Short-Term Effects of The Transdermal Contraceptive Patch on Bone Turnover in Premenopausal Women: A Pilot Study

Original Article

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ABSTRACT

Objective: To examine the short-term effects of the transdermal contraceptive patch on markers of bone turnover in young women.

Study Design: Prospective open-label study.

Patients and Methods: Nine healthy premenopausal women volunteered and were prescribed one cycle of the transdermal contraceptive patch containing 6.0 mg norelgestromin/0.6 mg ethinyl estradiol. Fasting blood samples were taken at Baseline and then for an additional four consecutive weeks to assess changes in bone formation (bone-specific alkaline phosphatase; BSAP) and bone resorption (serum collagen type I cross-linked C-telopeptide; SCTX-I).

Results: Compared to Baseline (0.61 ± 0.16 ng•mL^{-1}) SCTX-I was reduced by 40% (0.36 ± 0.10ng•mL^{-1}; P=0.002) after only one week and tended to remain suppressed by 26-30% ($P \leq 0.11$) during the second and third week, returning to 90% of Baseline (0.54 ± 0.15ng•mL^{-1}) after the withdrawal week. Compared to Baseline (25.8 ± 6.8U•L^{-1}) BSAP levels were 12% (22.8 ± 6.6U•L^{-1}, P=0.486) and 18% (21.2 ± 5.9U•L^{-1}, P=0.249) lower after two and three weeks, respectively, returning to 94% (24.4 ± 6.2U•L^{-1}) of Baseline values following the withdrawal week.

Conclusions: The transdermal contraceptive patch rapidly reduced bone resorption, but has a delayed and less suppressive effect on bone formation. Despite the observed reductions, the concentration of bone turnover markers remained within reference ranges for premenopausal women. Practitioners prescribing hormonal contraceptives to young women should be aware of the rapid response of bone metabolism to this class of drugs.

INTRODUCTION

Sixty-two million women between 15-44 years of age use some form of contraception, of which ~50% of women 15-24 years of age use the oral contraceptive pill (OCP)[1]. The OCP suppresses bone turnover[2,3] and might have a deleterious impact on bone health in premenopausal women[4,5]. Prospective studies have demonstrated a reduction in bone formation and resorption after three months of OCP[6-8]. Indeed Vescovi et al[9] reported a 25-35% reduction in bone formation and resorption after only two weeks of low-dose OCP in young women with hypothalamic amenorrhea; similar reductions being observed after three[10] and 10 months[11] for women who continue taking OCP. Despite the popularity of the OCP newer delivery mechanisms that do not call for daily compliance have been developed, such as the transdermal matrix.

A transdermal delivery mechanism has been used for the treatment of osteoporosis in post-menopausal women[12-14], demonstrating a dose response in bone turnover marker suppression after three and six months[12]. The transdermal contraceptive patch (TCP) results in a 60% greater estrogen exposure compared to OCP in premenopausal women[15], therefore, it is plausible that alterations to bone turnover could exceed previous observations while using OCP. Limited studies have been conducted examining the impact of transdermal contraceptives on bone turnover in premenopausal women[16,17]. Massaro et al[16] demonstrated a reduction in urinary markers of bone resorption with no change in bone formation after 6-12 months of TCP in young women. To date, no prospective data are available describing the short term effects of TCP on bone markers

in young women. Thus, we aimed to examine the response of bone formation and resorption markers to one standard regimen of TCP in premenopausal women.

PATIENTS AND METHODS

Experimental design

We used a prospective, open-label, single subject study design to examine the effects of TCP (EVRA®, Janssen-Ortho) on markers of bone turnover in premenopausal women. We used an A-B-A scheme, where A is no treatment and B is active TCP. Nine healthy premenopausal women volunteered for this study and were prescribed one standard regimen of EVRA® with the first patch being placed on day 2-5 of menses as recommended. Fasting venous blood samples were taken for 5 consecutive weeks between 0800-1000 hr to assess bone-specific alkaline phosphatase (BSAP) and serum collagen type I cross-linked C-telopeptide (SCTX-I). This study was approved by the Office of Research Ethics and all participants signed an informed consent form after all study procedures were verbally described. This study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Participants

Nine healthy premenopausal participants were included in this study. Descriptive characteristics are presented in Table 1. Eligibility criteria included: 1) aged 18 to 35 yrs; 2) gynecological age > 5 years; 3) BMI between 16 -26 kg•m^{-2} ; 4) good health as determined by a medical exam; 5) non-smoker; 6) not currently dieting and weight stable for the preceding six months (± 2.5 kg); 7) not taking any form of hormonal therapy for at least six months and 8) no other contraindications that would preclude participation in the study.

