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Effect of oral and transdermal oestrogen therapy on bone mineral density in functional hypothalamic amenorrhoea: a systematic review and meta-analysis

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ABSTRACT

Background Female athletes might develop reduced bone mineral density (BMD) and amenorrhoea due to low energy intake.

Objective To systematically review the literature of randomised controlled trials (RCTs) assessing the effect of oestrogen oral contraceptives (OCP), conjugated oestrogens (CE) and transdermal estradiol (TE) on BMD in premenopausal women with functional hypothalamic amenorrhoea (FHA) due to weight loss, vigorous exercise and/or stress.

Methods A comprehensive literature search in PubMed, MEDLINE, Cochrane Library, Ovid and CINAHL from inception to 1 October 2020.

Data extraction and synthesis Two authors independently extracted data. When possible, the data were pooled in a random-effects meta-analysis.

Main outcomes Difference in BMD (g/cm^2) at the lumbar spine.

Results Nine RCTs comprising 770 participants met the inclusion criteria; five studies applied OCP, two CE and two TE. Four RCTs (two OCP, two TE) found an increased BMD in premenopausal women with FHA, and five (three OCP, two CE) found a decreased BMD compared with controls. A meta-analysis showed no difference in BMD between the treatment and control groups, (standardised mean difference (SMD) 0.30, 95% CI −0.12 to 0.73). A secondary analysis for change scores from baseline to first assessment point, showed a similar overall result (SMD 0.17, 95% CI −0.16 to 0.51). No serious adverse events were reported.

Conclusion The literature suggests that TE might increase lumbar BMD in premenopausal women with FHA, but pooled results revealed no effect of the intervention. The findings do not support oestrogen therapy to improve BMD in these patient groups.

Key messages

What is already known

- Most commonly prescribed medication for bone mineral density in female athletes with functional hypothalamic amenorrhoea is oral contraceptive pills despite insufficient data on its effectiveness.
- Previous reviews have not investigated the effect of oestrogen therapy in the form of transdermal patch.
- Transdermal oestrogen does not undergo hepatic first-pass metabolism and is therefore not down-regulating insulin-like growth factor-1 (as do oral contraceptives).

What are the new findings

- This study is the first to review the evidence of transdermal oestrogen patch on bone mineral density in premenopausal women with functional hypothalamic amenorrhoea.
- Oral contraceptives should not be used to improve bone health.
- Transdermal estradiol administration may be considered as second-line comanagement in order to optimise bone health in amenorrhoeic athletes.

INTRODUCTION

Exercise and physical activity are associated with positive effects on the human body, prevent diseases and improve general health.[1] However, female athletes are at risk of developing the Female Athlete Triad, that is, low energy availability, menstrual dysfunction and reduced bone mineral density (BMD).[2] The triad is a compound of the more complex syndrome Energy Deficiency in Sport (RED-S), which refers to impaired physiological functioning as well as psychological consequences of relative energy deficiency.[3]

Many athletes reduce their energy intake intentionally in order to optimise body size and composition to achieve optimal performance.[4] Prolonged energy deficiency, due to inadequate energy intake or excessive exercise, leads to hormonal disturbances of the hypothalamic–pituitary–gonadal (HPG) axis, which can result in functional hypothalamic amenorrhoea (FHA).[5] FHA is a menstrual irregularity in absence of an organic cause, and occurs in 3%–66% of female athletes.[6] Suppression of the HPG axis causes oestrogen deficiency, which increases rate of bone

turnover, suppresses bone formation and prevents the attainment of peak bone mass in adolescents,[7 8] contributing to increased fracture risk.[1 9–11]

The most effective strategy to normalise menstrual function and improve BMD in amenorrhoeic women is to restore energy balance and weight.[3 12] However, resumption of menses only gives minimal improvements in BMD.[10 11] FHA and hypo-oestrogenism during adolescence, a critical time of bone accrual, may lead to permanent deficits in peak bone mass.[13] This underscores the need of alternative interventions for this population, including pharmacological management. The most commonly prescribed treatment for bone loss in premenopausal women with FHA is oral contraceptives (OCPs) or conjugated oestrogens (CE) to improve hypo-oestrogenic environment and, theoretically, protect bone. Systematic reviews have not found OCPs to significantly improve BMD in women with athletic FHA[14–16] or anorexia nervosa (AN).[14 17 18] However, some recent randomised controlled trials (RCTs) have reported that transdermal estradiol (TE) is effective in increasing BMD in anorexic and amenorrhoeic premenopausal women.[19 20]

Therefore, we conducted a systematic review of clinical RCTs to determine the effect of oestrogen replacement, that is, OCP, CE and TE on BMD in premenopausal women with FHA.

