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ORIGINAL ARTICLE

Sex-specific association of serum dehydroepiandrosterone and its sulfate levels with osteoporosis in type 2 diabetes

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Abstract

Introduction This study is to investigate the relation between serum dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) levels and the risk of osteoporosis in patients with T2DM.

Materials and Methods This cross-sectional study involved 938 hospitalized patients with T2DM. Linear regression models were used to explore the relationship between DHEA and DHEAS and the BMD at different skeletal sites. Multinominal logistic regression models and the restricted cubic spline (RCS) were used to evaluate the associations of DHEA and DHEAS with the risks of osteopenia and/or osteoporosis.

Results In postmenopausal women with T2DM, after adjustment for confounders including testosterone and estradiol, DHEA showed a significant positive correlation with lumbar spine BMD (P = 0.013). Moreover, DHEAS exhibited significant positive correlations with BMD at three skeletal sites: including femoral neck, total hip, and lumbar spine (all $P < 0.05$). Low DHEA and DHEAS levels were associated with increased risk of osteopenia and/or osteoporosis (all $P < 0.05$) and the risk of osteoporosis gradually decreased with increasing DHEAS levels (P overall = 0.018, P-nonlinear = 0.559). However, DHEA and DHEAS levels in men over the age of 50 with T2DM were not associated with any of above outcomes.

Conclusion In patients with T2DM, independent of testosterone and estradiol, higher DHEA and DHEAS levels are associated with higher BMD and lower risk of osteopenia/osteoporosis in postmenopausal women but not men over the age of 50.

Keywords Bone mineral density · Dehydroepiandrosterone · Dehydroepiandrosterone sulfate · Osteoporosis · Type 2 diabetes

Introduction

As an emerging and severe complication of type 2 diabetes (T2DM), osteoporosis significantly increases the risk of fractures, profoundly impacting physical activity and overall health in individuals with T2DM [1, 2]. This poses a substantial burden on healthcare systems, highlighting its rapid emergence as a pressing public health concern [3]. However, the mechanisms responsible for diminished bone strength in patients with T2DM are not yet fully understood.

DHEA and DHEAS are the abundant circulating steroids, decline significantly with aging, converting androgens and estrogens in peripheral tissues via specific enzymes. Previous studies have indicated that, compared to healthy individuals, levels of DHEA and DHEAS are reduced in patients with T2DM [4–6]. Furthermore, low DHEA has been identified as an independent risk factor for T2DM [5]. In addition, current research findings regarding the connection between DHEA and DHEAS and BMD are inconsistent. Several studies have reported a positive relation between DHEA and DHEAS levels and BMD [7–9], whereas others have found no correlation [10–12]. Importantly, the majority of the preceding research was conducted on the general population.

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To date, in individuals with T2DM, there are few available data illustrating the correlation between serum DHEA and DHEAS levels and the likelihood of osteoporosis. Only one study involving 196 Japanese postmenopausal women found a positive association between DHEAS and BMD in postmenopausal women with T2DM, but BMD was examined using quantitative ultrasound (QUS) rather than dual-energy X-ray absorptiometry (DXA) [13]. BMD assessed by DXA remains an important criterion for osteoporosis [14]. Furthermore, sex differences in the association between DHEA (S) levels and BMD have not been examined in patients with T2DM.

Therefore, the purpose of this study was to explore the association between serum DHEA(S) levels and DXA-derived BMD in various body regions as well as osteopenia and/or osteoporosis (defined by T scores) in a large population-based cohort of T2DM patients in China.

Materials and Methods

Study population

This cross-sectional study enrolled 2107 hospitalized patients with T2DM between October 12, 2020, and June 30, 2022, at the Department of Endocrinology and Metabolism, Tianjin Medical University General Hospital in China. Patients were excluded when they met the following criteria: deduplication for repeated hospitalization, age less than 18, pregnancy, lack of DXA data, history of primary hyperparathyroidism, FHH, Cushing syndrome, or use of drugs that affect bone metabolism, such as taking osteoporosis medications (e.g., bisphosphonate, calcitonin, denosumab, selective estrogen receptor modulators), glucocorticoids, thiazides, estradiol, testosterone. In addition, men under the age of 50 and premenopausal women were excluded. Finally, as depicted in Fig. 1, 938 patients with T2DM were enrolled, including 485 postmenopausal women and 455 men over the age of 50.

