).

Further, individuals who are being or have been treated within the indicated period prior to the beginning of the study with any of the following antiresorptive therapies are excluded from the clinical investigation:
• Bisphosphonates (due to residual effects of bisphosphonates after discontinuation):
o Intravenous (IV) zoledronate within the last 3 years.
o Oral alendronate within the last year, if (continuous) treatment duration before was > 1 year.
o Oral risedronate within the last year, if (continuous) treatment duration before was > 1 year.
o Ibandronate (IV or oral) within the last year, if (continuous) treatment duration before was > 1 year.
• Denosumab within the last 3 years
• Hormone replacement therapy (HRT) including combination therapy or oestrogen alone in postmenopausal women within the last 6 months.
• Raloxifene within the last 6 months.

Individuals who are being or have ever been treated with any of the following anabolic therapies are excluded from the clinical investigation:
• Teriparatide
• Romosozumab
• Abaloparatide.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	03-03-2025
Enrollment:	320
Type:	Anticipated

Medical products/devices used

Generic name:	POROUS R3C ultrasound device
Registration:	No

Ethics review

Approved WMO Date:	21-02-2025
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	NCT06567054
CCMO	NL86252.000.24