METHODS

This systematic review identified oestrogen treatment strategies to improve BMD in women with FHA, and applied the preferred reporting items for systematic reviews and meta-analyses.[21]

Search strategy and selection criteria

A comprehensive literature search was conducted on PubMed, MEDLINE, Cochrane Library, Ovid and CINAHL including English or Scandinavian human RCTs prior to 1 October 2020. The key words functional hypothalamic amenorrhoea, BMD, osteoporosis, osteopaenia, oestrogen, hormone replacement therapy and OCP were used in various combinations. Two reviewers (KA and AC) independently reviewed the papers' titles, abstracts and full texts and resolved disagreements with a third reviewer (FN).

Only RCTs with premenopausal women with functional hypothalamic oligo/amenorrhoea due to a negative energy balance, weight loss, vigorous exercise, eating disorders and/or stress who received oestrogen replacement therapy (OCP, CE or TE), were included.

Exclusion criteria were RCTs that enrolled patients with oligo/amenorrhoea resulting from anovulation, such as polycystic ovarian syndrome, diabetes, pituitary, renal and/or gastrointestinal disease, which can affect bone metabolism (BM). RCTs that enrolled patients on medications affecting BM such as glucocorticoids and anticonvulsants, were also excluded. We excluded RCTs that did not include controls or a placebo group, in addition to studies that did not include lumbar BMD as outcome measured by g/cm^2.

Quality assessment and data extraction

The methodological quality and internal validity of evidence were assessed individually by two reviewers (KA and AC) using the Physiotherapy Evidence Database (PEDro) scale, with a score range of 0–10.[22] An RCT with a score of ≥6 was considered to be of high quality, while a score of 4–5 was classified as fair quality, and ≤3 as poor quality. The same two reviewers independently extracted data, with discrepancies resolved through consensus. Extracted information was tabulated and included country/year; study population, method, intervention, diagnostic test used, and main results.

Outcomes

The primary outcome was change in BMD (g/cm^2), measured using dual-energy X-ray absorptiometry (DXA) or dual photon absorptiometry (DPA) at the lumbar spine, because vertebral bodies have a high proportion of trabecular bone relative to cortical bone.[23] Because trabecular bone has increased turnover compared with cortical bone, the effects of oestrogen may be apparent more rapidly in vertebral bodies than other anatomical sites such as the femoral shaft.[24]

Data analyses

The primary analysis identified a standardised mean difference (SMD) in each group receiving OCP, CE, TE versus control/placebo. We used data from the first assessment for each study, ranging from 9 to 12 months or 18–24 months after the baseline assessment. Random effects meta-analysis was conducted using the Hartung-Knapp-Sidak-Jonkman method,[25 26] which is recommended for analysis with few studies.[27–29]

Heterogeneity of the study results was analysed using the generalised I^2 statistic; a percentage of 25%, 50% and 75% has been suggested to indicate low, medium, and high heterogeneity, respectively.[30] We further examined heterogeneity using meta-regression with dichotomised independent variables. Here, assessed the impact of a priori identified sources of heterogeneity: (1) length of time from baseline to follow-up (18–24 months vs 9–12 months), (2) participants (competitive athlete/dancer vs anorexia/depression/anxiety), (3) age of participants (20–29 vs 15–19 years), (4) intervention in control arm (placebo control vs no intervention). We also prepared a funnel plot and used Egger's test for funnel plot asymmetry to identify possible publication bias with $p<0.05$ suggesting asymmetry.[31]

As a secondary analysis, we analysed the SMD of change in BMD for the studies with available data using a similar method. In this analysis, we also created subgroups according to administration mode in the active study arm (patch vs pill).