Serum steroid hormone measurements

Patients' fasting blood samples were gathered in the morning and stored at − 80 °C until analysis. Serum DHEA, DHEAS, testosterone (T), and cortisol concentrations were quantified using liquid chromatography tandem mass spectrometry (LCMS/MS) (Jasper™ HPLC system coupled to an AB SCIEX Triple Quad™ 4500MD mass spectrometer). The data were quantified by MultiQuant™ MD 3.0.2 software. In each set of samples, there were calibration standards and quality control samples. The calibration standards were utilized to construct standard curves through linear regression with $1/x^2$ weighting, resulting in correlation coefficients exceeding 0.99. The quality control samples were employed to assess the accuracy of the standard curves. Serum estradiol (E2) concentration was measured using chemiluminescence-based immunoassays (ARCHIRECT i2000 system, Abbott Laboratories, Abbott Park, USA).

Covariates

Potential confounding variables were gathered from the medical record system of the General Hospital of Tianjin Medical University as follows: sex, age, height, weight, current smoking and drinking, duration of T2DM, history of hypertension, history of dyslipidemia, hypoglycemic drugs including sulfonylureas, metformin, thiazolidinediones, α-glucosidase inhibitors, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, glinides, and insulin. Biochemical measurements included total cholesterol level (TC), triglyceride level (TG), high-density lipoprotein level (HDL), low-density lipoprotein level (LDL), plasma creatinine, serum phosphorus, serum calcium, parathyroid hormone (PTH), serum uric acid, fasting blood glucose level (FBG), glycosylated hemoglobin (HbA1c) and adrenocorticotropic hormone (ACTH).

Definitions

The diagnostic criteria for diabetes were fasting blood glucose and 2-h blood glucose, HbA1c l levels of 7.0 mmol/L, 11.1 mmol/L, and 6.5% or higher, respectively, a reported diabetes history, or usage of hypoglycemic medications [15]. Hypertension was defined as SBP, DBP greater than or equal to 140 or 90 mmHg, a self-reported history of hypertension, or the use of antihypertensive drugs [16]. The diagnostic criteria for dyslipidemia were TC, TG, LDL cholesterol greater than or equal to 6.2, 2.3, and 4.1 mmol/L, respectively; HDL cholesterol less than 1.0 mmol/L, or the use of lipid-lowering drugs [17]. Body mass index (BMI) was calculated by dividing weight (in kilograms) by the square of height (in meters). The estimated glomerular filtration rate (eGFR) was computed using the Chronic Kidney Disease Epidemiology Collaboration equation [18].

Menopause is defined retrospectively as the cessation of spontaneous menses for 12 months [19].

Bone mineral density measurements

BMD of the femur neck, total hip, and lumbar spine (L1-4) in grams/cm^2 were measured by dual-energy X-ray absorptiometry (DXA) using a Prodigy-GE densitometer (GE Healthcare, Chicago, IL, USA). According to T scores, converted from BMD values for each skeletal site individually, all the participants were classified by three groups:

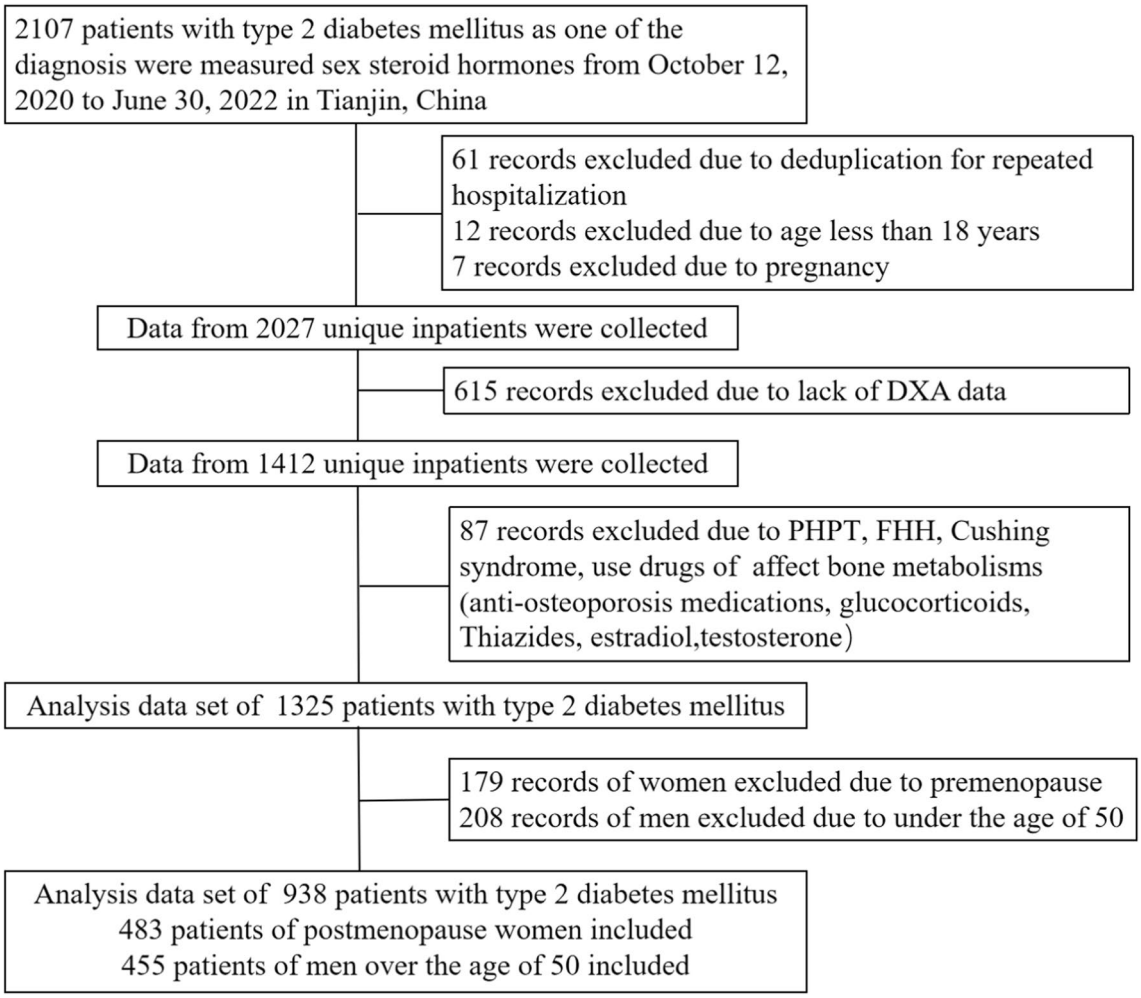

Fig. 1 Flow chart of the study population identification. There were 938 patients with type 2 diabetes mellitus (483 postmenopausal women and 455 men over the age of 50) involved in the final analysis. DXA Dual-energy X-ray absorptiometry; PHPT primary hyperparathyroidism; FHH Familial hypocalciuric hypercalcemia

normal bone mass (T score ≥ -1.0), osteopenia (T score from > -2.5 to < -1.0) and osteoporosis (T score ≤ -2.5) at any three sites: the femoral neck, total hip, and lumbar spine BMD (L1-4) for analyses.

Statistical analyses

Baseline participant characteristics were presented using the mean ± standard deviation (SD) in normal distribution or median with interquartile in skewed distribution for continuous variables. Counts and percentages for categorical variables. Analysis of variance (ANOVA) or the Kruskal–Wallis test was used as appropriate to compare patients across different BMD levels and categorical variables were tested by chi-squared tests or Fisher's exact test. Linear regression models were utilized to examine the relation between log-transformed DHEA and DHEAS and BMD in various region. The results were expressed in standardized β and SE. Multinominal logistic regression models were used to evaluate the risks of osteopenia and/or osteoporosis associated with serum DHEA and DHEAS levels. At the same time, DHEA and DHEAS levels were expressed per 1 SD increase. The results are presented as adjusted means and 95% CIs, and $P < 0.05$ is the statistical significance threshold. A restricted cubic spline approach was used for the assessment of the dose−response correlation of log-transformed DHEA and DHEAS concentrations with the risk of osteopenia and/or osteoporosis after adjusting for confounding factors. At the 10th, 50th, and 90th percentiles, the knots were located. SPSS for Windows (version 25.0, Chicago, IL, USA) and R software (version 4.3.0, R Foundation) were utilized for all analyses.

