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A register- and population-based cohort study

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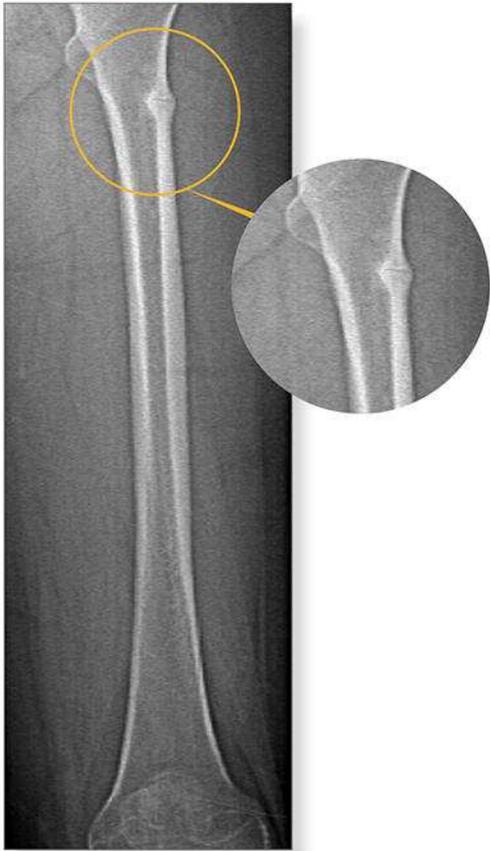
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Fracture Risk Is Decreased in Women With Polycystic Ovary Syndrome: A Register-Based and Population-Based Cohort Study

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ABSTRACT

Hyperandrogenism, obesity, and hyperinsulinemia may protect against osteoporosis, whereas amenorrhea, increased cortisol, and low growth hormone may be associated with higher fracture risk in polycystic ovary syndrome (PCOS). The objective of this study was to investigate fracture risk in PCOS. In the PCOS Denmark study, women with PCOS and/or hirsutism were identified in the Danish National Patient Register (1995–2012). Each patient was assigned three age-matched controls on the index date of PCOS diagnosis. Individuals with a previous endocrine diagnosis were excluded. Within PCOS Denmark, we embedded a well-characterized subcohort of patients, PCOS OUH, diagnosed with PCOS at Odense University Hospital ($n = 1217$). We identified incident fractures by International Classification of Diseases, 10th Revision (ICD-10) codes and used conditional Cox regression analyses to compare fracture risk. In the PCOS Denmark study, there were 19,199 women with PCOS and 57,483 controls were included, mean age 30.6 years (range, 12–60 years). Fracture rates were decreased in PCOS Denmark (10.3/1000 patient years) versus controls (13.6/1000 patient years). The adjusted ORs were 0.76 (95% CI, 0.71 to 0.80) for all fractures, 0.82 (95% CI, 0.74 to 0.92) for major osteoporotic fractures, and 0.57 (95% CI, 0.47 to 0.70) for fractures of head and face. The risk reduction was more pronounced below the age of 30 years at diagnosis. Women with PCOS had significant more hospital contacts due to strains and sprains. In the PCOS OUH subcohort, the risk reduction of fractures did not differ between PCOS women with elevated versus normal testosterone levels and the risk reduction was nominally smaller in overweight versus normal weight PCOS women. Women with PCOS had reduced risk of fractures, in particular of the appendicular skeleton. The risk reduction was greater in women with younger age at diagnosis suggesting that the skeletal effects of PCOS may be greater in women who have not yet reached peak bone mass. Reduced participation in sports activities was probably not the reason for the reduced risk of fractures. © 2015 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals, Inc. on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: POLYCYSTIC OVARY SYNDROME; FRACTURE RISK; REGISTER-BASED; NATIONWIDE; HIRSUTISM

Introduction

Osteoporosis is a major global health concern and osteoporotic fracture is particularly prevalent among postmenopausal women. Much research has naturally been conducted regarding determinants of accelerated bone loss rates, either after menopause or after the onset of major illnesses or introduction of drugs with adverse bone outcomes such as glucocorticoids, aromatase inhibitors, and glitazones.[1] However, a simple mathematical appraisal of the impact of peak bone mass demonstrates that a modest 1 SD higher peak bone mass is sufficient to offset almost three decades of bone loss at