Patient and public involvement

Patients were not involved in the development of the research question or its outcome measures, conduct of

the research, or preparation of the manuscript. Findings will, however, be disseminated to patients via social media, relevant professional associations and news media.

RESULTS

Study and subject selection and characteristics

We identified 469 relevant abstracts and reviewed 76 of them in full text. Nine RCTs met our inclusion criteria (online supplemental figure S1). The included studies comprised 770 participants (age 11–35 years) with FHA; 448 had athletic amenorrhoea and 322 AN. The duration of the RCTs ranged from 9 to 24 months with a median of 12 months.

Methodological quality

The methodological PEDro score of the included RCTs ranged from 4 to 9 points out of a maximum of 10 points (mean 6.6±1.5) (table 1). Seven RCTs were considered of high quality[19 20 32–36] and two RCTs were considered of fair quality.[37 38] Only one study concealed the outcome measures for the assessors,[35] while four studies had <15% drop-out.[32–34 37]

BMD in pooled studies

Online supplemental table S1 presents the data synthesis for study methodology and effectiveness for each of the nine RCTs.

When pooling the studies in the meta-analysis using the first assessment point, we found no difference in BMD between the treatment and control groups in the five studies included, that is, SMD of 0.30 (95% CI −0.12 to 0.73), and only one study reported results for 18–24 months (online supplemental figure S2). The results for subgroups according to diagnostic classification, that is, anorexia/depression/anxiety vs competitive athletes/dancers, was remarkably similar (online supplemental figure S3).

When exploring sources of heterogeneity in meta-regression analysis, there was no difference in SMD between subgroups according to time of follow-up (18–24 months vs 9–12 months) −0.74 (95% CI −1.97 to 0.49), no intervention in controls vs placebo control −0.02 (-0.95 to 0.90), age group included in the studies (20–29 vs 15–19 years) −0.34 (−1.18 to 0.49), competitive athlete/dancer versus anorexia/depression/anxiety 0.00 (−0.94 to 0.94). A funnel plot of the studies (online supplemental figure S5), and Egger's test (p=0.90), did not suggest asymmetry.

Four studies were included in the secondary analysis for change scores from baseline to first assessment point, with a pooled SMD of 0.17 (95% CI −0.16 to 0.51). There was no apparent difference between subgroups according to time of follow-up (online supplemental figure S4), or mode of administration, i.e., patch vs pill (online supplemental figure S6).

Overall, the RCTs were fairly homogeneous, as indicated by an I^2 <34% for subgroups in the pooled analyses (online supplemental figures S1-S4 and S6).

Table 1 The methodological PEDro score of the nine included randomised controlled trials

	USA, 1997[32]	GB, 1999[33]	Spain, 2001[37]	USA, 2002[34]	USA, 2003[38]	USA, 2006[35]	USA, 2007[36]	USA, 2011[19]	USA, 2019[20]
Random allocation	Y	Y	Y	Y	Y	Y	Y	Y	Y
Concealed allocation	Y	N	N	Y	N	Y	Y	Y	Y
Baseline comparability	Y	Y	Y	Y	Y	Y	Y	Y	Y
Blinding of subjects	N	N	N	Y	N	Y	N	Y	N
Blinding of therapists	N	N	N	N	N	Y	N	Y	N
Blinding of assessors	N	N	N	N	N	Y	N	N	N
More than 85% follow-up	Y	Y	Y	Y	N	N	N	N	N
Intention-to-treat analysis	Y	Y	N	Y	N	Y	Y	Y	Y
Between-groups statistical comparisons	Y	Y	Y	Y	Y	Y	Y	Y	Y
Point and variability measures	Y	Y	Y	Y	Y	Y	Y	Y	Y
PEDro score	**7/10**	**6/10**	**5/10**	**8/10**	**4/10**	**9/10**	**6/10**	**8/10**	**6/10**

PEDro, Physiotherapy Evidenc Database.