Results

Characteristics of the study participants

In Table 1, the baseline characteristics of the cohort of 483 postmenopausal women and 455 men over the age of 50 with T2DM were compared among three groups (normal bone mass, osteopenia and osteoporosis). As expected, there were significant differences in BMD and T score for the femur neck, total hip, and lumbar spine among three groups in both sexes. We observed a trend of increase in age and a corresponding decrease in BMI across different groups (from normal bone mass to osteoporosis) in both sexes. In addition, duration of T2DM, PTH, HbA1c, serum phosphorus, serum uric acid and using the drug of metformin were significantly different among three groups in postmenopausal women. For men, current smoking, serum uric acid and dyslipidemia showed significant differences among three groups (Table 1).

In postmenopausal women, both the DHEA and DHEAS levels were significantly lower in the osteopenia and osteoporosis groups compared to the normal bone mass group (P value < 0.05). Furthermore, the DHEAS level in the osteoporosis group was notably lower than that in the osteopenia group (P value < 0.05). In terms of E2 level, there was no discernible difference between groups (all postmenopausal women with suppressed E2). However, the opposite result was shown in men; that is, the E2 levels of osteopenia and osteoporosis groups were lower than that of normal bone mass group, with a statistically significant difference observed between the osteopenia group and the normal bone mass group (Table 1).

DHEA and DHEAS levels were associated with BMD at different skeletal sites in postmenopausal women with T2DM

The multivariable linear regression models assessing the association between log-transformed DHEA and DHEAS and BMD at different skeletal sites in postmenopausal women with T2DM were presented in Table 2. In fully adjusted models, a significant positive correlation was observed between serum DHEA concentration and lumbar spine BMD (stdβ = 0.165; SE = 0.054; p = 0.013). Furthermore, serum DHEAS concentration exhibited a remarkable positive relation with BMD at various skeletal sites, including femoral neck BMD (stdβ = 0.141; SE = 0.025; p = 0.015), total hip BMD (stdβ = 0.171; SE = 0.027, p = 0.002), and lumbar spine BMD (stdβ = 0.219; SE = 0.037, p < 0.001). Correspondingly, there was on average 0.141 g/cm^2 higher femoral neck BMD, and 0.171 g/cm^2 higher hip BMD, 0.219 g/cm^2 higher lumbar spine BMD for every standard deviation higher serum DHEAS concentration.

However, in men over the age of 50 with T2DM, there was no significant association observed between DHEA and DHEAS levels and BMD at different skeletal sites (Table 3).

Low DHEA and DHEAS levels were associated with increased risks of osteopenia and/or osteoporosis in postmenopausal women with T2DM

Multinominal logistic regression analyses, adjusted for confounding factors, revealed that low levels of DHEA and DHEAS were significantly associated with increased risks of osteopenia and osteoporosis in postmenopausal women with T2DM (Fig. 2). In women, with per SD increase in DHEA, the risks of osteopenia and osteoporosis were significantly reduced. However, compared to the osteopenia group, the risk of osteoporosis was not significantly reduced (Fig. 2). In addition, with per SD increase in DHEAS, the risk of osteoporosis was significantly reduced compared to the other two groups. However, the risk of osteopenia was not significantly reduced compared to the normal bone mass group (Fig. 2).

We further combined osteopenia group and osteoporosis group into a low bone mass group and analyzed the risk of low bone mass associated with DHEA and DHEAS. The restricted cubic spline (RCS) analysis depicted the dose–response relation between DHEA and DHEAS and the risks of osteopenia and/or osteoporosis in postmenopausal women with T2DM (Fig. 3). Following adjustments for various confounding factors, including testosterone and estradiol, Fig. 3 illustrates that the risk of osteopenia/osteoporosis gradually decreased with increasing DHEA levels (P overall = 0.007, P-nonlinear = 0.256) and DHEAS levels (P overall = 0.028, P-nonlinear = 0.067), and the risk of osteoporosis gradually decreased with increasing DHEAS levels (P overall = 0.018, P-nonlinear = 0.559). Additionally, similar findings were observed regarding the association between the tertiles of DHEA and DHEAS and the risk of osteopenia/osteoporosis (Supplementary Table 1).

In men, however, low DHEA and DHEAS levels were not associated with increased risks of osteopenia and/or osteoporosis (Fig.2**,** Supplementary Table 2).

