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ORIGINAL ARTICLE

The impact of depot medroxyprogesterone acetate on fracture risk: a case-control study from the UK

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Abstract
Summary There has been concerning about women receiving depot medroxyprogesterone acetate (DMPA) contraception because of the prolonged hypoestrogenemic state regarding the potential negative effects on bone health. This study showed that DMPA exposure is associated with increased fracture risk and that fracture risk increases with longer DMPA exposure.
Introduction DMPA has been associated with impaired bone mineral acquisition during adolescence and accelerated bone loss in later life. We performed this large population-based study to assess the association between use of DMPA or combined oral contraceptives and the incident risk of fracture.
Methods We identified 4189 women between 20 and 44 years of age with a first-time fracture diagnosis, matched them with 4189 random controls using the Disease Analyzer database and investigated the relation with DMPA exposure.
Results Overall, 11 % of the fracture cases and 7.7 % of the controls had DMPA use recorded. The adjusted OR for developing a fracture in patients with current use of DMPA compared to non-users was 0.97 (95 % CI 0.51–1.86), 2.41 (95 % CI 1.42–4.08), and 1.46 (95 % CI 0.96–2.23) for 1–2, 3–9, and ≥10 prescriptions, respectively. The adjusted OR for developing a fracture in patients with past use of DMPA compared to non-users was 0.96 (95 % CI 0.73–1.26), 1.14 (95 % CI 0.86–1.51), and 1.55 (95 % CI 1.07–2.27) for 1–2, 3–9, and ≥10 prescriptions, respectively. The highest fracture risk was identified in young patients less than 30 years with longer DMPA exposure (≥10 prescriptions; OR 3.04, 95 % CI 1.36–6.81), as well as in patients in the late reproductive years with past use of DMPA (OR 1.72, 95 % CI 1.13–2.63).
Conclusions Our results indicate that DMPA exposure is associated with increased fracture risk and may have negative effects on bone metabolism, resulting in impaired bone mineral acquisition during adolescence and accelerated bone loss in adult life.

Keywords Contraception · DMPA · Fracture risk · Osteoporosis

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Introduction

Healthy women with normal ovarian estrogen production achieve peak bone mass by their third decade of life. Thereafter, bone resorption begins to outpace accumulation, resulting in progressive bone mineral content loss in the late reproductive years and during menopause [1]. Low estrogen levels can result in premature loss of bone mineral density and increased risk of fracture [2]. Depot medroxyprogesterone acetate (DMPA) retrieves its contraceptive properties from the suppression of gonadotropin secretion, which in turn prevents from ovulation and inhibits ovarian estradiol production [3]. DMPA is a progestin-only contraceptive, administered by a 3-monthly intramuscular injection and is used by more than 9

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million women worldwide, especially in the USA and UK [4]. As a consequence of its mechanism of action, most women receiving DMPA become amenorrhoic after 1 year of use, and there has been concerning because of the prolonged hypoestrogenemic state regarding the potential negative effects on bone health.

On the contrary, combined oral contraceptives (COCs) may even increase estrogen exposure in women who are already estrogen deficient in the late reproductive years and prevent them from further bone loss. As such, Michaelsson et al. [5] reported that COC use in late reproductive life may reduce the risk of fracture. The mechanisms of estrogen on the bone are not yet completely understood, but estrogen might work directly by decreasing the number and depth of resorptive lacunae, leading to decreased bone turnover, higher bone density and stronger trabeculae [6].

In the absence of appropriate estrogen levels following DMPA treatment, Kaunitz et al. [7] observed a significant decline in bone mineral density (BMD) of 5.16 % at the total hip and of 5.38 % at the lumbar spine after 240 weeks of treatment. The authors elucidated the sustained negative effects of DMPA even after 96 weeks posttreatment. Further studies have associated DMPA use with increased bone turnover in serum markers of bone resorption [8]. Thus, all cross-sectional studies available to date indicate that DMPA is associated with accelerated bone turnover similar to that seen in postmenopausal women.