Oral contraceptives

Out of the five RCTs conducted with OCP, two studies showed a significant between-group change favouring the intervention group in lumbar BMD,[32 37] and three studies showed no significant between-group effect (online supplemental table S1).[34–36]

Conjugated oestrogens

The two RCTs conducted with CE did not find a significant between-group difference in lumbar BMD in the intervention groups as compared with the control groups (online supplemental table S1).[33 38] However, one study did find an increase in lumbar BMD of 5.7% in the CE group (n=7) as compared with a 0.3% decrease in the control group (n=9), with an adjusted calculated net effect of 1.5% after drop-outs and return of menses.[33]

Transdermal estradiol

Two high-quality RCTs applied TE patch (17-β estradiol) and found a significant increased between-group change in spinal BMD in the active group in women with AN and FHA as compared with controls (online supplemental table S1).[19 20]

Adverse events

Six RCTs reported adverse events (AEs).[32 37 38] OCP and CE AEs were breast tenderness, headaches, bloating, nausea and mood swings.[33 35 36] TE AEs were headaches, bloating and erythema at patch application site.[19 20] None of the RCTs classified the severity or the duration of the AEs. No serious AEs were reported.

DISCUSSION

Our systematic review showed no significant increase in lumbar BMD by OCP and CE. However, the two TE patch RCTs showed an increase in spinal BMD in adolescents with athletic amenorrhoea and AN.[19 20] The meta-analysis found no pooled difference in BMD between the treatment and control groups.

Methodological considerations

All the included RCTs had overall small sample sizes, ranging from 24 to 150 participants with high drop-out rates (mean 22%±17%), which introduce attrition bias. Four RCTs did not report method of randomisation,[20 33 37 38] and three RCTs whether the allocation was concealed.[33 37 38] In one RCT participants were allocated to study arms by personal choice, which introduces selection bias.[37]

RCTs that include a placebo control group are advantageous to pragmatic studies and RCTs that use no interventions as control. To establish the true net effect of an intervention and quantify the actual placebo effect, one should ideally include both a placebo and a control group[39 40]; however, none of the included RCTs were designed this way. Five of the RCTs included a placebo arm.[19 32 34 35 38] Reported reasons and justifications for not including a placebo control group were ethical considerations regarding contraceptive status and the high probability of un-blinding, as OCP may withdraw bleeding in amenorrhoeic subjects.[34 36]

The current systematic review included premenopausal women with FHA due to a negative energy balance caused by various underlying aetiologies, such as weight loss, vigorous exercise, eating disorders and/or stress. The various aetiologies makes a heterogeneous study population, but was decided on because patients with eating disorders and athletic amenorrhoea are believed to have similar aetiology, that is, chronic energy deficit where energy availability falls below a threshold of 20–30 kcal/kg per day.[41]

The RCTs used different definitions of FHA, that is, no menstruation for ≥3 months,[19 20 34 35] ≥5 months[38] and 6 months,[32 37] while others defined FHA as ≤3 cycles per year during the last 12[36] or 18 months.[33] This necessitates a concern about different baseline characteristics. The international classification of FHA defines it as the cessation of previously regular menstruation for 3 months or the cessation of irregular menses for 6 months.[42] In comparison, the RCTs with anorexic subjects were diagnosed after the current Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for classical AN, which include no menstruation for ≥3 months.[43]

Other factors affecting the results include differences in type, dose and formulation of hormones in the studies reviewed. The RCTs on OCP used various doses (range 0.03–35 mg) of the synthetic ethinyl estradiol,[32 34–37] in combination with different progestins, that is, norgestrel,[36] norgestimate,[35] norethindrone[32 34] and desogestrel.[37] The studies on CE used different doses of CE (estriol and estradiol) in combination with the progestins medroxyprogesterone acetate,[38] and norethisterone.[33] This makes it challenging to compare the results between studies, and it leaves uncertainty about the dose–response relationship. It is also difficult to determine whether the results with certainty were exclusive of oestrogens.

The current standard method for measuring BMD in the spine is DXA,[44] but one of the included studies used DPA due to unavailability of a DXA instrument.[38] DPA systems are less precise than DXA scanning and is reported to give higher measurements in BMD compared with DXA scans.[45]

A challenge pooling the results, were that some RCTs presented SE and not SD and had to be converted to a common unit.

Only two RCTs reported on fracture incidence, which is a clinically relevant outcome measure and gives clinicians information regarding absolute and relative risk ratio for patients with FHA.[20 36] However, due to the low incidence of fractures, generally the sample size in the RCTs were too small to encounter this side effect.