Discussion

In this retrospective cohort study of T2DM, we found that the effects of DHEA and DHEAS on BMD varied by sex. To the best of our knowledge, this is the first study to investigate the associations between DHEA, DHEAS and BMD in individuals with T2DM stratified by sex. Our findings revealed a

Table 1 Baseline characteristics of the study population of postmenopausal women and men over the age of 50 with T2DM

Variables	Women (N = 483)			P value	Men (N = 455)			P value
	Nomal bone mass	Osteopenia	Osteoporosis		Nomal bone mass	Osteopenia	Osteoporosis	
Participants, n%	182(37.70)	229(47.40)	72(14.90)		324(71.21)	120(26.37)	11(2.42)	
Age, years	62.30 ± 7.80	66.18 ± 6.85	68.33 ± 7.22	**< 0.001**[a,b]	62.30 ± 7.53	65.12 ± 7.51	68.1 ± 8.32	**< 0.001**[a,b]
BMI, kg/m^2	26.88 ± 4.07	25.35 ± 3.72	24.09 ± 3.54	**< 0.001**[a,b,c]	26.39 ± 3.49	25.44 ± 3.73	22.67 ± 2.56	**< 0.001**[a,b,c]
Current smoking, n%	8(4.4)	13(5.7)	24(5.0)	0.785	142(43.8)	67(55.8)	2(18.2)	**0.016**[c]
Current drinking, n%	4(2.2)	6(2.6)	0(0.0)	0.613	150(46.3)	55(45.8)	3(27.3)	0.450
Duration of type 2 diabetes, year	10.00(14.00)	12.00(15.00)	11.00(12.00)	**0.018**[a]	10.00(14.25)	10.00(16.00)	10.00(10.00)	0.287
FBG, mmol/L	7.54 ± 2.86	7.18 ± 2.57	6.94 ± 2.38	0.211	7.30 ± 2.52	7.68 ± 3.10	6.67 ± 2.15	0.285
HbA1c, %	8.30(3.00)	8.10(2.50)	7.70(2.30)	**0.028**[b]	8.20(2.80)	8.45(3.28)	7.10(2.90)	0.161
PTH, pmol/L	3.02(1.83)	3.24(2.69)	3.95(3.08)	**< 0.001**[a,b,c]	3.03(2.80)	3.53(2.70)	3.75(3.15)	0.906
ACTH, pg/ml	29.05(24.85)	28.15(24.25)	27.10(24.70)	**0.862**	35.00(25.10)	34.35(26.32)	34.20(20.10)	0.927
Serum phosphorus, mmol/L	1.20 ± 0.16	1.17 ± 0.18	1.12 ± 0.20	**0.005**[b,c]	1.09 ± 0.17	1.08 ± 0.17	1.07 ± 0.17	0.780
Serum calcium, mmol/L	2.30 ± 0.11	2.31 ± 0.11	2.27 ± 0.13	0.124	2.27 ± 0.11	2.27 ± 0.09	2.27 ± 0.10	0.990
Serum uric acid, umol/L	326.54 ± 92.13	307.33 ± 100.89	276.81 ± 69.57	**0.001**[b]	351.93 ± 139.24	320.79 ± 86.35	309.73 ± 78.84	**0.049**[a]
Serum steroids								
DHEA, nmol/L	8.73(6.79)	6.64(5.81)	6.33(6.63)	**0.006**[a,b]	7.23(5.27)	6.88(4.93)	6.41(10.81)	0.439
DHEAS, umol/L	2.29(1.51)	1.82(1.83)	1.37(1.06)	**< 0.001**[a,b]	3.49(2.92)	3.15(2.66)	2.33(2.52)	0.064
Estradiol, pg/mL	10.00(3.00)	10.00(1.00)	10.00(1.00)	0.490	25.10(13.00)	23.00(11.75)	22.00(17.00)	**0.021**[a]
Testosterone, ng/dL	137.38(107.74)	120.82(103.16)	127.5(116.69)	0.123	3602.88(1928.48)	3559.38(1994.49)	3675.63(1966.43)	0.784
Cortisol, pg/ml($^a10^5$)	1.45 ± 0.45	1.39 ± 0.47	1.43 ± 0.57	0.422	1.34 ± 0.48	1.36 ± 0.45	1.46 ± 0.31	0.652
eGFR, mL/(min^{a}1.73 m^2)	98.21(17.44)	98.39(16.76)	98.32(14.06)	0.905	104.15(21.77)	102.44(23.14)	98.25(12.15)	0.927
Hypertension, n%	130(71.4)	161(70.3)	44(61.1)	0.251	219(67.6)	82(68.3)	4(36.4)	0.090
Dyslipidemia, n%	116(63.7)	144(62.9)	34(47.2)	**0.036**[b]	185(57.1)	62(51.7)	2(18.2)	**0.028**[b]
hypoglycemic drugs%	143(78.6)	183(79.9)	56(77.8)	0.899	237(73.1)	95(79.2)	9(81.8)	0.368
Sulfonylureas, n%	28(15.4)	46(20.1)	7(9.7)	0.107	48(14.8)	19(15.8)	1(9.1)	0.815
Metformin, n%	85(46.7)	95(41.5)	19(26.4)	**0.017**[b]	132(40.7)	47(39.2)	2(18.2)	0.290
Thiazolidinediones, n%	7(3.8)	7(3.1)	0(0.0)	0.261	7(2.2)	2(1.7)	0(0.0)	0.842
α-Glucosidase inhibitors, n%	75(41.2)	93(40.6)	35(48.6)	0.374	125(38.6)	50(41.7)	4(36.4)	0.806
DPP-4 inhibitors, n%	26(14.3)	43(18.8)	12(16.7)	0.465	36(11.1)	19(15.8)	0(0.0)	0.179
GLP-1 receptor agonists, n%	13(7.1)	9(3.9)	4(5.6)	0.363	20(6.2)	3(2.5)	1(9.1)	0.264
SGLT-2 inhibitors, n%	17(9.3)	23(10.0)	5(6.9)	0.756	49(15.1)	12(10.0)	2(18.2)	0.353
Insulin, n%	73(40.1)	97(42.4)	24(33.3)	0.451	121(37.3)	49(40.8)	4(36.4)	0.779
Glinides, n%	13(7.1)	19(8.3)	7(9.7)	0.751	26(8.0)	10(8.3)	1(9.1)	0.990
Femur neck BMD	0.92 ± 0.09	0.76 ± 0.06	0.64 ± 0.08	**< 0.001**[a,b,c]	1.00 ± 0.10	0.79 ± 0.06	0.60 ± 0.21	**< 0.001**[a,b,c]
Total hip BMD	0.99 ± 0.10	0.82 ± 0.07	0.68 ± 0.09	**< 0.001**[a,b,c]	1.07 ± 0.11	0.85 ± 0.07	0.65 ± 0.10	**< 0.001**[a,b,c]
Lumbar spine BMD(L1-4)	1.22 ± 0.15	1.01 ± 0.12	0.85 ± 0.11	**< 0.001**[a,b,c]	1.32 ± 0.19	1.09 ± 0.15	0.97 ± 0.25	**< 0.001**[a,b,c]

