Osteoporosis research using peripheral quantitative computarized tomography (pQCT) of the tibia

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Primary ObjectiveThis proposal concerns the inclusion of a peripheral quantitative computed tomography (pQCT) device in the Rotterdam Study to perform osteoporosis etiological research. Since 1990, the Rotterdam Study has performed research in the...

Ethical review	Approved WMO
Status	Pending
Health condition type	Fractures
Study type	Observational non invasive

Summary

ID

NL-OMON56827

Source
ToetsingOnline

Brief title
Osteoporosis research using pQCT

Condition

- Fractures

Synonym
osteoporosis

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Vidi subsidie project nummer :NWO-ZonMW Vidi 016.136.367).

Intervention

Keyword: cortical BMD, osteoporosis, tibia, trabecular BMD

Outcome measures

Primary outcome

The main outcome measure by the device is volumetric bone mineral density (vBMD) expressed in mg/cm2. To measure vBMD one needs to consider that bone consists of an organic and a mineral phase. About 38% of bone volume consists of hydroxyapatite and about 62% consist of collagen. The density of hydroxapatite is 3.2 g/cm³, the density of collagen is about 1.1 g/cm³. The density proportion of mineral is therefore 3.2*0.38 = 1.2 g/cm³, for collagen it is 0.68 g/cm³. Adding both yields a material density of 1.9 g/cm³. The calibration of the machine accounts only for the mineral portion. Therefore the measured material density of bone is about 1.2 g/cm³. In addition, vBMD can be measured for the trabecular and cortical compartments of the cross section. Trabecular density is defined as the mass of trabecular bone divided by endosteal volume, i.e. including bone marrow. Since cortical bone is composed to 90 - 98% of bone material and 2 - 10% of osteons, the measured cortical density is 90 - 98% of the material density.

Secondary outcome

Estimation of bone bending strength indexes: the SSI is directly proportional to the fracture load in a three-point bending test. If material properties and the geometry are known, the fracture load can be calculated according to the following formula: FB=4sB*SSI/l. In addition values for muscle- and fat areas are also calculated in the scans. The ratio of cortical to muscle area

(bone-muscle ratio) should be around 5% if the adaptation of bone to the muscle force is normal. Lower values might indicate a disturbance of this adaptation process. The Rotterdam Study withholds a very rich set of additional measurements and information collected from the participants, general practitioners and pharmacies that will allow studying diverse outcomes and with the ability to correct for a vast set of confounders.

Study description

Background summary

The Rotterdam Study is a single-center prospective population-based study of determinants of chronic disabling diseases in the elderly and has been approved by the medical ethics committee of Erasmus MC. The design and rationale of the study has been described earlier1. The original cohort (RS-I) includes 7,983 respondents. As of April 2000, an extension cohort of 3,011 individuals (RS-II) was included; and since March 2007, a younger cohort, including 3,932 individuals age >45 years are being assessed under the same protocols. Historically, DXA measurements have been obtained using GE-Lunar densitometers (DPX-L, Prodigy and iDXA). Incident fractures are collected from computerized records of the general practitioners (GPs) followed from baseline currently until January 1, 2007 (mean follow-up 12.2 years). In addition, X-rays scans of the thoracolumbar region have been collected and scored for vertebral fracture.

Osteoporosis has been operationally defined using bone mineral density (BMD). Nevertheless, the BMD measurement alone is not optimal for detecting individuals at high risk of fracture. Even though fracture risk is very high when BMD is low (high specificity), risk is not negligible when BMD is normal (low sensitivity). Bone strength needs to be significantly weakened before density criteria are met to diagnose osteoporosis. By implementing a high-resolution imaging technique one can expect to identify parameters of bone structure and quality that are subject to be detected earlier and can help in the prediction of osteoporosis and fracture. Most important this can be done in a timely manner and within a period when the consequences of the disease are still reversible.

One of these techniques is computerized tomography (CT). CT scanning allows higher spatial resolution and improved delineation of bone architecture overcoming many limitations of the DXA measurements. Yet, volumetric CT has

limitations including cost, accessibility and radiation exposure. The peripheral quantitative computerized tomography (pQCT) has become the method of choice in large scale projects, being fast, requiring no external shielding for radiation protection (radiation exposure < 0.001 mSV) and being highly reproducible.Trabecular architecture and cortical thinning are readily appreciable in the osteoporotic subject, and are reflected on the strength indexes measured by pQCT. Cortical bone parameters measured with pQCT include volumetric BMD, periosteal circumference and cortical thickness assessments. Trabecular volume, spacing, connectivity and number can only be assessed with MRI or high-resolution pQCT. Nevertheless, trabecular vBMD by pQCT is strongly correlated with total to trabecular bone volume (BV/TV) ratio and can be used as a reliable surrogate.

