The effect of low-dose rhythmic 17-β-estradiol administration on bone turnover in postmenopausal women

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To investigate the effect of low-dose rhythmic transdermal 17-β-estradiol on serum P1NP (marker of bone formation) and CTX (marker for bone resorption), versus continuous low-dose and standard-dose continuous transdermal 17-β-...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON53396

Source
ToetsingOnline

Brief title
REBEL

Condition

- Other condition
- Bone disorders (excl congenital and fractures)

Synonym
Osteoporosis prevention

Health condition

preventie osteoporose

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: bone turnover markers, estrogen, hormone replacement therapy, postmenopause

Outcome measures

Primary outcome

The endpoint is the interaction between treatment and time on serum P1NP levels. (Does the change over time differ between the treatment arms?). The primary outcome will be measured every two weeks from baseline until 16 weeks of treatment.

Secondary outcome

1. The secondary endpoint is the interaction between treatment and time on serum CTX levels. (Does the change over time differ between the treatment arms?) The outcome will be measured every two weeks from baseline until 16 weeks of treatment.

2. Mean change of fasting glucose, fasting insulin, 2-hour post OGTT glucose and insulin and liver steatosis (CAP score) after 16 weeks of treatment. These parameters will be measured at baseline and after 16 weeks.

3. Sleep quality (PSQI) and chronotype (MCTQ) and menopausal symptoms (GCS) after 16 weeks in relation to baseline.

4. In a subgroup: To assess the effect of low-dose rhythmic transdermal 17-β-estradiol versus continuous low-dose and standard-dose continuous transdermal 17-β-estradiol on 17-β-estradiol transcriptional regulation in adipose tissue

using ChipSeq and RNA seq analysis (hypothesis-generating).

Study description

Background summary

Postmenopausal estrogen deficiency leads to accelerated bone resorption, resulting in an increased risk of osteoporosis and osteoporotic fractures. Continuous estrogen replacement therapy (ERT) with 17-β-estradiol is an effective treatment for the prevention of osteoporosis in postmenopausal women. ERT normalizes bone turnover by attenuating bone remodelling, reflected by a decrease of bone turnover markers procollagen type 1 N propeptide (P1NP) and C-terminal telopeptide of type 1 collagen (CTX). Notably, estrogen replacement can also induce an anabolic effect in bone tissue, which is not well studied.
The anabolic effect of 17-β-estradiol occurs when continuous estrogen replacement therapy is first initiated. After initiation of 17-β-estradiol therapy, serum concentrations of bone formation marker P1NP rise, while a decrease of bone resorption marker CTX is observed, suggesting that an increase of serum 17-β-estradiol generates an initial anabolic response in bone tissue. Similarly, when serum 17-β-estradiol levels physiologically increase during the luteal phase of the menstrual cycle, a simultaneous increase of P1NP is observed, in combination with a decrease of CTX levels. Therefore, we hypothesize that, by mimicking the rhythmic estrogen concentrations during the menstrual cycle in postmenopausal women, a subsequent rhythmic rise of bone formation marker P1NP can be induced, and as a result, improved bone formation.
In addition to the regulation of bone metabolism, estrogens regulate key features of glucose metabolism and energy expenditure. Estrogen deficiency after menopause leads to accumulation of visceral fat, as well as altered insulin sensitivity and insulin secretion. A previous meta-analysis demonstrated that estrogen replacement therapy (ERT) has beneficial effects on insulin resistance and fasting glucose levels in postmenopausal women. Oral HRT produced larger beneficial effects glucose than transdermal HRT. However, transdermal estrogen was administered continuously in all studies. We hypothesize that rhythmic transdermal estrogen administration may produce larger beneficial effects on glucose regulation than continuous transdermal estrogen administration, in postmenopausal women.
The increase in visceral fat that is observed in estrogen deficiency is partly the result of classical (genomic) estrogen effects on adipose tissue. Estrogen therapy in postmenopausal women decreases the expression of genes involved in lipogenesis (including LPL and FAS). However, it is unknown how rhytmic 17-β-estradiol will affect this gene expression on a transcriptional level. We will perform ChipSeq and RNA Seq analysis of the effect of rhythmic 17-β-estradiol versus low-dose and standard-dose continuous 17-β-estradiol on

transcriptional regulation in subcutaneous adipose tissue.

Study objective

To investigate the effect of low-dose rhythmic transdermal 17-β-estradiol on serum P1NP (marker of bone formation) and CTX (marker for bone resorption), versus continuous low-dose and standard-dose continuous transdermal 17-β-estradiol administration.

This study will aid to improve understanding of estrogen-mediated effects on bone turnover in postmenopausal women. Furthermore, this study will lead to advancements of knowledge to improve the estrogen treatment regimen for prevention of osteoporosis in postmenopausal women.

Study design

We will conduct a monocenter open-label randomized controlled trial, investigating the effect of rhythmic 17-β-estradiol versus low-dose and standard-dose continuous 17-β-estradiol on bone turnover markers P1NP and CTX. This monocenter study will be set at Amsterdam UMC, location AMC and the study duration is 16 weeks.

Intervention

Each treatment arm has a treatment duration of 16 weeks (4 cycles of 4 weeks).

A transdermal treatment regimen will be implemented. The risk venous thromboembolism is not elevated in transdermal estrogen users when compared to non-users of estrogen. The risk of breast cancer and ovarian cancer is not increased when estrogen replacement therapy is used for less than 1 year. Recent prospective studies suggest that transdermal estrogen therapy (<=50ug/24hrs) does not elevate stroke risk.