Table 1 (continued)

Variables	Women (N = 483)			P value	Men (N = 455)			P value
	Nomal bone mass	Osteopenia	Osteoporosis		Nomal bone mass	Osteopenia	Osteoporosis	
Femur neck T score	− 0.05 ± 0.76	− 1.44 ± 0.47	− 2.39 ± 0.67	**< 0.001**[a,b,c]	0.17 ± 0.81	− 1.45 ± 0.43	− 2.44 ± 0.55	**< 0.001**[a,b,c]
Total hip T score	0.15 ± 0.78	− 1.18 ± 0.51	− 2.30 ± 0.64	**< 0.001**[a,b,c]	0.63 ± 0.88	− 1.05 ± 0.5	− 2.65 ± 0.74	**< 0.001**[a,b,c]
Lumbar spine T score (L1-4)	0.85 ± 1.26	− 0.83 ± 1.00	− 2.23 ± 0.90	**< 0.001**[a,b,c]	1.95 ± 1.59	0.05 ± 1.23	− 0.90 ± 2.08	**< 0.001**[a,b,c]

BMI body mass index; *FBG* fasting blood glucose; *HbA1c* glycosylated hemoglobin; *PTH* parathyroid hormone; *ACTH* adrenocorticotropic hormone; *DHEA* dehydroepiandrosterone; *DHEAS DHEA* sulfate; *eGFR* estimated glomerular filtration rate; *DPP-4* dipeptidyl peptidase-4; *GLP-1* glucagon-like peptide-1; *SGLT-2*, sodium-glucose cotransporter-2

Bold results are statistically significant

[a]The difference between normal bone mass group and osteopenia group was statistically significant

[b]The difference between normal bone mass group and osteoporosis group was statistically significant

[c]The difference between osteopenia group and osteoporosis group was statistically significant

positive correlation between DHEA and DHEAS levels, as measured using LCMS/MS, and BMD assessed via DXA. In particular, we observed a robust correlation between DHEAS and BMD at various skeletal sites, including the femoral neck, total hip, and lumbar spine, in postmenopausal women with T2DM. However, it is noteworthy that this positive association was not statistically significant among men over the age of 50 with T2DM. Therefore, DHEA and DHEAS can serve as a predictive indicator for osteopenia/osteoporosis in postmenopausal women with T2DM.