Body composition was determined using bio-electrical impedance (BC-418 Segmental Body Composition Analyzer, Tanita Corporation of America, Inc., Arlington Heights, IL) while wearing shorts and t-shirt. Participants completed a continuous ramp protocol on an electronically braked cycle ergometer (Lode Excalibur Sport cycle ergometer, Lode B.V., Groningen, Netherlands) to volitional fatigue for the determination of VO$_{2peak}$. The initial intensity and increments were set at 20W and 20W•min^{-1}, respectively[18]. Expired respiratory gases were measured continuously using a Moxus Modular Metabolic System (AEI Technologies, Pittsburgh, PA). Values for VO$_2$ were averaged over 30 seconds with the highest value recorded as VO$_{2peak}$.

Treatment

All participants received one standard regimen of EVRA® containing 6.0 mg norelgestromin (NGMN) and 0.6 mg ethinyl estradiol (EE). Each patch is designed to gradually release approximately 150 µg•day^{-1} of NGMN and 20 µg•day^{-1} of EE into the systemic circulation.

Blood sampling and bone turnover markers

Blood samples were taken at Baseline (immediately prior to placement of the first patch) and each subsequent week for four weeks. Blood samples were taken after a 12-hour fast and were collected between 0800 and 1000 hr following at least 15 minutes of resting quietly. Blood samples were allowed to clot for 30 minutes at room temperature and then centrifuged at 3000 rpm for 15 minutes at 4°C. The serum was aliquoted into 2mL polyethylene storage tubes and stored frozen at -80°C until analysis.

Assays on all samples were performed in the Centre for Biological Timing and Cognition at the University of Toronto. BSAP (Quidel Corp., San Diego, CA) and SCTX-I (IDS Inc., Scottsdale, AZ) were measured in serum using an ELISA. Analytical sensitivity for the BSAP assay was 0.7 U•L-1 with an intra and inter-assay CV of less than 5.9% and 4.7%, respectively. Analytical sensitivity for the SCTX-I assay was 0.02 ng•mL^{-1} with an intra and inter-assay CV of less than 3.0% and 7.7%, respectively.

Statistical analysis

To assess for treatment effects of TCP on bone turnover markers a repeated measures analysis of variance (RM-ANOVA) was used to compare absolute changes from Baseline with post-hoc paired t-tests when appropriate. Pearson product correlations were used to determine the relationship between body composition, aerobic fitness and maximal reductions in bone turnover markers. Effect sizes (Cohen's d) were estimated from the ratio of the mean difference to the pooled standard deviation and considered trivial (<0.2), small (0.2- 0.6), moderate (0.61- 1.20), large (1.21 -2.0) and very large (>2.0)[19, 20]. Statistical significance was accepted at $P<0.05$. Data are presented as mean ± SD. Statistics were performed using SPSS Version 20.0 (Chicago, IL).

RESULTS

No adverse events were reported. Side effects included minor headaches, breast tenderness, itchiness at the application site and weight gain (~1.5 kg; $P≤0.02$). Percent body fat and VO$_2$ peak were within reference ranges for women of this age[21].

Markers of bone turnover are shown in Figure 1. The RM-ANOVA indicated a main effect for SCTX-I ($P=0.01$; partial $\eta^2 = 0.90$). Compared to Baseline (0.61±0.16 ng•mL^{-1}) mean SCTX-I was reduced after one week of the TCP (0.36±0.10 ng•mL^{-1}; P=0.002;

d=1.86) and tended to remain suppressed after the second and third weeks ($P \leq 0.11$; *d*=1.07-1.38), returning to near Baseline values after the withdrawal week (0.54±0.15 ng•mL^{-1}; *P*=0.998; *d*=0.41). The RM-ANOVA indicated a significant effect for BSAP (*P*=0.043; partial η^2 = 0.82). Compared to Baseline (25.8±6.8 U•L^{-1}) mean serum BSAP levels were 22.8±6.6 U•L^{-1} (*P*=0.486; d=0.45) and 21.2±5.9 U•L^{-1} (*P*=0.249; *d*=0.74) after two and three weeks, respectively and returned to 24.4±6.2 U•L^{-1} (*P*=1.0; *d*=0.22) following the withdrawal week. There were no relationships observed between the absolute or relative maximal change in bone turnover markers with body composition or aerobic fitness.