1 SD above the normal rate.[2] The importance of bone health in uteri, in childhood, adolescence, and young adulthood on the subsequent risks of osteoporosis is slowly becoming recognized.[3]

Polycystic ovary syndrome (PCOS) affects 6% to 20% of women of reproductive age and the syndrome is therefore the most frequent endocrinopathy in premenopausal women.[4] PCOS is most often defined according to the Rotterdam criteria, which include two out of the following three: (1) irregular/no ovulations; (2) clinical/biochemical hyperandrogenemia; and (3) polycystic ovaries.[5] Secondary etiologies such as hyperprolactinemia, acromegaly, Cushing's syndrome, adrenogenital

syndrome, and Turner's syndrome should be excluded.[5] The prevalence of hirsutism is 5% to 25% in women of reproductive age[6] and PCOS is diagnosed in more than 90% of these patients.[6] PCOS has so far not been extensively studied in terms of skeletal outcomes, though the associated hyperandrogenemia, obesity, and insulin resistance may protect patients' bone health, whereas amenorrhea, increased risk of type 2 diabetes, hypovitaminosis D, low growth hormone levels, and increased cortisol may be associated with lower bone mineral density (BMD).[7,8]

Studies regarding BMD in premenopausal study populations found comparable or higher BMD in patients with PCOS and/or hirsutism compared to controls.[8] The majority of these studies were, however, performed in very small study populations (<50 patients) with hirsutism and/or PCOS and uniform criteria were not applied for the diagnosis of PCOS.[8] One Swedish study found no difference in fracture risk over more than 20 years in women with PCOS and elevated androgen levels, but the study only included 25 patients and 68 control subjects.[9] We are not aware of other studies on fracture risk in patients with PCOS.

The aim of this study was to investigate fracture risk in patients diagnosed with PCOS/hirsutism. We hypothesized that fracture risk could be lower in patients with PCOS than in healthy controls due to higher androgen levels, hyperinsulinemia, and obesity, which could lead to increased BMD.

Materials and Methods

Study population and data sources

We have conducted an open, observational, register-based cohort study using national health data. Study design and baseline data of the cohort have been reported previously.[10]

In brief, we used Danish National Registers to identify all women in the country who were diagnosed through a hospital contact (inpatient or outpatient) as having PCOS (E282) and/or hirsutism (L680) between January 1, 1995, and the end of 2012 (PCOS Denmark). We excluded patients who were below age 12 years or over age 60 years, and patients with a history of endocrine disorders that could give rise to signs or symptoms similar to PCOS, namely E221 (hyperprolactinemia), E220 (acromegaly), E24 (Cushing's syndrome), E25 (adrenogenital syndrome), and Q96 (Turner syndrome). For each patient with PCOS/hirsutism, three control women born in the same year as the patient were randomly drawn from the civil population register. Controls were assigned the index date (date of first PCOS diagnosis) of their matched PCOS cases. Controls had to be alive on the index date of their respective PCOS case. We retrieved information about hospital contacts and prescriptions filled, along with dates of death if applicable, in both PCOS patients and control subjects from Danish National Registers, the National Prescription Registry, and the National Cause of Death Register. The Registers are in relation to this study population described elsewhere.[10]

Within the national PCOS cohort, we embedded a local subcohort of all patients with PCOS treated at Odense University Hospital (OUH) (n = 1,217). As described,[10] this subcohort (PCOS OUH) is very similar to patients in PCOS Denmark though the mean age and the number of childbirths were marginally lower in the local cohort. Although the PCOS Denmark cohort contained information about hospital diagnoses and filled prescriptions only, the PCOS OUH subcohort also had detailed information on androgen levels, body mass index, and other key biochemical and clinical characteristics as described by Glintborg and colleagues.[11]

The study was not a clinical trial. Ethics committee approval was therefore not required. Data was accessed through Statistics Denmark, project number 704175, and was approved by the Data Protection Agency.

Outcome

The primary outcome was any fracture, whereas secondary outcomes were (1) major osteoporotic fractures (fractures assumed to be BMD-dependent), ie, fractures of the forearm, spine, hip, or humerus[12] and (2) fractures not likely to be BMD-dependent, ie, fractures of the hands, head, and face.[13] We identified incident fractures by International Classification of Diseases, 10th Revision (ICD-10) codes (Table 1) from the Danish National Registers.