Previous studies have provided insights into the potential mechanisms by which DHEA can impact bone health. Vitro experiments have demonstrated that DHEA may inhibit osteoclast activity by promoting the viability of osteoblasts and inducing the production of osteoprotegerin through the ERK1/2 signaling pathway [20]. Furthermore, DHEA has been found to regulate osteoblast differentiation by upregulating the expression of genes associated with osteoblast function and increasing the presence of Foxp3$^+$ Tregs [21]. Animal studies have indicated that DHEA might protect against bone loss in ovariectomized mice by inhibiting the production of CD4$^+$ T cells and tumor necrosis factor TNF-α, with its effect on bone preservation being independent of estrogen levels [22].

Existing evidence regarding the relation between DHEA, DHEAS and BMD in postmenopausal women has been inconsistent and conflicting. Some previous studies have reported no significant correlation between DHEA, DHEAS and BMD in postmenopausal women [10–12, 23]. Conversely, a substantial body of research has shown a positive

Table 2 Multiple regression analysis to determine the independent association between serum DHEA(S) and BMD at various skeletal sites in postmenopausal women with T2DM

	Femur neck BMD			Total hip BMD			Lumbar spine BMD(L1-4)		
	stdβ	SE	P value	stdβ	SE	P value	stdβ	SE	P value
DHEA									
Model 1	0.032	0.021	0.455	0.047	0.023	0.273	0.075	0.032	0.096
Model 2	0.094	0.029	0.079	0.099	0.031	0.056	0.150	0.045	**0.007**
Model 3	0.121	0.036	0.059	0.120	0.038	0.057	0.165	0.054	**0.013**
DHEAS									
Model 1	0.108	0.018	**0.012**	0.131	0.019	**0.002**	0.182	0.026	**< 0.001**
Model 2	0.142	0.024	**0.009**	0.168	0.025	**0.001**	0.226	0.036	**< 0.001**
Model 3	0.141	0.025	**0.015**	0.171	0.027	**0.002**	0.219	0.037	**< 0.001**

DHEA (nmol/L) and DHEAS (μmol/L) were log-transformed

Model 1: Adjusted for age + BMI

Model 2: Model 1 + duration of type 2 diabetes + HbA1c + FBG + metformin + hypertension + dyslipidemia + eGFR + serum uric acid + serum calcium + serum phosphorus + PTH

Model 3: Model 2 + cortisol + testosterone + estradiol + ACTH

BMI body mass index; *HbA1c* glycosylated hemoglobin; *FBG* fasting blood glucose; *eGFR* estimated glomerular filtration rate; *DHEA* dehydroepiandrosterone; *DHEAS* dehydroepiandrosterone sulfate; *PTH* parathyroid hormone; *ACTH*, adrenocorticotropic hormone

Bold results are statistically significant

Table 3 Multiple regression analysis to determine the independent association between serum DHEA(S) and BMD at various skeletal sites in men over the age of 50 with T2DM

	Femur neck BMD			Total hip BMD			Lumbar spine BMD(L1-4)		
	stdβ	SE	P value	stdβ	SE	P value	stdβ	SE	P value
DHEA									
Model 1	−0.081	0.029	0.091	−0.082	0.030	0.084	−0.140	0.042	**0.003**
Model 2	−0.033	0.041	0.609	−0.042	0.044	0.514	−0.086	0.059	0.175
Model 3	−0.017	0.052	0.824	0.001	0.054	0.998	−0.084	0.073	0.279
DHEAS									
Model 1	0.032	0.021	0.495	0.053	0.022	0.260	0.013	0.031	0.787
Model 2	0.076	0.028	0.230	0.090	0.030	0.155	−0.013	0.041	0.831
Model 3	0.052	0.032	0.460	0.075	0.034	0.292	−0.065	0.045	0.350