Investigations on the effects of hormonal contraception with DMPA on fracture risk are limited. Meier et al. [9] conducted a case-control analysis with female participants with an incident fracture from 1995 to 2008 and concluded that DMPA is associated with a slightly increased risk of fracture. Moreover, three further observational studies [10–12] suggested similar associations in adult women. However, despite the public-health importance of fractures and the widespread use of hormonal contraceptives, there is still limited epidemiological data regarding age at beginning DMPA and fracture associations. Apart from this, the small number of cases, potential confounders, and timing of exposure have not been addressed in the most previous studies. Considering the increasing use of DMPA among young women because of its contraceptive efficacy and compliance, any risk associated with its use may have important consequences. We therefore performed this large population-based study to assess the association between use of DMPA or combined oral contraceptives and the incident risk of fracture.

Patients and methods

The study was conducted according to the German law and the declaration of Helsinki. We analyzed the risk of having a first time fracture in relation to current or past use of DMPA and estrogen-containing oral contraceptives within the UK-based Disease Analyzer database (IMS HEALTH).

Disease Analyzer database

The Disease Analyzer database (IMS HEALTH) compiles drug prescriptions, diagnoses, and basic medical and demographic data directly obtained from the computer systems of the practices of general practitioners and specialists [13]. Diagnoses (ICD-10), prescriptions (Anatomical Therapeutic Chemical (ATC) Classification System), and the quality of reported data are continuously monitored by IMS with respect to a number of quality criteria (e.g., completeness of documentation, linkage of diagnoses, and prescriptions, etc.). In the present analysis, we identified patients in reproductive age with fractures and matched controls and analyzed the exposure to DMPA 150 mg intramuscular every 3 months and other estrogen-containing hormonal contraceptives. We were not able to investigate the 104 mg dose, because the product was not available in UK during the investigation's period. Furthermore, we investigated the fracture risk according to exposure time measured by the number of prescriptions and analyzed it according to current or past use. The data were derived directly from the computers of the physicians' practices via standardized interfaces, and they provide daily routine information on patients' diseases and therapies. Practices transmit patient data stored in the physicians' computers to IMS on a monthly basis. Before transmission, the data are encrypted for data protection. The validity of the Disease Analyzer data was previously evaluated and described elsewhere [13, 14]. The analyses carried out in comparison with reference statistics did not show any lack of representativeness or validity of the Disease Analyzer Database. As such, the current database appears suitable for pharmacoepidemiological and pharmacoeconomic studies [13]. This approach has been the basis of a number of studies and peer-reviewed scientific publications in the field of epidemiology and in osteoporosis research [15–19].

Study population

First-time fracture diagnosis (including vertebral and non-vertebral fractures) from January 2010 to December 2015 was defined as the index date. In this regard, the fractures were all clinically diagnosed. The latest follow-up date was identified at 31 December 2015. Patients with a follow-up time of less than 365 days prior to the index date were excluded. This exclusion criterion was necessary for the per protocol identification of the first treatment initiation time. We were able to include 4189 women between 20 and 44 years of age with a first-time fracture diagnosis and matched them with 4189 random controls according to age and sex. We excluded patients

with a diagnosis of cancer, Paget's disease, osteoporosis, osteomalacia, alcoholism, HIV, or use of anti-osteoporotic drugs for osteoporosis such as bisphosphonates, teriparatide, calcitriol, and raloxifene before the index date.

Patients were classified as current users if the last prescription for a study drug of interest was recorded less than 180 days or as past users if it was recorded 180 or more days before the index date. Furthermore, we identified patients by time of exposure before the index date, using the number of prescriptions as proxy (one to two, three to nine, or over 10 for DMPA and COC) and analyzed them additionally by age at treatment start.