Statistical analyses

Baseline characteristics are shown as mean ± SD or median (range) as appropriate. Chi square test and Mann-Whitney U tests were used to test for difference between PCOS and control group for categorical and continuous variables, respectively. Values of $p < 0.05$ were considered statistically significant.

Cox proportional hazard models were used to calculate incidence rates, hazard ratios, and 95% confidence intervals (95% CIs) for fracture outcomes using the ICD-10 codes for fractures shown in Table 1.

Sensitivity analyses were performed by reanalyzing data stratified by age (<30 years and ≥30 years), omitting the women below the age of 50 years and in analyses only including women and their respective controls from the PCOS OUH cohort.

The SAS Greedy Match macro (SAS Institute, Inc., Cary, NC, USA) was used in the matching procedure and STATA version 13 (Stata Corporation, Inc., College Station, TX, USA) was used for the analyses.

Results

The National cohort included 76,682 women and was composed of 19,199 patients making up PCOS Denmark and 57,483 control subjects (Fig. 1). The cohort contained an embedded local cohort of 1217 patients (PCOS OUH) from Odense University Hospital as described in the Materials and Methods section.

Key baseline characteristics of the participants are shown in Table 1 (additional clinical characteristics are described in the article by Glintborg and colleagues[10]).

In PCOS Denmark, the mean age was 30.6 years (range, 12–60 years) at diagnosis. Patients with PCOS were less likely to have a prior history of fractures (12.0% versus 16.1%, $p < 0.001$). This was also true for sites not conventionally considered linked to BMD; eg, fractures of head and face, hands, or feet. Patients in PCOS Denmark had significant more hospital contacts compared to controls due to strains and sprains both with regard to typically sports-related strains and sprains and also with regard to strains and sprains in general (21.8% versus 20.9%, $p = 0.01$, and 24.6% versus 23.7%, $p = 0.01$, respectively). They also had a higher prevalence of most baseline conditions compared to controls, in particular diseases related to the cardiovascular system—with a three times higher prevalence of dyslipidemia

Table 1. Baseline Characteristics of Patients and Controls

| | | PCOS | | Controls | | |
		n = 19,199		n = 57,483		p
Age (years), mean ± SD		30.6 ± 9.6		30.6 ± 9.6		0.96
Age (years), range		12 to 60		12 to 60		
Charlson index, mean ± SD		0.155 ± 0.537		0.096 ± 0.435		<0.001
	ICD-10 codes	n	%	n	%	P
Fracture history						
All prior fractures		2,481	12.92	9,280	16.14	<0.001
Head or face	S02	251	1.31	1,349	2.35	<0.001
cervical spine	S12	8	0.04	57	0.10	0.015
Sternum	S222	3	0.02	10	0.02	1.000
Ribs	S223-S225	16	0.08	119	0.21	<0.001
Pelvis	S321-S329	43	0.22	88	0.15	0.043
Spine	S220, S221, S320	29	0.15	125	0.22	0.077
Clavicle and scapula	S420, S421	81	0.42	540	0.94	<0.001
Humerus	S422-S499	118	0.61	435	0.76	0.043
Forearm	S52	676	3.52	2,267	3.94	0.008
Hand	S62	909	4.73	3,548	6.17	<0.001
Hip and femur	S720-S729	22	0.11	140	0.24	0.001
Lower leg	S82	375	1.95	1,302	2.27	0.010
Foot	S92	462	2.41	1,519	2.64	0.074
Major osteoporotic fractures[a]		796	4.15	2,757	4.80	<0.001
All strains and sprains		4,721	24.59	13,605	23.67	0.010
Sports related strains and sprains	S63, S83, S93	4,185	21.80	12,024	20.92	0.010
Medical history						
Obesity	E66	2,306	12.01	791	1.38	<0.001
Diabetes	E10, E11, E13, E14	429	2.23	423	0.74	<0.001
Dyslipidaemia	E78	107	0.56	108	0.19	<0.001
Hypertension	I109	343	1.79	365	0.63	<0.001
Cardiovascular disease	I20, I50	72	0.38	177	0.31	0.16
Myocardial infarction	I21, I22, I23, I24, I25	39	0.20	121	0.20	0.85
Thyroid disease	E04, E05, E03	476	2.48	379	0.66	<0.001
Hyperthyroidism	E05	150	0.78	159	0.28	<0.001
Hypothyroidism	E03	213	1.11	106	0.18	<0.001
Medication history (last year)	ATC codes	n	%	n	%	P
Prednisolone	H02AB06, H02AB07	882	4.59	1,687	2.93	<0.001
Metformin	A10BA02	1,795	9.35	146	0.25	<0.001
Oral contraceptives	G03AA, G03AB	3,716	19.36	10,031	17.45	<0.001
Cyproterone acetate/ ethinylestradiol	G03HB01	1,347	7.02	533	0.93	<0.001

