Author(s): Jussila, Ilkka; Ahtiainen, Juha P.; Laakkonen, Eija K.; Siltari, Aino; Kaipia, Antti; Jokela, Tiina; Kärkkäinen, Minta; Newton, Rob; Raastad, Truls; Huhtala, Heini; Murtola, Teemu J.; Seikkula, Heikki

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Original Article

Transdermal oestradiol and exercise in androgen deprivation therapy (ESTRACISE): protocol

Ilkka Jussila[1,2], Juha P. Ahtiainen[2], Eija K. Laakkonen[2], Aino Siltari[3], Antti Kaipia[5], Tiina Jokela[2], Minta Kärkkäinen[2], Rob Newton[6], Truls Raastad[7], Heini Huhtala[4], Teemu J. Murtola[3,5] and Heikki Seikkula[1]

[1]*Surgery Clinic, Wellbeing Services County of Central Finland, Jyvaskyla,* [2]*Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä,* [3]*Faculty of Medicine and Health Technology,* [4]*Faculty of Social Sciences, Tampere University,* [5]*Department of Urology, TAYS Cancer Center, Tampere, Finland,* [6]*Sports Science and Exercise Medicine, Edith Cowan University, Joondalup, WA, Australia, and* [7]*Department of Physical Performance, Norwegian School of Sport Sciences, Norwegian, Norway*

Objective

To report the protocol of a study evaluating the efficacy of transdermal oestradiol (E2) gel in reducing the adverse effects of androgen deprivation therapy (ADT), specifically on sexual function, and to assess the utility of E2 in combination with supervised exercise.

Study Design and Methods

The primary endpoint of this open-label Phase IIA randomized controlled trial is the efficacy of transdermal E2 gel. Secondary endpoints include: (i) the occurrence of ADT-induced adverse effects; (ii) the safety and tolerability of E2; (iii) the impact of E2 with or without exercise on physical, physiological, muscle, and systemic biomarkers; and (iv) quality of life. The trial will recruit high-risk PCa patients (n = 310) undergoing external beam radiation therapy with adjuvant subcutaneous ADT. Participants will be stratified and randomized in a 1:1 ratio to either the E2 + ADT arm or the ADT-only control arm. Additionally, a subset of patients (n = 120) will be randomized into a supervised exercise programme.

Results

The primary outcome is assessed according to the efficacy of E2 in mitigating the deterioration of Expanded Prostate Cancer Index Composite sexual function domain scores. Secondary outcomes are assessed according to the occurrence of ADT-induced adverse effects, safety and tolerability of E2, impact of E2 with or without exercise on physical performance, body composition, bone mineral density, muscle size, systematic biomarkers, and quality of life.

Conclusion

The ESTRACISE study's innovative design can offer novel insights about the benefits of E2 gel, and the substudy can reinforce the benefits resistance training and deliver valuable new novel insights into the synergistic benefits of E2 gel and exercise, which are currently unknown.

Trial Registration

The protocol has been registered in euclinicaltrials.eu (2023-504704-28-00) and in clinicaltrials.gov (NCT06271551).

Keywords

prostate cancer, androgen deprivation therapy, transdermal oestradiol, exercise, resistance training

Introduction

Prostate cancer (PCa) is the most common cancer among men, with approximately 5000 new cases annually in Finland [1]. Treatment strategies vary depending on tumour staging, risk category, comorbidity, presence of symptoms, and patient preferences. For patients with intermediate- and high-risk PCa, external beam radiation therapy (EBRT) combined with

androgen deprivation therapy (ADT) is superior to EBRT alone [2–5].

Androgen deprivation therapy is typically achieved using LHRH agonists (LHRHa) or antagonists, which cause regression of PCa and enhance the effects of radiation and chemotherapy. However, ADT also leads to significant adverse effects, such as sexual dysfunction, diminished male secondary sexual characteristics, impotence, hot flashes, osteopenia, muscle weakness, and changes in body composition [6,7]. Approximately half of these adverse effects are attributed to the depletion of oestradiol (E2), a secondary condition resulting from ADT [8].