The largest relative change in SCTX-I and BSAP was 58.0±12.2% and 24.5±12.2%, respectively. The distribution for when the largest change occurred differed between the two bone markers. There were three, two, and four participants who had the largest change in SCTX-I during the second, third and fourth week, respectively. In contrast, all but one participant had the largest change in BSAP during the fourth week.
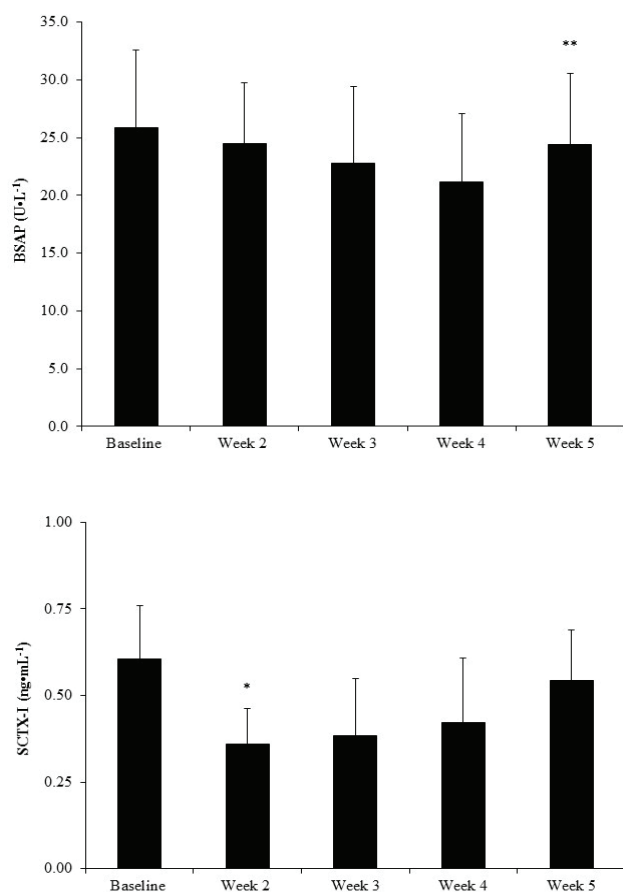
Table 1: Characteristics of participants (n=9).

Parameter	Value
Age (yr)	23.0 (3.0)
Age at menarche (yr)	13.8 (2.4)
Gynecological Age (yr)	9.2 (4.0)
Average cycle length (d)	29.0 (3.0)
Height (cm)	167.9 (5.3)
Body mass (kg)	62.3 (6.1)
BMI (kg•m^{-2})	21.9 (1.5)
Percent fat (%)	23.5 (5.7)
VO$_{2peak}$ (mL•min^{-1}•kg^{-1})	37.3 (4.3)
FSH (IU•L^{-1})	3.0 (1.2)
LH (IU•L^{-1})	5.9 (3.5)
17-β estradiol (pmol•L^{-1})	598.2 (295.3)
Prolactin (ug•L^{-1})	12.6 (6.9)
HCG (IU•L^{-1})	< 5

BMI: body mass index; FSH-follicle stimulating hormone; LH-luteinizing hormone; HCG-human chorionic gonadotrophin. Values are mean (SD).

DISCUSSION

To our knowledge, this is the first prospective investigation to examine the effects of short-term TCP use on bone turnover in premenopausal women. We report that bone resorption and bone formation were suppressed by 40% and 18% after 1 week and 3 weeks, respectively, supporting our hypothesis that a reduction of bone turnover would occur after short-term TCP use. After the withdrawal week the concentrations of turnover markers reverted back towards baseline (≥90%) indicating the rapid response associated with the application and removal of this type of hormonal contraceptive. Additionally, the number of participants were evenly distributed across the study when observing the maximal change in SCTX-I and revealed a mean reduction of nearly 60% from baseline values. It is of interest that SCTX-I did not demonstrate a maximal response in some women until the third or fourth week, highlighting the individual impact TCP has on bone resorption. In contrast, the occurrence of the maximal change in BSAP was consistently observed during the fourth week.