• Group 1. Rhythmic 17-β-estradiol:
Alternating cycles consisting of transdermal 17-β-estradiol 25 µg/24 hr for two weeks,
followed by two weeks of transdermal 17-β-estradiol 50 µg /24 hr. Estrogen therapy will be
combined with continuous oral micronized progesterone 100 mg once daily in the evening.

• Group 2. Low-dose continuous 17-β-estradiol:
Continuous transdermal 17-β-estradiol 25 µg/24 hr, combined with continuous oral micronized progesterone 100mg daily once daily in the evening.

• Group 3. Standard-dose continuous 17-β-estradiol:

Continuous transdermal 17-β-estradiol 50 µg/24 hr, combined with continuous oral micronized progesterone 100mg daily once daily in the evening.

Study burden and risks

Baseline: Participants* medical history and family history will be collected. The participants* height, weight and blood pressure will be measured, and a chronotype and sleep quality questionnaire (MCTQ and PSQI) will be filled in at baseline.
For screening purposes, blood samples will be collected (3 tubes) to assess complete blood count, calcium, creatinine, ALAT, alkaline phosphatase, serum FSH, TSH, HbA1c(%) and 25-hydroxyvitamin D (25(OH)D.
In addition, baseline measurements of P1NP, CTX, estradiol, fasting glucose, and fasting insulin will be conducted (4 tubes), an oral glucose tolerance test (OGTT) will be performed and an ultrasound of the liver will be performed (fibroscan).
During treatment: P1NP, CTX, and serum estradiol will be measured every other week from baseline until week 16 (one tube at each time point).
A fasting glucose, fasting insulin, and an oral glucose tolerance test (OGTT) and an ultrasound of the liver will be performed (fibroscan) after 16 weeks of treatment.
A chronotype questionnaire and sleep quality questionnaire and menopausal symptoms questionnaire will be filled in at baseline and after 16 weeks of treatment.

Benefits: Participation in the trial does not involve an expected individual benefit for the participant other than relieving possible climacteric symptoms. However, there might be a group benefit if physiological low-dose estrogen therapy leads to increased bone turnover and improved treatment for the prevention of osteoporosis in postmenopausal women.

Risks: Blood draws may cause bruising at the site of the punctured vein. Participants may experience side effects of the transdermal 17-β-estradiol treatment. The most common side effects are rash at the site of the transdermal patch (20.8%), redness at the site of the patch (8.5%), itchiness at the site of the patch (19.8%), headache (7.8%), and breast tenderness (6.6%) (SmPC systen). Progesterone may cause the following side effects: vaginal bleeding, breast tenderness, nausea, dizziness, somnolence (1-4 hours after administration), headache (SmPC uterogestan). There is no excess risk of venous thromboembolism in transdermal 17-β-estradiol users. Hormone replacement therapy for less than 1 year does not lead to increased risk of breast cancer (SmPC Systen).

Risks fat biopsy: Participants will experience discomfort during the application of local anaesthesia, but thereafter the procedure is painless. A subcutaneous hematoma will develop after the fat biopsy, but this will gradually resolve. The subcutaneous fat biopsy can possibly cause bleeding or

an infection around the site of the biopsy.

Contacts

Public
Amsterdam UMC

Meibergdreef 9
Amsterdam 1105AZ
NL
Scientific
Amsterdam UMC

Meibergdreef 9
Amsterdam 1105AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Postmenopausal, defined as final menstrual cycle more than 12 months prior to inclusion and FSH>30 IU/L
- Final menstrual cycle < 10 years prior to inclusion
- Age 45-60 years

Exclusion criteria

• Contra-indication for estrogen and/or progesterone therapy: Presence or

suspicion or history of breast cancer, endometrial cancer, ovarian cancer, presence or history of venous thromboembolism, arterial thrombosis (e.g. myocardial infarction, angina pectoris) inherited or acquired thrombophilia, presence of liver disease, untreated endometrial hyperplasia, abnormal vaginal bleeding, porphyria, uncontrolled or severe hypertension)
• First-grade family member with inherited thrombophilia or history of VTE under the age of 60 years
• Hysterectomy
• Premature menopause (menopause age <40 years)
• Known hypersensitivity to the excipients in the estradiol patch: acrylate copolymer, polyethylene terephthalate, α-tocopherol, soy allergy or peanut allergy (component of progesterone capsule)
• Hormonal contraception or hormone replacement therapy use (estradiol with or without progesterone) in the past 12 months
• Presence or history of any clinically relevant metabolic, endocrinological, hepatic, renal, cardiovascular, gastrointestinal, or respiratory conditions, history of bone disease or bone marrow disease, known vitamin D deficiency (25-OH vitamin D <30 nmol/L)
• Recent fracture (<12 months)
• BMI <20 or BMI >=30
• Use of drugs including herbal medicine known to affect bone metabolism (e.g. corticosteroids) or to interfere with cytochrome P450 enzyme (CYP) pathways. Exceptions are occasional use of paracetamol, ibuprofen, acetylsalicylic acid or topical medication
• For adipose tissue biopsy: anticoagulant treatment, allergy to lidocaine

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	19-07-2023
Enrollment:	48
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	17-beta-estradiol
Generic name:	Systen
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	progesterone
Generic name:	uterogestan
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	27-03-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-05-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC

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
EudraCT	EUCTR2022-003866-19-NL
CCMO	NL83336.018.23