High-dose oral oestrogen, once used for PCa castration, has been replaced by parenteral oestrogen because of the thromboembolic risks linked to the hepatic metabolism of oral oestrogen [7]. Parenteral routes, avoiding this metabolism, are less likely to cause such complications. Phase II trials indicate no cardiovascular event increase with transdermal E2 compared to LHRHa in ADT [9]. An understanding of the effects of oestrogen and androgen deficiency from castration has led to renewed interest in non-oral E2 for mitigating the adverse impacts of ADT [9–12]. Non-oral E2 has been shown to lessen the bone, brain and metabolic adverse effects of ADT, reducing hot flashes, and improving patient quality of life [9,11,13,14]. As such, the primary aim of the ESTRACISE study is to evaluate the efficacy of transdermal E2 concomitant with LHRHa in mitigating ADT-induced adverse effects, especially on sexual function.

In addition to E2, regular exercise during ADT has been shown to reduce the adverse effects on musculature, enhancing aerobic fitness, muscular strength, physical function, body composition, and overall well-being [15–17]. However, the potential synergistic effects of combining E2 with exercise in mitigating ADT-induced adverse effects are not yet fully known. Based on previous studies [9,11,13–17], this study hypothesizes that these two interventions complement each other, with synergistic effects providing superior benefits. Thus, the secondary research aim is to investigate the combined utility of transdermal E2 and exercise in addressing the multifaceted spectrum of ADT-induced adverse effects by (i) determining the occurrence of ADT-induced adverse effects; (ii) estimating the safety and tolerability of transdermal E2 concomitant with ADT; (iii) assessing the impact of E2 with or without resistance training in mitigating the adverse effects of ADT on physical performance, body composition, bone mineral density, muscle size and quantity, and muscle and systemic biomarkers; and (iv) determining the influence of E2, with or without resistance training, on quality of life.

The novel potential of this study lies in its seeking to demonstrate the efficacy of low-dose transdermal E2 concomitant with ADT in mitigating the adverse effects of ADT, especially on sexual function. Furthermore, the integrated approach combining E2 with exercise can offer new valuable insights into the combination benefits, which are currently unknown.

Study Design and Methods

The ESTRACISE study is an open-label, Phase IIA randomised controlled clinical trial. The study will recruit 310 patients with high-risk PCa who are scheduled for EBRT with adjuvant subcutaneous ADT leuprorelin (LHRHa). Figure 1 shows the study design. Potential participants are identified from the patient pool at Wellbeing Services County of Central Finland, Tampere University Hospital Urology Outpatient Clinic, and possibly from other collaborating centres. These individuals are screened based on the inclusion and exclusion criteria. Eligible participants are informed about the study details, risks and benefits, and consent is obtained.