Bone remodeling is a tightly coordinated process where osteoclasts and osteoblasts continually cycle through three consecutive phases – resorption, reversal and formation – allowing the skeleton to adapt to mechanical stress, repair micro-damage and help maintain mineral homeostasis[22]. The initial, rapid phase of bone resorption and the reversal phase last approximately 2- 3 weeks and are then followed by a lengthy bone formation phase[22]. We observed reduced bone resorption within one week, followed by a delayed

Figure 1: Changes in bone resorption (a) and formation (b) with one cycle of TCP. * SCTX-I reduced compared with Baseline (P=0.002; *d*=1.86). There was a tendency to remain suppressed after week 2 and week 3 ($P \leq 0.11$; *d*=1.07-1.38). ** BSAP different than week 4 (*P*=0.004; *d*=0.54).

impact on bone formation (after 3 weeks). This temporal alignment suggests that TCP likely had a direct effect on osteoclasts and that the resulting reduction in bone resorption could have been responsible for the subsequent suppression of bone formation that was observed several weeks later. The current outcomes differ compared to previous findings where bone formation was suppressed 39.2 ±5.5% after two weeks of low dose oral contraceptive use in premenopausal women with hypothalamic amenorrhea[9]. Bone resorption was also suppressed (30.1± 7.4%) but a temporal link for the changes between resorption and formation in that study were not observed. These findings taken together do not support the notion that greater estrogen exposure with TCP results in larger alterations in the short-term responses of bone turnover in premenopausal women.

Variations in sex steroid hormones have been demonstrated to alter bone turnover during the menstrual cycle[23, 24] with oestrogen being a potent regulator of the remodelling process[25]. Bone resorption is higher during the follicular phase when endogenous levels of oestrogen and progesterone are low[23], whereas bone formation appears to be higher in the luteal phase[24]. Zitterman et al[26] reported the highest levels of bone resorption and lowest levels of bone formation occurred on day three of the follicular phase in a group of eumenorrheic premenopausal women. The current findings are in contrast to what would be expected during a eumenorrheic menstrual cycle; we observed suppressed SCTX-I and BSAP after the first and third week of TCP use which would correspond to the follicular and luteal phases, respectively. Interestingly, the largest single day reduction in bone resorption with TCP occurred between day two and three of the first week (data not shown), which corresponds to the approximate timing of the peak ethinyl estradiol concentration from TCP[27, 28], further suggesting a direct effect of exogenous estrogen on osteoclasts function. However, the underlying mechanism is currently unknown.

Researchers have previously reported reductions in markers of bone formation and bone resorption in premenopausal women taking oral[2, 7, 29, 30] and transdermal[16, 17] contraceptives containing various doses of ethinyl estradiol. Massaro et al[16] and Harel et al[17] reported suppressed bone turnover that was observed as early as 3 months and persisted for 12 months in young women while taking TCP (Evra® and Ortho Evra®). The rapidity of suppression in bone resorption found in the current study has also been observed after two weeks of oral contraceptive use in premenopausal women with hypothalamic ameneorrhea[9] and similarly the effects persist for as long as individuals continued taking oral contraceptives[10, 11]. Taken together, the pronounced effects of this class of drugs on bone turnover are immediate and persistent, lasting as long as women remain on hormonal contraceptives. Despite the observed alterations in bone formation and resorption, recent evidence suggests TCP use does not have a deleterious effect on bone mineral density after 12 months in older (25-30 yr) premenopausal women[16] but has been reported to attenuate bone accretion in younger women (12-21 yr)[17]. Since peak bone mass occurs prior to 25 yr in women[31, 32] these findings have important clinical implications for young women who are interested in using hormonal contraceptives and for prescribing physicians.

The current study is limited due to the small number of women who participated, however the effect sizes observed suggest a modest impact of TCP and the short term treatment effects on bone turnover markers. This study did not use a control group, however the results display a trend in the opposite direction from what has been observed during the menstrual cycle in premenopausal, eumenorrheic women[23, 24, 26], therefore it appears the changes to bone turnover are the result of TCP.

CONCLUSION

The outcomes from this study uniquely demonstrate that TCP rapidly reduced bone resorption (within one week) up to 40%, but has a delayed (three weeks) and less suppressive effect (12-18%) on bone formation. Regardless of the motivation for use, practitioners prescribing hormonal contraceptives to young women should be aware of the potential for rapidly suppressing bone metabolism. Despite the observed reductions, the concentration of bone turnover markers remained within reference ranges for premenopausal women[33-35].

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST

Th ere are no confl icts of interes.

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