Covariates

Demographic data included age, body mass index (BMI), smoking status, and comorbidities such as asthma or epilepsy. The relative risk of fracture was adjusted for BMI, smoking, asthma, epilepsy, use of progestins (single preparations) MPA low dose, beta-blockers, proton pump inhibitors, systemic corticosteroids, benzodiazepines, serotonin reuptake inhibitors, anticonvulsants, and contraceptives not under investigation. We further identified the type of fractures according to site (Fig. 1).

Statistical analysis

All variables in Table 1 have been considered in the analyses. After the selection procedure, and considering statistically significant variables from Table 1 with a p value of $p < 0.05$, we included the significant co-variables in the model shown in Table 2. The adjusted odd ratios (OR) and 95 % confidence intervals (CI) are presented in Table 2 for the independent variables.

The proportional hazards assumption was assessed and upheld for all analyses. Furthermore, potential confounders, co-diagnoses, and co-medication were included as independent variables. Two-sided tests were used, and a p value of less than 0.05 was considered to be statistically significant. All analyses were performed using SAS 9.3. (SAS Institute, Cary, USA). Best practice methods for retrospective database studies were considered [20].

Results

Altogether, 4189 patients with first time fractures and 4189 matched controls between 20 and 44 years were identified. Baseline characteristics are depicted in Table 1. Figure 1 presents the type of clinically diagnosed fractures.

Overall, 11 % of the fracture cases and 7.7 % of the controls had DMPA use recorded. The adjusted OR for developing a fracture in patients with current use of DMPA compared to non-users was 0.97 (95 % CI 0.51–1.86), 2.41 (95 % CI 1.42–4.08), and 1.46 (95 % CI 0.96–2.23) for 1–2, 3–9, and ≥10 prescriptions, respectively. The adjusted OR for developing a fracture in patients with past use of DMPA compared to non-users was 0.96 (95 % CI 0.73–1.26), 1.14 (95 % CI 0.86–1.51), and 1.55 (95 % CI 1.07–2.27) for 1–2, 3–9, and ≥10 prescriptions, respectively.

We further analyzed the group of current or past DMPA users of more than 10 prescriptions by age. The adjusted OR for current users less than 30 years was 3.04 (95 % CI 1.36–6.81), while the adjusted OR for current users between 30 and 44 years was 1.34 (95 % CI 0.82–2.18). Accordingly, the adjusted OR for past users less than 30 years was 1.83 (95 % CI 0.87–3.85), while the adjusted OR for past users between 30 and 44 years was 1.72 (95 % CI 1.13–2.63).

With regard to current users of estrogen-containing contraceptives, we found a significant increase of the relative fracture risk for patients who received between three to nine prescriptions with an OR of 1.39 (95 % CI 1.12–1.73), but not in those patients who received over 10 prescriptions (OR 1.07; 95 % CI 0.88–1.30). In contrast, past use of estrogen-containing contraceptives did not affect the relative fracture risk even in patients with longer exposure time (≥10 prescriptions, OR 1.04 95 % CI 0.90–1.21).

A series of further sensitivity analyses have been conducted. Compared with non-smokers, both current and ex-smokers showed an increased relative fracture risk with ORs of 1.78 (95 % CI 1.57–2.01) and 1.41 (95 % CI 1.21–1.64). Moreover, overweight and obese patients presented an increased risk for fracture. As such, we found an OR of 1.25 (95 % CI 1.10–1.43) for overweight and an OR of 1.32 (95 % CI 1.15–1.52) for obese patients. Regarding comorbidities, asthma was associated with an increased relative fracture risk (OR 1.39; 95 % CI 1.22–1.58), while epilepsy showed no association (OR 1.30; 95 % CI 0.86–1.98). With regard to drugs, there was a significantly increased risk for paracetamol (OR = 1.42; 1.25–1.62) and NSAIDs (OR 1.48; 1.31–1.68), but not for opioids (OR 1.16; 0.73–1.86).