Randomisation

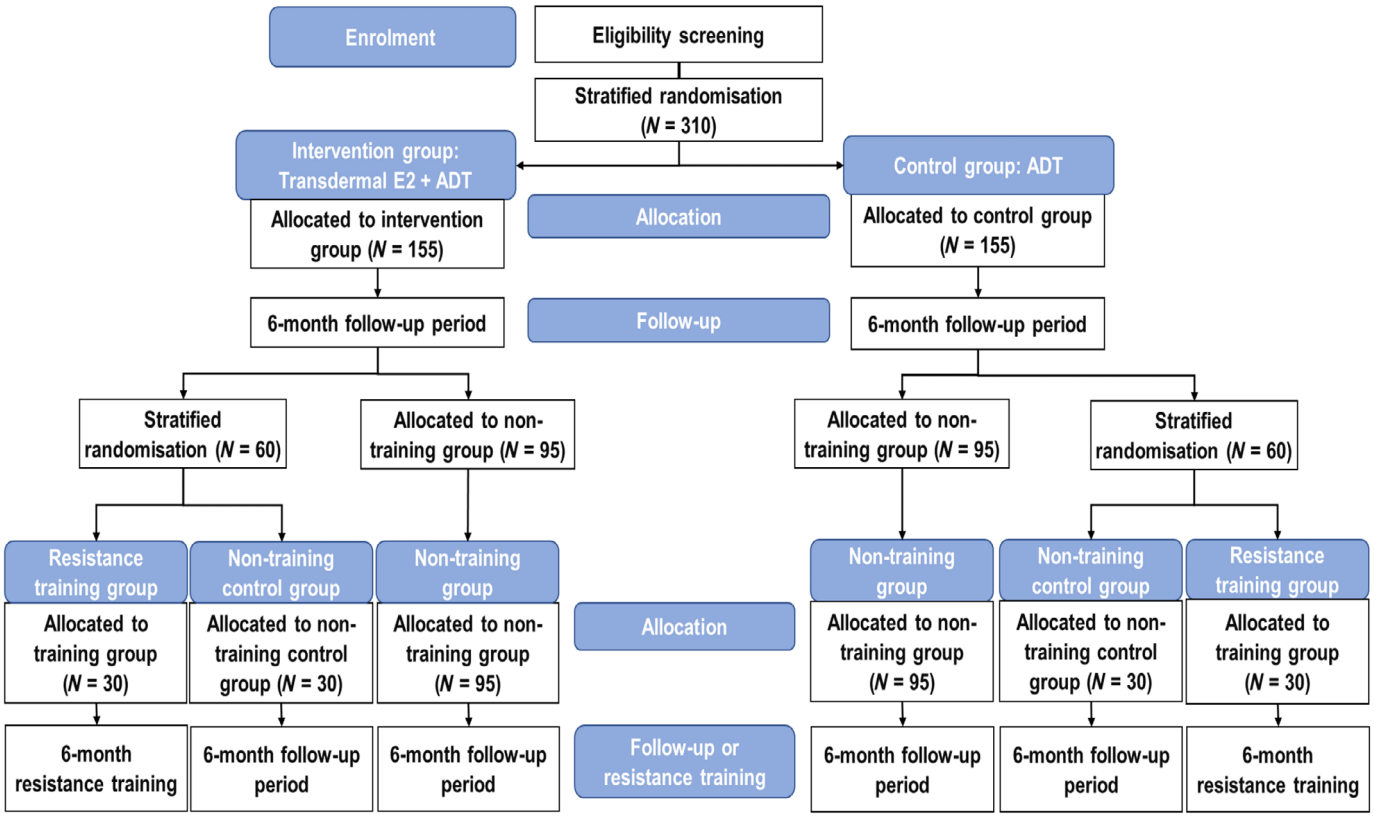
Participants (n = 310) will undergo stratified randomisation in a 1:1 fashion to either the E2 + ADT arm or the control arm of ADT only. The stratification will be based on two main covariates: sexual dysfunction score and body mass index (BMI). Additionally, a total of 120 participants will be recruited into a substudy focusing on supervised resistance training during ADT. The participants in the substudy will undergo stratified randomisation in a 1:1 ratio to either the training group or the non-training control group. This randomisation will be based on two main covariates, which are age and self-reported physical activity level. Randomisation will be conducted by the research coordinator and research nurse in REDCap, using computer-generated random numbers.

Endpoints

The primary endpoint of the ESTRACISE study is the efficacy of transdermal E2 in mitigating the deterioration of sexual function caused by ADT. This is quantified through comparison of the Expanded Prostate Cancer Index Composite (EPIC-26) sexual function domain scores between the main arms. Scores are scaled from 0 to 100; a higher score means better sexual function. The primary time point of analysis is 12 months, and the secondary is 6 months. The primary analysis consists of comparing the EPIC-26 scores between the E2 + ADT arm and the control arm.