Discussion of results

Five RCTs assessed efficacy of OCP on lumbar BMD,[32 34–37] of which two small studies demonstrated a mean positive effect in the intervention groups (total n=51) compared

with control groups (total n=23).[32 37] The mean lumbar BMD increased in these two studies by 3.9% in the OCP group with a net effect of 4.8% (SD ±1.8). The net effect was higher because the control group had decreases in BMD compared with baseline. However, in contrast to all the other RCTs included in the study, none of these studies reported on resumption of normal menstruation during the 12-month follow-up. This introduces a large bias, as resumption of menses is a clinical sign of recovery from energy deficiency, which may increase vertebral BMD of approximately 6.5% over 15 months.[46] Previous systematic reviews and meta-analysis have similarly found OCP to be ineffective in increasing BMD in patient with AN[17 18] or FHA.[14 16]

Both RCTs on TE patch with cyclic progesterone were well conducted and showed a significant improvement in BMD in amenorrhoeic girls at 12 and 18-month follow-up with a mean within-group change in the treatment groups of 2.51% (n=98) and a mean net effect of 2.50% (SD ±0.28).[19 20] One of the TE patch RCTs did also include a placebo patch group, which is a better approach for assessing efficacy and safety data.[19]

Treatment strategies and clinical implications

Although TE patch with cyclic progesterone show promising results, there is still uncertainty regarding the efficacy. Weight and energy balance restoration is the first-line treatment of FHA, and early detection is critical in order to prevent life-long ramifications on bone health.[47] Relative risk for stress fractures and osteoporotic fractures of the hip and spine is two to four times higher in amenorrhoeic than eumenorrheic athletes.[48] Two studies suggested that increasing energy intake to more than 30 kcal/kg of fat free mass per day may restore the menstrual cycle.[41 49]

The International Olympic Committee statement on RED-S from 2018 recommends non-pharmacological management in terms of a multidisciplinary approach is recommended as first-line management for recovery.[3] A multidisciplinary team should include a primary healthcare practitioner, sport physiologist, a sport dietitian and mental health practitioner.[50] If menstrual cycles is not restored after 1 year of specific individualised modification through a multidisciplinary team approach, second-line pharmacological interventions can be supplemented to prevent further bone loss.[2 3]

In cases where second-line management is warranted, clinicians need to consider different metabolic factors. First, oral oestrogens undergo hepatic first-pass metabolism and downregulate insulin-like growth factor 1 (IGF-1), which is a bone-trophic hormone that increases during puberty and is critical in order to enhance bone accrual.[51] Second, athletes with FHA already have diminished levels of IGF-1,[52] and a further reduction in IGF-1 levels by OCP is likely to limit the otherwise antiresorptive effects of oestrogen.[53] Finally, ethinyl estradiol has a dose-dependent stimulatory effect on hepatic sex hormone-binding globulin production, which may lower physiologic and bioavailable estradiol in the female.[54] In comparison, TE do not undergo hepatic first-pass metabolism and is therefore not downregulating IGF-1.[55 56] In fact, studies have found that TE may even increase levels of circulating IGF-1.[57]

Thus, based on our results, TE therapy with cyclic oral progestin can be considered in a short period as second-line supplement for young adolescents in cases where first-line management fall short.

Limitations

The present study might have possible biases. Although we did perform a comprehensive and systematic search, we may have missed RCTs published in non-English languages. Furthermore, the body of evidence is small, since only a total of 770 subjects are included with a median follow-up of 12 months. We included subjects with various conditions that were classified as AN (clinical eating disorder) and athletic amenorrhoea (subclinical eating disorder). Nevertheless, the underlying physiology is considered to be similar, that is, energy deficit. Thus, the current systematic review is based on an inhomogeneous patient population, and results should be interpreted with caution.

CONCLUSION

Current evidence does not support oral oestrogen replacement in the form of OCP or CE to improve BMD in patients with FHA. Pharmacological treatment in the form of TE patch can be considered as second-line comanagement in order to optimise bone health, but only if weight and energy balance restoration through a non-pharmacological multidisciplinary management approach fall short within 1 year. Further longitudinal and prospective studies are needed to confirm the effect of TE therapy on BMD.

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