Discussion

This large, population-based case-control study indicates that current or past use of DMPA may be associated with an increased risk of fracture in women of reproductive age. The increased risk was observed in women with current use of DMPA between 9 and 27 months, as well as in women with past DMPA exposure of more than 30 months. Moreover, we found a significant increase in relative fracture risk in young women less than 30 years, who currently use DMPA for more than 30 months, as well as in women between 30 and 44 years with past exposure of DMPA. These findings indicate that DMPA exposure may have negative effects on bone

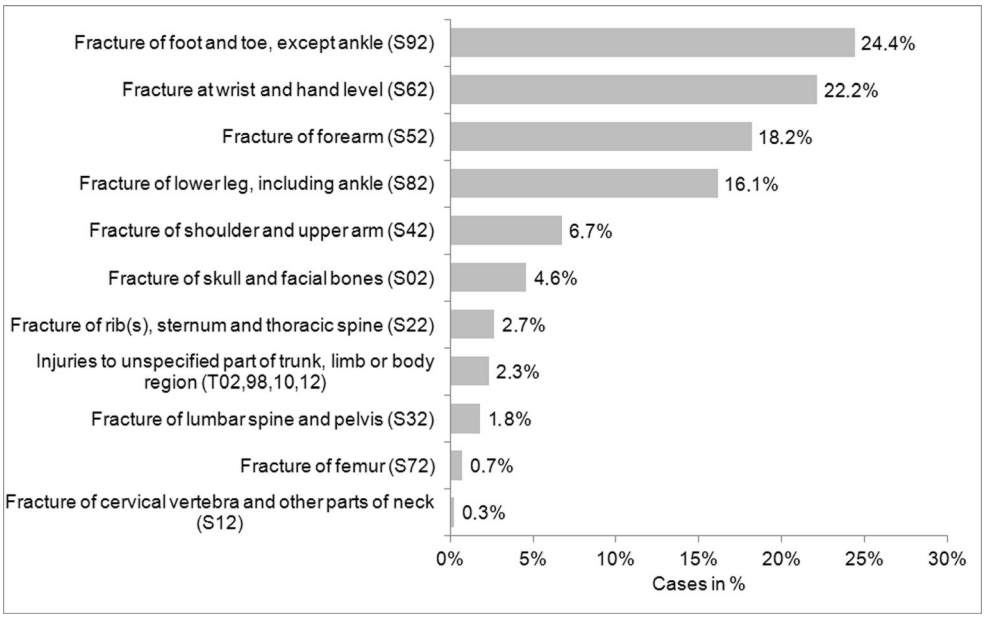

Fig. 1 Type of fractures

metabolism, resulting in impaired bone mineral acquisition during adolescence and accelerated bone loss in adult life [9]. Our results are in line with the study of Meier et al. [9], which showed an increasing relative risk of fracture with increasing DMPA exposure duration, independent of the timing of exposure. However, the authors presented significant increases in relative fracture risk after age stratification (<30 and >30) for current users of DMPA, but not for past users less than 30 years. As a consequence, restoration of bone loss may take longer in advanced age [7]. DMPA use has been associated with bone loss, probably due to the lower ovarian estrogen production resulting from the suppression of gonadotropin secretion [21]. Notably, we demonstrated an increased fracture risk in women with a BMI above 25 kg/m^2. This is in

Table 1 Characteristics of case patients with fractures and matched controls

Variable	No. of cases (N = 4189)	Percent	No. of controls (N = 4189)	Percent	OR adjusted[a] (95 % CI)
Age group (year)[b]					
20–29	1838	43.9	1844	44.0	
30–39	1536	36.7	1524	36.4	
40–44	815	19.5	821	19.6	
Smoking status					
Non-smoker	1236	29.5	1736	41.4	Reference
Current smoker	1002	23.9	704	16.8	1.78 (1.57–2.01)
Ex-smoker	485	11.6	440	10.5	1.41 (1.21–1.64)
Unknown	1466	35.0	1309	31.3	NA
BMI (kg/m^2)					
12–18.4	135	3.2	135	3.2	1.11 (0.86–1.43)
18.5–24.9	1410	33.7	1686	40.3	Reference
25–29.9	738	17.6	665	15.9	1.25 (1.10–1.43)
> =30	645	15.4	513	12.3	1.32 (1.15–1.52)
Unknown	1261	30.1	1190	28.4	NA
Comorbidities					
Asthma	793	18.9	555	13.3	1.39 (1.22–1.58)
Epilepsy	74	1.8	45	1.1	1.30 (0.86–1.98)