The secondary endpoints' primary time point of analysis is 12 months, with a secondary time point of 6 months, when acceptable (e.g., secondary endpoint 1 and 2). The primary analysis consists of comparing the change in the outcome

Fig. 1 Study design. ADT, androgen deprivation therapy; E2, oestradiol.



parameter between different groups, if not otherwise mentioned. Secondary endpoints are:

1. Occurrence of ADT-induced adverse effects, quantified by the EPIC-26 overall and subdomain scores, for which the scale ranges from 0 to 100. The primary analysis consists of comparing the EPIC-26 scores between the E2 + ADT arm and the control arm.
2. Tolerability and safety of transdermal E2 concomitant with ADT. Quantified by the adverse event screening, which includes known and unknown adverse events and their grade (Common Terminology Criteria for Adverse Events [CTCAE]). Number and grading of adverse events is from 1 to 5. Higher grading means worse adverse events. The primary analysis consists of comparing the adverse events between the E2 + ADT arm and the control arm.
3. Impact of transdermal E2 with or without 6-month supervised resistance training on one-repetition maximum (1RM) tests of both the leg press and barbell biceps curl, and maximal hand grip strength assessed with a dynamometer. Assessed as kilograms or newtons.
4. Impact of transdermal E2 with or without 6-month supervised resistance training on explosive strength of the leg extensors assessed with a countermovement jump (CMJ). CMJ flight time is defined in milliseconds. Higher flight time in milliseconds represents higher jump height and explosive strength.
5. Impact of transdermal E2 with or without 6-month supervised resistance training on a 6-min walk and loaded 10-stair climb test (functional capacity). Walking distance and heart rate will be collected from a 6-min walk test, and time taken to ascend and descend from a 10-stair climb test. A greater walking distance with a lower heart rate and less time taken to complete the 10-stair climb test indicates better functional capacity.
6. Impact of transdermal E2 with or without 6-month supervised resistance training on body composition. More lean mass and less fat mass indicate better body composition.
7. Impact of transdermal E2 with or without 6-month supervised resistance training on bone mineral density. Higher bone mineral density indicates a better outcome.
8. Impact of transdermal E2 with or without 6-month supervised resistance training on mid-thigh muscle and fat mass. Higher mid-thigh muscle cross-sectional area, quantity, and lower adipose tissue size indicate higher mid-thigh muscle and less fat mass.
9. Impact of transdermal E2 with or without 6-month supervised resistance training on hormone (testosterone

and E2) levels and cancer (PSA) status. Higher or lower hormone levels could indicate a better outcome, depending on the arm of the participant and overall status. Lower PSA concentration usually indicates a better outcome.

10. Impact of transdermal E2 with or without 6-month supervised resistance training on the concentration of basic blood count (PVK), interleukin-6, TNF-α, alkaline phosphatase (AFOS), Alat, creatin (Krea), cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and other biomarkers. Higher or lower concentrations of biomarkers can indicate better outcomes, depending on the exact biomarker.
11. Impact of transdermal E2 with or without 6-month supervised resistance training on type I and II myofibre cross-sectional area, myonuclei, myonuclear domain, the satellite cell count, androgen receptor, myostatin content, and oestrogen receptors. Higher type I and II myofibre cross-sectional area indicates improved skeletal muscle characteristics. Higher myonuclei, myonuclear domain, satellite cell count, and androgen and myostatin content usually indicate improved cellular function.
12. Impact of transdermal E2 with or without 6-month supervised resistance training on muscle cellular function (e.g., HSP70, and cytochrome c oxidase subunit IV proteins). Higher or lower concentrations of proteins could indicate improved or worsened muscle cellular function, depending on the exact protein.
13. Number of participants with resistance training-induced adverse events. Assessed by CTCAE, the number of participants with training-induced adverse events and grading of an adverse event from 1 to 5 will be evaluated. Higher grading indicates worse adverse events.
14. Impact of transdermal E2 with or without 6-month supervised resistance training on quality of life, assessed with the WHO Quality of Life Brief Version (WHOQOL-BREF) measure and the Patient Health Questionnaire (PHQ-9) overall and subdomain scores. Higher overall and subdomain score in WHOQOL-BREF indicates higher quality of life. A higher overall score on the PHQ-9 indicates more depressive symptoms.