PCOS = polycystic ovary syndrome; ICD-10 = International Classification of Diseases, 10th Revision; ATC = Anatomical Therapeutic Chemical.
[a]Spine, humerus, and forearm.

and hypertension—and endocrine disorders, with an increased prevalence of diabetes, obesity, and thyroid disorders (Table 1). PCOS patients more often had a history of prednisolone, metformin, oral contraceptives, and cyproterone acetate/ethinyl estradiol exposure than controls (Table 1).

Fracture incidence

A total of 1596 (8.3%) in PCOS Denmark and 6148 (10.7%) controls suffered at least one fracture, corresponding to an incidence rate of 10.3 versus 13.6 per 1000 patient-years (Table 2). Most fractures occurred at sites not regarded as major osteoporotic, or classically BMD-dependent, fracture sites. The rate of major osteoporotic fractures was 2.6 per 1000 patient-years in PCOS Denmark and 3.0 per 1000 patient-years in control subjects, whereas fractures of the hands occurred at a rate of 3.0 (PCOS Denmark) versus 4.5 (control) per 1000 patient-years. The overall fracture risk was significantly reduced in patients with PCOS (HR 0.76; 95% CI, 0.72 to 0.80; $p < 0.001$) and adjustment for Charlson index, comorbid conditions (obesity, diabetes,

dyslipidemia, hyperthyroidism, and hypothyroidism), prior fractures, and prior prednisolone use did not change results (Table 2, Fig. 2). The risk reduction was more pronounced in fractures of the hands (adjusted HR 0.68; 95% CI, 0.62 to 0.76; $p < 0.001$), head and face (adjusted HR 0.57; 95% CI, 0.47 to 0.70; $p < 0.001$) than at major osteoporotic sites (adjusted HR 0.82; 95% CI, 0.74 to 0.92; $p = 0.001$) (Table 2). There was no interaction with baseline fracture prevalence, but a significant interaction with age was observed for fractures in general ($p < 0.001$) and for fractures of the hands ($p < 0.001$) or head and face ($p = 0.04$). Sensitivity analyses, where women above the age of 50 years at the first diagnosis of PCOS were excluded, did not significantly change findings at any of the fracture sites (data not shown). Stratifying the analyses for age (Table 3) by dividing the population into those aged <30 years or ≥30 years, revealed a more pronounced relative risk reduction in patients <30 years at the time of diagnosis. Though fractures of the hip and femur nominally exhibited a smaller risk reduction in the older age group, this difference was not statistically significant ($p_{interact}$ 0.63).
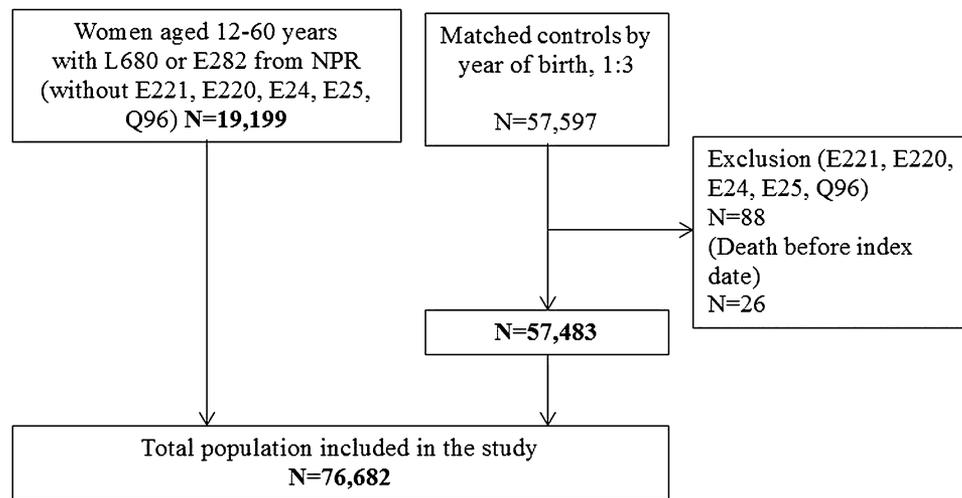
Fig. 1. Flowchart of included participants.