The current proposal is to acquire a STRATEC XCT2000 device to make pQCT measurements in all (n~13,000) Rotterdam study participants. CT scanning allows higher spatial resolution and improved delineation of bone architecture overcoming many limitations of the DXA measurements. Yet, volumetric CT has limitations including cost, accessibility and radiation exposure. pQCT has become the method of choice in large scale projects, being fast, requiring no external shielding for radiation protection (radiation exposure < 0.001 mSV) and being highly reproducible. Trabecular architecture and cortical thinning are readily appreciable in the osteoporotic subject, and are reflected on the strength indexes measured by pQCT. Cortical bone parameters measured with pQCT include volumetric BMD, periosteal circumference and cortical thickness assessments. Trabecular volume, spacing, connectivity and number can only be assessed with MRI or high-resolution pQCT. Nevertheless, trabecular vBMD by pQCT is strongly correlated with total to trabecular bone volume (BV/TV) ratio and can be used as a reliable surrogate.

The current proposal envisions using an STRATEC XCT 2000 device to make pQCT measurements in ~12,000 Rotterdam study participants. This is attempted considering that further research is needed to understand the underlying biology, improve risk prediction and develop novel disease interventions (treatments) for osteoporosis disease. The implementation of this pQCT imaging technology in the Rotterdam Study will bring the field one step further in this direction.

Note: the use of the exact same device has been approved by the ERASMUS MC METC (MEC-2012-165 amendment 2 NL40020.078.12 v06) to measure all children from the Generation R study (n ~6000 children).

Study objective

Primary Objective
This proposal concerns the inclusion of a peripheral quantitative computed tomography (pQCT) device in the Rotterdam Study to perform osteoporosis etiological research. Since 1990, the Rotterdam Study has performed research in

the general population, regarding diverse conditions and disease including osteoporosis. Most of this research has been done using a dual-energy X-Ray Absorptiometry (DXA) device, measuring bone mineral density to assess the presence of osteoporosis and risk of fracture. One of the disadvantages of DXA is that it is a two dimensional assessment, which does not characterize appropriately the three-dimensional structure of bone. Bone parameters like trabecular and cortical structures and material distribution (geometry) cannot be studied using DXA. It is for this reason that we want to expand the osteoporosis research program by means of including a peripheral quantitative computerized tomography (pQCT) device. PQCT is a 3-D technique, which allows the study of skeletal and muscle tissue at the tibia. Including this complementary measure in the Rotterdam Study will allow studying additional determinants of fracture in the elderly general population.

Secondary objectives
Given the multidisciplinary origin of the Rotterdam study we will be able to use the pQCT measurements to address additional research questions surrounding the use of additional assessments already present in the study, like medication use, comorbidity and detailed state of the art genetic measurements among others. This approach will allow identifying new approximations for the diagnosis and treatment of osteoporosis. In particular, we will study the biomechanics determinants of osteoporosis and fracture susceptibility in individuals from the general population aged 45 years and over. Ultimately we will pursue the construction of a risk profile that can complement the existent risk factor by inclusion of genetic and imaging data of the pQCT.

Study design

The Rotterdam Study is a long-standing prospective population-based study in 15.000 aged 45 years and over living in the Rotterdam suburb Ommoord. The Rotterdam Study is an initiative from the Department of Epidemiology of the Erasmus University Medical Center in Rotterdam. The Rotterdam Study is nationally and internationally recognized for its contribution to the understanding of the determinants of disease and disability of hundreds of entities, including those related to locomotor disease. Description of the rationale of the study with a succinct listing of the scientific publications is to be found in a recent publication in the European Journal of Epidemiology (Hofman et al. 2014). All scientific publications (more than 1000) are listed in the website of the Department of Epidemiology of Erasmus MC (http://www.epib.nl). The medical ethics committee of Erasmus MC has approved the Rotterdam Study and all participants have provided written informed consent.

Study burden and risks

As with any device employing radiation sources care must be taken to avoid

unnecessary exposure. The device is approved for use by the Erasmus MC Radiation Protection Unit (Stralingsbeschermingseenheid - SBE). This provisions are clearly described for the operator in the protocol of operations of the pQCT device (see Annex) and for the Rotterdam Study participants in the information folder (see Annex).

The XCT 2000 radiation dose is measured using thermoluminescent dosimetry in order to simulate the x-ray attenuation and scatter of a human forearm. An array of TLD chips is used so that the actual distribution of the dose may be determined. The skin dose is 90 µSv for the CT scan and 35 µSv for the scout scan. According to W. Kalender (Osteoporosis Int (1992) 2: 83-97) the effective dose can be calculated: Multiplication of the skin dose of 90 µSv with a relative amount of 2% of the irradiated marrow from the total bone marrow yields the organ dose of 1.8 µSv. Multiply this value with the weighting factor for bone marrow recommended by the ICRP of 0.12. The resulting effective dose is 0.22 µS. For the operator the dose is negligible. During a scan procedure, the total leakage plus scatter radiation is less than 10 µSv/hr at the scanner aperture.

The Stratec device has been used since 1998 in numerous studies including hundreds of thousands of individuals placing no question about the safety of its operation.

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

All Rotterdam Study participants

Exclusion criteria

none

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-07-2015
Enrollment:	15000
Type:	Anticipated

Ethics review

Approved WMO Date:	02-05-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
CCMO	NL53038.078.15