[a] Adjusted for all covariates listed in the table plus use of ß-blockers, proton pump inhibitors, systemic corticosteroids, benzodiazepines, serotonin reuptake inhibitors, and anticonvulsants

[b] Matching variables

Table 2 Exposure to DMPA and other hormonal contraceptives and relative risk of fracture

Variable	No. of cases ($N = 4189$)	Percent	No. of controls ($N = 4189$)	Percent	OR adjusted[a] (95 % CI)
DMPA					
Non-use	3729	89.0	3866	92.3	Reference
Current					
1–2	20	0.5	19	0.5	0.97 (0.51–1.86)
3–9	54	1.3	20	0.5	2.41 (1.42–4.08)
≥10	61	1.5	37	0.9	1.46 (0.96–2.23)
Past					
1–2	119	2.8	107	2.6	0.96 (0.73–1.26)
3–9	128	3.1	94	2.2	1.14 (0.86–1.51)
≥10	78	1.9	46	1.1	1.55 (1.07–2.27)
Hormonal contraception (estrogen-containing)					
Nonuse	2100	50.1	2084	49.8	Reference
Current					
1–2	94	2.2	111	2.7	0.98 (0.73–1.31)
3–9	208	5.0	184	4.4	1.39 (1.12–1.73)
≥10	265	6.3	261	6.2	1.07 (0.88–1.30)
Past					
1–2	397	9.5	426	10.2	0.90 (0.77–1.05)
3–9	570	13.6	616	14.7	0.90 (0.78–1.03)
≥10	555	13.3	507	12.1	1.04 (0.90–1.21)
Current and past use of ≥10 DMPA prescriptions by age (year)					
<30, current use	23	1.3	8	0.4	3.04 (1.36–6.81)
30–44, current use	38	1.6	29	1.2	1.34 (0.82–2.18)
<30, past use	19	1.0	11	0.6	1.83 (0.87–3.85)
30–44, past use	59	2.5	35	1.5	1.72 (1.13–2.63)

[a] Adjusted for BMI, smoking, asthma, epilepsy, use of progestins (single preparations), MPA low dose, ß-blockers, proton pump inhibitors, systemic corticosteroids, benzodiazepines, serotonin reuptake inhibitors, anti-convulsants, paracetamol, opioids, non-steroid antirheumatics, and contraceptive not under investigation

contrast with previous analyses, which have shown a slightly decreased fracture risk in women with a BMI above 25 kg/m^2 [9]. However, this study included also women above the age of 50. Our data support the meta-analysis by De Laet et al. [22], which concluded that the gradient of risk per unit of BMI increased with advancing age, predominantly after 55 years of age, without adjustment for BMD.

Evidence from the studies reviewed strongly suggests that DMPA use is associated with increased risk of fracture. Lappe and colleagues [11] investigated stress fractures among female army recruits and found a 70 % increased relative risk of fractures among those with history of DMPA use. Compared with their non-stress-fracture counterparts, recruits who developed stress fractures were more likely to report current or past smoking, alcoholic drinking of >10 drinks/week, corticosteroid use, and lower adult weight. Consequently, this study was not representative. Vestergaard et al. [12] concluded in a case-control study that DMPA results in a 44 % increased fracture risk compared with non-users, while the interpretation of the results was limited because of potential confounders and the small number of DMPA users.