Contributing factors as assessed in the embedded clinical PCOS OUH cohort

Addressing the influence of obesity and androgen levels for fracture risk was possible in PCOS OUH ($n = 1217$) (Table 4). As reported,[10] these women had a mean age of 29.3 (median 29; interquartile range [IQR], 23 to 35) years, BMI median 27.3 (IQR, 23.0 to 32.7) kg/m^2, total testosterone 1.74 (IQR, 1.24 to 2.38) nmol/L, free testosterone 0.033 (IQR, 0.021 to 0.050) nmol/L (data not shown). Repeating the analyses of overall fracture risk in the PCOS OUH cohort confirmed a similarly decreased risk of fractures as observed in the full PCOS Denmark cohort (adjusted HR 0.66; 95% CI, 0.51 to 0.84; $p = 0.001$). Data on BMI was available in 1130 women in the PCOS OUH cohort, and subdividing this cohort into patients with BMI <25 kg/m^2 ($n = 431$) and BMI ≥ 25 kg/m^2 ($n = 699$) revealed that the risk reduction relative to population controls was nominally more pronounced in patients with BMI <25 kg/m^2 (HR, 0.52; 95% CI, 0.34 to 0.78; $p = 0.002$) than in overweight patients (HR, 0.74; 95% CI, 0.53 to 1.03; $p = 0.08$). A formal interaction test should not be undertaken because it is not possible to subdivide population controls by BMI status but overlapping confidence intervals should be noted. A total of 64 patients in PCOS OUH had BMI <20 kg/m^2. Omitting these patients in a sensitivity analyses did not significantly change the results. PCOS OUH patients with elevated free or total testosterone levels had a significantly reduced risk of fractures compared with population controls (Table 4). Patients with normal testosterone levels had a risk reduction of the same magnitude though the risk reduction was short of statistical significance here ($p = 0.065$).

Discussion

This study—the first large population-based analyses of fracture risk in patients with PCOS—shows that the risk of fractures is reduced in women with PCOS. Interestingly, the risk reduction tended to be more pronounced in women diagnosed with PCOS at a younger age and the risk reduction was not confined to traditional BMD-dependent fracture sites. We found no indication that women with PCOS were less exposed to daily trauma,

judged on their hospital contacts for strains and sprains. An embedded subcohort analyses showed that the risk reduction for fractures was, if anything, more pronounced in normal-weight women though confidence intervals overlapped. The presence of hyperandrogenemia did not materially modify fracture risk, which was reduced by about a third both in PCOS women with normal and raised androgens—albeit statistically significant only in the latter subgroup.

Adolescent girls with PCOS are characterized by hyper-insulinemia and androgen excess,[14] which could be consistent with the results of the present study. Here the risk reduction for fractures tended to be more pronounced in women with a younger age at diagnosis. With aging, beta-cell function declines in women with PCOS and the risk of type 2 diabetes increases, and testosterone levels have also been found to be lower in women diagnosed after the age of 30 years.[15] Both these reductions in bone anabolic hormones could theoretically contribute to a less favorable fracture outcome in women with a higher age at the time of PCOS diagnosis. Although insulin resistance may protect against osteoporosis, the risk of fractures is clearly increased once type 2 diabetes mellitus has developed, and especially if this is long-standing and accompanied by diabetes complications.[16–20] Young women with PCOS are often characterized by anovulatory cycles.[21] As covered in greater detail previously,[8] estradiol levels in late-cycle days are often decreased in hirsute patients with oligomenorrhea despite normal estradiol levels in the follicular phase, so it is likely that regularly-cycling PCOS patients have normal or high (due to aromatase activity in more abundant adipose tissue) estradiol levels, whereas PCOS patients with amenorrhea or irregular cycles as a group have lower serum estradiol. There is some uncertainty about the net effect on the skeleton of having a relatively high androgen level at the cost of reduced estrogens in young women. After all, in postmenopausal women, androgen treatment does increase BMD, albeit accompanied by undesirable changes in lipoprotein levels.[22] Menopause itself is accompanied by approximately a doubling of the activation frequency even in cortical bone, thus creating a high turnover state with an increased remodeling space and increased cortical porosity,[23] accompanied by an increase in