Eligibility Criteria

To be eligible for inclusion in the study, participants have to: (i) be diagnosed with localised PCa and scheduled for EBRT with adjuvant subcutaneous ADT using leuprorelin for at least 12 months; (ii) be aged 18 years or older; (iii) have sufficient performance status, indicated by an Eastern Cooperative Oncology Group score of 0–1; and (iv) have a BMI between 18.5 and 30.0 kg/m^2.

Exclusion criteria are: (i) low-risk PCa (International Society of Urological Pathology Gleason Grade 1) or being expected to undergo adjuvant ADT for <1 year; (ii) distant bone, lymph node, or soft tissue metastasis, or other untreated or unstable malignancies at risk of recurrence or progression; (iii) history of recent cardiovascular events or stroke within the past 12 months; (iv) past or current venous thromboembolism; (v) known allergies to E2 or its adjuvant compounds; (vi) conditions or medications considered contraindications to E2, such as history of thromboembolic disorders, liver disease, or use of cytochrome P450 enzyme-metabolising drugs; (vii) undergoing concurrent glucocorticoid treatment; (viii) physical disabilities preventing regular exercise; (ix) expected poor compliance with study requirements, or an expected survival time of <1 year.

Interventions

Participants allocated to the intervention group will use transdermal E2 gel (EstroGel) at a dose of 750 μg daily for 12 months concomitant with ADT. To prevent gynaecomastia, participants using E2 will receive one-time prophylactic breast irradiation (10 Gy) 2 weeks before starting the E2. After prophylactic breast irradiation, participants will receive the first dosage of ADT (subcutaneous injection) and transdermal E2 (in the intervention arm) at the same time. The recommended site for application of E2 gel is a large skin area.

Those in the resistance training groups will attend expert-guided group exercise sessions twice a week for 6 months. The training programme is carefully structured to maximise muscle strength and hypertrophy gains. Participants in the non-training groups are advised to stay physically active at their own discretion.

Standard Treatment Routine

According to the standard treatment protocol in Finland, all participants will receive leuprorelin as subcutaneous injections at 3-month intervals for a minimum of 1 year and standard EBRT for PCa with standard clinical dosing and fractionation at the discretion of the radiation oncologist. EBRT will usually start 2–3 months after the initiation of ADT.

Sample Size

The sample size for the ESTRACISE study was determined based on a priori power analysis, considering the primary outcome of the efficacy of transdermal E2 in mitigating the deterioration of sexual function caused by ADT. The analysis is based on the sexual domain scores of the EPIC-26 questionnaire. With an assumed difference in means of 10, a standard deviation of 30, a Type I error probability of 0.05, and a desired power of 0.8, the required sample size is 142

subjects in each of the E2 and ADT groups. Factoring in a 10% dropout rate, the total estimated sample size is 310 subjects, which is deemed more than adequate to detect a statistically significant difference in the mean sexual domain score between the E2 and ADT arms.

The aim of integrating the exercise component is to exploratively assess the multifaceted effect or potential additive effect of supervised exercise with or without transdermal (E2) gel. Thus, a pragmatic approach has been used in determining the sample size for this substudy. The sample size of 120 is anticipated to provide sufficient data to enable exploratory analyses.

Methods of Data Collection and Schedule of Events

The research measures conducted for all participants include questionnaires, adverse event screening, medication compliance screening, CT of the thigh muscle, bioimpedance analysis, three-dimensional imaging of the body composition, body composition, and bone mineral assessment by dual-energy X-ray absorptiometry (DXA), strength, functional capacity, physical activity measurements, and blood samples. In addition, muscle biopsies are collected from a subset of participants allocated to the training groups. Primary data collection points are study baseline, 6 months, and end of study. More detailed measurement time points are presented in Fig. 2.