Further studies have investigated the impact of DMPA on BMD. Kaunitz et al. [7] conducted a 5-year prospective cohort study comparing the BMD in women initiating DMPA versus non-users. The authors reported a loss of BMD at the lumbar spine and at the hip of −5.4 and 5.2 %, respectively, at the end of the follow-up. Interestingly, the loss was more pronounced during the first 2 years and stabilized thereafter. Another study of Cromer et al. [23] demonstrated a 1.5 and 3.1 % decrease in lumbar spine BMD in adolescents treated with DMPA after 1 and 2 years of use compared with a 2.9 and 9.5 % BMD increase in controls over the same study period. Hereby, these findings indicate that DMPA use prevents adolescents from achieving the reference range of peak bone mass [24].

A further point of interest to address is the change of serum bone turnover markers. Walsh et al. [25] observed in a case-control study with 100 DMPA users a 5 % deficit in BMD at the lumbar spine and femoral neck, accompanied by

significantly higher levels of serum N-terminal propeptide of type I procollagen (PINP) and urinary aminoterminal cross-linked telopeptide of type I collagen (NTX-I). Interestingly, the differences were more pronounced in younger women (<25 years) than in older women (35–45 years). To the best of our knowledge, all cross-sectional studies available to date seem to indicate that DMPA is associated with accelerated bone turnover similar to that seen in postmenopausal women [8]. As such, DMPA seems to induce an imbalance between bone resorption and bone formation in favor of bone resorption, which is accompanied by clinically relevant bone loss.

In the present study, we also investigated the effects of combined estrogen-containing contraceptives (COCs). Our results do not indicate any association between current or past use of COCs and fracture risk. However, the small number of COC users might have interfered as a potential confounder and did not allow further analyses with dose stratification. According to literature [21], COC therapy does not seem to exert any significant effect on BMD or fracture risk in the general population. Nevertheless, in adolescents, the effects of COC use on BMD seem to be determined by the dose of ethinylestradiol (EE). Hereby, 30 μg of EE seem to be enough to ensure a sufficient bone accrual during adolescence, while studies on COC use with 20 μg EE doubt on their ability to support peak bone mass acquisition [26]. In contrast, in perimenopausal women over 40 years, several randomized controlled trials showed that the use of COCs reduces bone demineralization and may increase BMD even at the 20 μg dose [26, 27]. The authors underlined also the reduction of fracture risk in users above the age of 40 years.

Our study is accompanied by certain limitations. Unfortunately, no power analyses prior to study start have been performed. This should be considered as a potential weakness of the study, because the fracture risk could be underestimated. However, several reports have demonstrated the validity of the information recorded by the Disease Analyzer database [13]. Because of the small number of fractures, we were not able to associate fracture sites or specific osteoporotic fractures with DMPA use. However, similar studies could not prove any significant impact of DMPA on osteoporotic fractures [9]. Moreover, of particular concern is the lack of data with regard to the individual indication of DMPA. It might be assumed that patients with higher risk of fracture, such as epileptic patients, patients with lower socioeconomic status, and patients with specific dietary habits opted for DMPA use [26]. This could not be addressed, as the assessment of these variables was not possible within the database used. Finally, although hospital diagnosis codes (ICD-10) are useful for assessing hip fracture rates in population-based studies, there are not reliable to differentiate hip fractures that occur in the sub-trochanteric region. Hereby, identification of sub-trochanteric fractures requires review of radiographic images to distinguish these fractures from the more common trochanteric fractures [28]. Despite these limitations, our study has several strengths. This analysis used real-life data from GPs, indicating the realistic impact of access to medical care on treatment with DMPA. Hereby, the present study reflects the fracture risk according to current or past exposure to DMPA.

In conclusion, our results indicate that DMPA exposure is associated with increased fracture risk and may have negative effects on bone metabolism, resulting in impaired bone mineral acquisition during adolescence and accelerated bone loss in adult life. In accordance to existing literature DMPA exposure over 2 years especially in younger women should be avoided.

Compliance with ethical standards The study was conducted according to the German law and the declaration of Helsinki.

Conflicts of interest None

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