Table 2. Incidence Rate and Hazard Ratios Among PCOS Patients and Controls

	Control		PCOS		Hazard Ratio and 95% CI		Interaction terms	
	n	Per 1000 patient years	n	Per 1000 patient years	Unadjusted	Adjusted[a]	Interaction with age	Interaction with prior fracture
Any fracture	6,148	13.6	1,596	10.3	0.76 (0.72–0.80) $p < 0.001$	0.76 (0.71–0.80) $p < 0.001$	$p < 0.001$	$p = 0.73$
Likely to be BMD dependent								
Major osteoporotic fractures	1,459	3.0	414	2.6	0.85 (0.76–0.95) $p = 0.003$	0.82 (0.74–0.92) $p = 0.001$	$p = 0.31$	$p = 0.37$
Forearm fractures	1063	2.2	293	1.8	0.83 (0.73–0.94) $p = 0.005$	0.81 (0.71–0.93) $p = 0.002$	$p = 0.09$	$p = 0.78$
Lower leg fractures	968	2.0	295	1.8	0.91 (0.80–1.04) $p = 0.15$	0.89 (0.78–1.03) $p = 0.111$	$p = 0.16$	$p = 0.73$
Fractures of femur or hip	141	0.3	29	0.2	0.61 (0.41–0.92) $p = 0.017$	0.59 (0.38–0.90) $p = 0.013$	$p = 0.63$	$p = 0.54$
Likely to be BMD independent								
Fractures of hands	2,144	4.5	484	3.0	0.67 (0.61–0.74) $p < 0.001$	0.68 (0.62–0.76) $p < 0.001$	$p < 0.001$	$p = 0.98$
Fractures of head or face	691	1.4	130	0.8	0.56 (0.46–0.68) $p < 0.001$	0.57 (0.47–0.70) $p < 0.001$	$p = 0.04$	$p = 0.54$

PCOS = polycystic ovary syndrome; CI = confidence interval; BMD = bone mineral density.
[a]Adjusted for Charlson index, prior fracture, prednisolone use, obesity, diabetes, dyslipidaemia, hyperthyroidism and hypothyroidism.
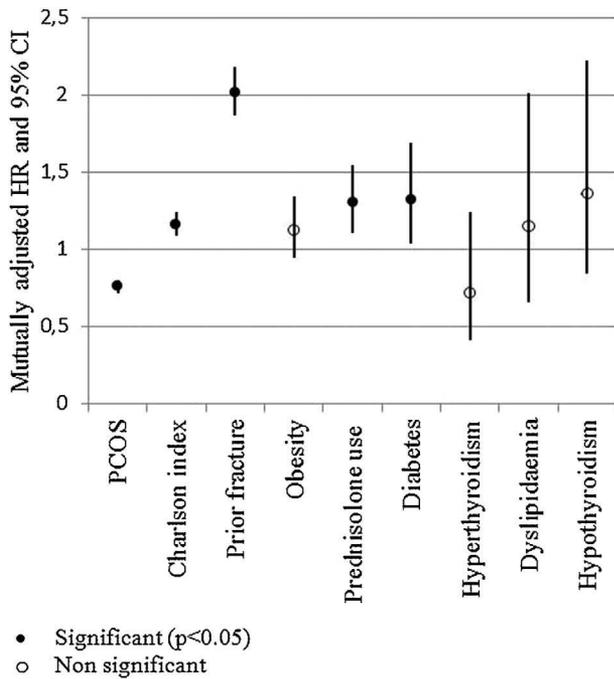
Fig. 2. Hazard ratios from the total Cox regression model with any fracture as outcome and adjusted for all the baseline confounders.