The superscripts contained in Fig. 2 are explained below. (a) Stratified randomisation of PCa patients (N = 310) in a 1:1 fashion to the E2 + ADT arm (intervention arm) or ADT-only arm (control arm). (b) Stratified randomisation of PCa patients (N = 60 per arm) in a 1:1 fashion to the training group or non-training control group. Nonrandomised patients will be allocated to the non-training group (N = 95 per arm). (c) The prophylactic breast irradiation will be conducted for the participants using transdermal E2. (d) The muscle biopsies are collected only from the participants allocated to training or non-training control groups. (e) The participants allocated to the intervention arm will use transdermal E2 (EstroGel) daily. (f) The traditional treatment in the study includes the use of leuprorelin for ADT. All participants will receive injection of leuprorelin once every 3 months. (g) Adverse event screening will be conducted monthly for both arms. This consists of recording all adverse events caused by the transdermal E2 or leuprorelin. (h) Compliance monitoring of the transdermal E2 will be conducted monthly, while the compliance monitoring of leuprorelin will be performed once every 3 months. (i) The measurements will be only conducted for the participants allocated to the training groups. (j) The measurements will be only performed on the participants allocated to the training and non-training control groups.

Questionnaires

The study uses several questionnaires to gather subjective data. The EPIC-26 is employed to assess the subjective adverse effects of ADT. This encompasses domains of sexual function, urinary symptoms, bowel habits, and hormonal symptoms. The WHOQOL-BREF evaluates the general quality of life across physical health, psychological health, social relationships and environmental domains. The PHQ-9 is used for screening, diagnosing, monitoring and measuring the severity of depression. Additionally, training logs and diaries document exercise frequency, intensity and volume in the resistance training substudy.

Adverse Event Screening

The adverse event screening of E2 is continuously monitored throughout the study. Regular monitoring for adverse events is conducted monthly for all participants receiving E2. The EPIC-26 questionnaire is specifically used to detect and quantify known adverse effects of E2, such as breast growth and tenderness. Unexpected adverse events are mainly captured through open-ended questions. For those in the E2 group, extra safety checks are conducted via telephone calls at 1 and 3 months after the initiation of treatment. All adverse events are meticulously graded in accordance with National Cancer Institute CTCAE version 4.02.

Assessment of Strength

The assessment of strength includes assessment of leg, upper body, and hand grip strength via 1RM, repetition maximum (RM) and CMJ tests. 1RM tests will be performed in leg press, knee extension, bench press, arm curls, and hand grip dynamometer. RM tests will be only performed in a leg press machine. CMJ will be performed on force plates placed on the ground.

Assessment of Functional Capacity

Functional capacity will be estimated using the 6-min walk test and loaded 10-stair climb test. The 6-min walk test will be used to estimate aerobic capacity in cancer patients, while a loaded 10-stair climb test estimates lower extremity functional strength and power. In the 10-stair climb test participants will carry 10 kg extra weight while ascending and descending 10 stairs.

Assessment of Body Composition

The study employs a range of methodologies to accurately measure body composition, which are DXA, bioimpedance analysis, and three-dimensional body imaging. These methods will be used to determine the lean and fat body mass,

Fig. 2 Measurement time points and schedule of events.

Study period	Screening	Baseline				Follow-up period					Follow-up or before training		Follow-up or resistance training period					End of trial and after training	
Study procedure	Screening visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18
Timeline in months with allowed time window in weeks	0	0 ± 0.5	0 ± 1	0 ± 1	0 ± 0.5	1 ± 1	2 ± 1	3 ± 1	4 ± 1	5 ± 1	6 ± 1	6 ± 1	7 ± 0.5	8 ± 0.5	9 ± 0.5	10 ± 0.5	11 ± 0.5	12 ± 1	12 ± 1
Eligibility criteria	X																		
Informed consent	X																		
Randomisation I[a]	X																		
Randomisation II[b]											X								
Prophylactic breast irradiation[c]		X																	
Background questionnaires		X																	
Questionnaires		X										X						X	
Bioelectrical impedance analysis of body composition			X									X	X[i]	X[i]	X[i]	X[i]	X[i]	X	
3D-image of body composition			X									X						X	
Muscle biopsy of vastus lateralis[d]			X[j]									X[j]						X[j]	
Blood samples			X									X						X	
Strength measurements			X									X	X[i]	X[i]	X[i]	X[i]	X[i]	X	
Functional capacity assessment			X									X						X	
Physical activity assessment by acclerometer			X									X						X	
Body composition assessment by dual-energy X-ray absorptiometry				X							X								X
Bone mineral density assessment by dual-energy X-ray absorptiometry				X							X[j]								X
Computed tomography image of thigh				X							X								X
Use of the investigational medical product[e]					X	X	X	X	X	X	X		X	X	X	X	X	X	
Use of traditional treatment[f]					X			X			X				X			X	
Adverse event screening[g]					X	X	X	X	X	X	X		X	X	X	X	X	X	
Medication compliance[h]					X	X	X	X	X	X	X		x	X	X	X	X	X	
Recording of the concomitant medications	X				X	X	X	X	X	X	X		X	X	X	X	X	X	
Start of local radiotherapy							X												

providing a comprehensive picture of the participant's body composition. DXA will also be used to estimate bone mineral density. Bone mineral density will be estimated from the femoral neck and lumbar spine. CT will be employed to assess changes in muscle size, quantity, quality, and adipose tissue size from the mid-thigh muscles.

Assessment of Systemic Biomarkers

The blood sample analysis will be used to monitor hormonal levels, inflammation, health state, and lipid profiles. Hormonal levels tracked include testosterone and E2. The inflammatory state includes PVK, interleukin-6 and

TNF-α. Health state includes AFOS, Alat, Krea. Lipid profile will be monitored through cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. In addition to the current analyses, serum, plasma and whole blood samples are collected for storage for potential future analysis of nucleic acid-based measurements, such as DNA or RNA sequencing.

Assessment of Myofibres and Muscle Cellular Function

We aim to collect muscle biopsies from at least 15–20 participants per group to allow detailed investigations of the effects of E2 with or without training on skeletal muscle characteristics, and cellular and molecular functions. The muscle biopsies will be obtained using a 5-mm Bergström muscle biopsy needle from the quadriceps femoris. From the muscle biopsies, type I and II myofibre cross-sectional area, myonuclei and myonuclear domain, satellite cell count, androgen receptor and myostatin content can be determined. In addition, HSP70, HSP27, alpha B-crystallin, HSP60, cytochrome c oxidase subunit IV, citrate synthase, free ubiquitin, and total ubiquitinated proteins could be determined.

Compliance Monitoring

Compliance monitoring for transdermal E2 is carried out monthly via a dual approach: a self-reported questionnaire through REDCap and, when necessary, additional remote contact by telephone. The questionnaire addresses the actual usage amount of the investigational medicinal product and reasons for any non-compliance. A participant falling below an 80% usage ratio triggers a proactive response from the study team to address and potentially rectify compliance issues. In contrast, the compliance monitoring for LHRHa, administered quarterly, follows a similar self-reported questionnaire format without additional follow-up for non-compliance, as LHRHa are not the investigational medicinal product in this study.

Analysis Plan

The primary analysis will be carried out on an intention-to-treat basis. A secondary analysis of the population will be made on a per-protocol basis. Missing data exceeding 5% will be imputed using appropriate methods, and intercurrent events will be managed individually, with participants experiencing such events censored at the time of the event.

The primary endpoint analysis will assess the efficacy of transdermal E2 in mitigating the deterioration of sexual function caused by ADT, using the EPIC-26 sexual subdomain scores. The analysis will compare the mean scores and standard deviations between the intervention and control arms, primarily at the 12-month mark and secondarily at 6 months. A linear mixed model will be employed, incorporating covariates such as baseline sexual function, BMI, age, and smoking history.

The secondary endpoint, tolerability and safety of E2 analysis will focus on two variables: the total frequency of adverse events in each group and the number and grading of these events (from 1 to 5). Grading will follow the CTCAE. The primary analysis will involve Poisson regression to compare the number of reported adverse events and their grading in the intervention and control arms at the 12-month mark. Descriptive statistics will be used to describe the adverse events, and additional adjusted analyses may incorporate covariates such as age, BMI, and smoking history.