- ● Significant (p<0.05)
- ○ Non significant

fracture risk. Another scenario, in which the skeletal effects of artificial androgen excess has been studied in younger women, is in female-to-male transsexuals. Here, testosterone therapy given in doses sufficient to lower estradiol levels to the postmenopausal range were able to induce BMD gains, suggesting that androgen excess can increase BMD in adult women in some settings.[24] However, findings in men have revealed that estrogens appear to be critical in maintaining skeletal health, at least in men, an area where androgen sufficiency seems entirely unable to substitute for the lack of estrogen bioactivity.[25] Certainly, extreme phenotypes such as men with genetic defects in estrogen formation—due to aromatase deficiency—or signaling—due to an inactivating estrogen alpha receptor mutation—have displayed severe osteoporosis as a pronounced feature.[26,27] Also, there may be gender-specific differences in the nature of the skeletal

response to sex steroids, including the receptor subtypes involved[28] and the direction of effect of some of the genetic receptor variants.[29] Finally, the effect of male versus female sex steroid hormones on the skeleton likely also depends on the stage of skeletal development, so the effects of hyperandrogenism in women of fertile age could depend on whether hyperandrogenism debuted at a time when accretion of bone mass was still taking place or at a later time in adult life.

In the present study, the fracture risk reduction was nominally more pronounced in patients with BMI $<25\,\mathrm{kg/m^2}$ than in overweight patients. For osteoporotic fractures, the conventional view among clinicians has long been that a high BMI was protective against fracture, especially in postmenopausal women where higher peripheral estrogen production and higher weight bearing of bones would preserve strong bones and prevent fractures. Recent research has shown this to be a somewhat misguided view. Taken together, large cohort studies[30] have consistently shown the association to be chiefly driven by the strongly increased risk of fracture in those with low BMI, whereas obesity confers little if any fracture risk reduction. Although the risk of hip fracture is lower in obese postmenopausal women, several studies have found an increased risk of ankle and lower leg fractures as well as a possible increase in the risk of vertebral fractures.[31] Women of normal body weight are also less likely to be vitamin D–deficient, but it is not clear if the tendency for poorer vitamin D status in obesity is chiefly due to lack of outdoor activity and sun exposure or whether the amount of vitamin D deposited into adipose tissue also contributes to this difference.[32] It is even possible that vitamin D deficiency in itself affects adipogenesis (as reviewed in detail elsewhere[33,34]) and the metabolic changes in PCOS show an inverse relation with vitamin D status.[35] In premenopausal women, abdominal adiposity is associated with decreased bone formation rates, lower trabecular bone volume, and higher cortical porosity.[36] In PCOS, central obesity is prevalent and is present also in normal weight patients with PCOS.[37] Increased secretion of interleukins and chemokines and decreased adiponectin levels in PCOS may link central obesity, inflammatory risk, and insulin resistance.[6,38] Our finding of reduced fracture rate in PCOS suggests that the potential negative effects on bone of visceral obesity, the associated low growth hormone levels and increased cortisol levels,[39–41] did not materially degrade bone strength in this age group.

A history of thyroid disorders—especially hypothyroidism—was four times as prevalent among PCOS women compared with population controls (Table 1). These findings were in

Table 3. Adjusted Hazard Ratios for PCOS Patients and Controls Stratified by Age <30 years and ≥30 years

	HR, adjusted[a] (95% CI)	
	Age <30 ($n=38{,}618$)	Age ≥30 ($n=38{,}064$)
Any fracture	0.66 (0.60–0.71) $p<0.001$	0.86 (0.76–0.93) $p<0.001$
Likely to be BMD dependent		
Major osteoporotic fractures	0.75 (0.62–0.90) $p=0.002$	0.87 (0.76–1.01) $p=0.07$
Forearm fractures	0.69 (0.55–0.85) $p=0.001$	0.90 (0.76–1.08) $p=0.26$
Lower leg fractures	0.80 (0.64–1.00) $p=0.05$	0.96 (0.81–1.15) $p=0.69$
Fractures of femur or hip	0.65 (0.31–1.34) $p=0.24$	0.60 (0.36–1.02) $p=0.06$
Likely to be BMD independent		
Fractures of hands	0.58 (0.50–0.67) $p<0.001$	0.82 (0.71–0.95) $p=0.008$
Fractures of head or face	0.46 (0.35–0.60) $p<0.001$	0.79 (0.59–1.06) $p=0.12$

PCOS = polycystic ovary syndrome; HR = hazard ratio; CI = confidence interval; BMD = bone mineral density.
[a]Adjusted for Charlson index, prior fracture, prednisolone use, obesity, diabetes, dyslipidaemia, hyper- and hypothyroidism.