The exercise effectiveness will be assessed using linear mixed models to analyse changes in secondary outcomes over time between the exercise and non-exercise groups, with and without the adjunctive use of E2. These models will account for repeated measures within subjects, providing estimates of the treatment effect while adjusting for potential confounders such as baseline characteristics, age, BMI, and initial physical activity levels. Interaction terms between treatment (E2 vs no E2) and exercise (exercise vs no exercise) will be included to assess potential synergistic effects.

The other secondary endpoints will be compared within both study arms, also encompassing the training and non-training control groups. Exploratory comparisons will also be conducted between the training and control groups of both research branches. The primary methods for analysing these endpoints include linear mixed models, correlation coefficients, and repeated measures of ANOVA for continuous variables, providing a comprehensive view of the impacts across different groups.

Discussion

The ESTRACISE study can offer crucial novel managing strategies for ADT-induced adverse effects in PCa patients. This is the first randomised controlled trial estimating the efficacy of transdermal E2 in mitigating the deterioration of sexual function caused by ADT. Previous studies have shown that the administration of high-dose E2 by replacing LHRHa [9,11,13,14] or concomitant with LHRHa [18] significantly mitigates some of the adverse effects of ADT. However, the full arc of benefits is still unknown. Thus, the study could fill the gaps by offering new insights and discoveries into the benefits of transdermal E2.

The rationale behind our chosen dose of E2 (0.75 mg daily) is based on a review of the literature [9,11,13,14,19], which suggests that replacing LHRHa with a high dose of E2 can

effectively suppress testosterone levels and mitigate some of the adverse effects of ADT. However, it would be more practical to use a low dose of E2 concomitant with LHRHa to achieve the mitigation benefits of E2. In addition, even though the previous clinical studies show no difference in cardiovascular events between high-dosage transdermal E2 and LHRHa [9], it should be noted that currently there is not enough evidence about the long-term effects of transdermal E2 in PCa patients. The most comparable evidence about the potential adverse effects of long-term high-dosage E2 in cardiovascular events is from transgender women trials that show mixed results on the high-dosage E2 potential risks on cardiovascular outcomes [20–22].

In addition, supporting our chosen dosage, a study in men with PCa undergoing ADT and treated with 0.9 and 1.8 mg daily doses of transdermal E2 showed that, after 1 month, serum E2 levels slightly surpassed healthy reference values for their age group. This finding highlights that even lower E2 doses effectively alter E2 levels, validating our 0.75-mg daily dose as evidence-based, likely minimising adverse effects [19] and being practical in the clinical setting.

In summary, the innovative design of the ESTRACISE study can offer novel insights into the benefits of E2 gel, and the substudy can reinforce the benefits resistance training and deliver valuable new novel insights about synergistic benefits of E2 gel and exercise, which are currently unknown.

Ethical Considerations

The ESTRACISE study has received the approval of the National Committee on Medical Research Ethics (T/88/2023) and Medical Agency (FIMEA/2023/004834) under the directive (2001/20/EY). The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice, as well as in accordance with the ethical principles underlying European Union Regulation (EU) No 536/2014.

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Disclosure of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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Correspondence: Ilkka Jussila, Surgery Clinic, Wellbeing Services County of Central Finland, Hoitajantie 3, Jyvaskyla, Central Finland, Finland.

e-mail: ilkka.jussila@hyvaks.fi

Abbreviations: 1RM, one-repetition maximum; ADT, androgen deprivation therapy; CMJ, countermovement jump; DXA, dual-energy X-ray absorptiometry; E2, oestradiol; EBRT, external beam radiation therapy; EPIC-26, Expanded Prostate Cancer Index Composite; LHRHa, LHRH agonists; PCa, prostate cancer; PHQ-9, Patient Health Questionnaire; RM, repetition maximum; WHOQOL-BREF, WHO Quality of Life Brief Version.