Table 4. Adjusted Hazard ratios in the PCOS-OUH Clinical Subcohort Against Population Controls

	PCOS-OUH	Any fracture
	(n)	HR, adjusted[a] (95% CI)
All	1,217	0.66 (0.51–0.84), $p = 0.001$
BMI <25kg/m^2	431	0.52 (0.34–0.78), $p = 0.002$
BMI ≥25kg/m^2	699	0.74 (0.53–1.03), $p = 0.076$[b]
Normal testosterone level	361	0.62 (0.37–1.03), $p = 0.065$
Increased testosterone level	499	0.64 (0.43–0.96), $p = 0.030$[c]

PCOS = polycystic ovary syndrome; OUH = Odense University Hospital; HR = hazard ratio; CI = confidence interval; BMI = body mass index.
[a]Adjusted for Charlson index, prior fracture, prednisolone use, obesity, diabetes, dyslipidaemia, hyper- and hypothyroidism.
[b]The risk reduction was not significantly different between the two BMI categories.
[c]The risk reduction was not significantly different between the two testosterone categories.

accordance with recent studies in which thyroid autoantibodies and autoimmune thyroiditis were more prevalent in patients with PCOS compared to controls.[42] Prolonged periods of thyroid-stimulating hormone (TSH) suppression, whether from overzealous thyroxine replacement therapy or from thyrotoxicosis (in this age group generally Graves' disease rather than toxic nodular goiter) are known to substantially increase the risk of fractures in adulthood.[43,44] However, though increased relative to the background population, thyroid disorders were still relatively infrequent and adjusting for a history of thyroid disease did not affect our findings.

In this study, the women with PCOS had more contacts due to strains and sprains that would typically be the consequence of participation in sports. This indicates that it is not likely that the women with PCOS were less physically active, at least not in the time leading up to the diagnosis of PCOS. There are limited data available regarding physical activity in women with PCOS compared with controls.[45,46] The studies have opposite results and included a small number of women.[45,46] One study from Spain that included 22 women with PCOS and 59 controls showed no overall significant differences in the proportion of women exercising regularly or in the number of hours of exercise per week between overweight women with PCOS and controls.[45] By contrast, another study from Greece, reporting on 81 girls (35 with PCOS and 46 controls) showed that girls with PCOS participated much less in physical activities than controls.[46] Though a small study has reported increased cortical BMD in the appendicular skeleton in PCOS women, attributing our findings to this is premature.[47]

A major strength of this study is that it is population-based and drew on a well-characterized local clinical cohort embedded in national health databases, with a long follow-up period and a complete prescription history since 1995. The National Patient Register and the use of registries for diagnosis has high validity.[48,49] The diagnosis of fractures has previously been reported with an accuracy of 97%.[50]

Our study also has some potential limitations. In the age group in question, many women have few or no hospital contacts with the exception of childbirth. About one-quarter of the control group participants had a hospital contact for non-obstetric reasons in 1 calendar year (data not shown), highlighting the importance of going over several years when accounting for comorbid conditions or fracture outcomes. We identified all PCOS patients from the Danish National register based on all hospital contacts in Denmark, but some patients with PCOS are treated by their general practitioner or by a private gynecologist. Therefore, a group of women with PCOS will not have been captured by national databases; we cannot preclude the possibility that the women with PCOS not attending the hospital differ from the women included in terms of disease severity or socioeconomic status. This also leads to the possibility that some of the "undiagnosed" PCOS women in the study can be included in the control group and cause an underestimation of the fracture risk reduction in PCOS women by attenuation of the epidemiological signal.

Second, we lack direct information about physical activity patterns and BMD information that would have allowed us to further explore the potential mechanisms behind the reduction in fracture risk in PCOS women.

Finally, there is a lack of information on BMI and biochemistry data in the national cohort and in all controls, but the differences between the embedded clinical subcohort and the national PCOS cohort was very small in terms of age, comorbidity, and prescription history.[10] Further, the risk estimates were remarkably similar whether originating from the national cohort or from the embedded subcohort with extensive clinical information.

Conclusion

This study demonstrates that women with PCOS have a substantially reduced risk of fractures, in particular of the appendicular skeleton, which may not be fully explained by obesity or reduced sports activity. The risk reduction was greater in women with younger age at diagnosis, suggesting that the skeletal effects of PCOS are more pronounced in women who have not yet reached peak bone mass.

Disclosures

All authors state that they have no conflicts of interest.

Acknowledgments

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