DHEA (nmol/L) and DHEAS (μmol/L) were log-transformed

Model 1: Adjusted for age + BMI + current smoking

Model 2: Model 1 + duration of type 2 diabetes + HbA1c + FBG + hypertension + dyslipidemia + eGFR + serum uric acid + serum calcium + serum phosphorus + PTH

Model 3: Model 2 + cortisol + testosterone + estradiol + ACTH

BMI body mass index; *HbA1c* glycosylated hemoglobin; *FBG* fasting blood glucose; *eGFR* estimated glomerular filtration rate; *DHEA* dehydroepiandrosterone; *DHEAS* dehydroepiandrosterone sulfate; *PTH* parathyroid hormone; *ACTH* adrenocorticotropic hormone

Bold results are statistically significant

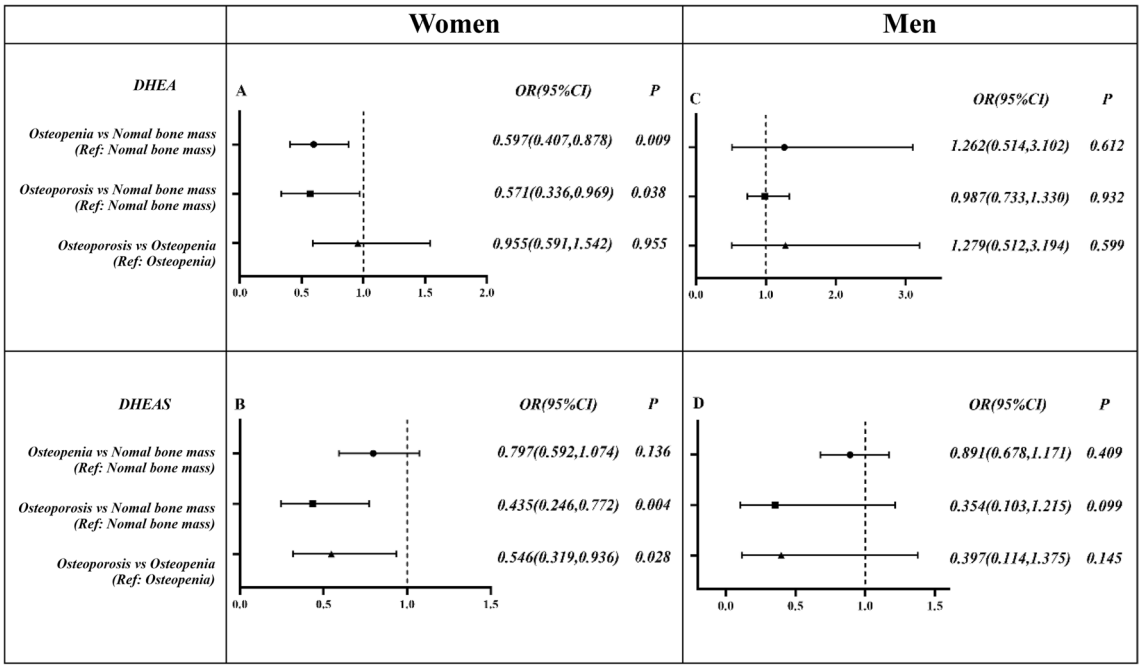

Fig. 2 Multinominal logistic regression analysis of DHEA, DHEAS associated with osteopenia/osteoporosis in both sexes. Multinominal logistic regression analysis of DHEA(**A**), DHEAS(**B**) associated with osteopenia/osteoporosis in women and DHEA(**C**), DHEAS(**D**) in men. Dependent variables included normal bone mass, osteopenia and osteoporosis. Independent variables included age, BMI, current smoking, duration of T2DM, HbA1c, FBG, metformin, hypertension, dyslipidemia, eGFR, serum uric acid, serum calcium, serum phosphorus, cortisol, testosterone, estradiol, ACTH and PTH

association between DHEA, DHEAS and BMD in postmenopausal women [7–9, 13, 24–26]. Clinical trials have also indicated that DHEA supplementation has a moderately positive impact on BMD in postmenopausal women [27–32]. Furthermore, a mendelian study revealed a strong association between DHEAS and lumbar BMD, although not femoral neck BMD [26]. In addition, a randomized clinical trial found that 12 months of DHEA treatment increased lumbar

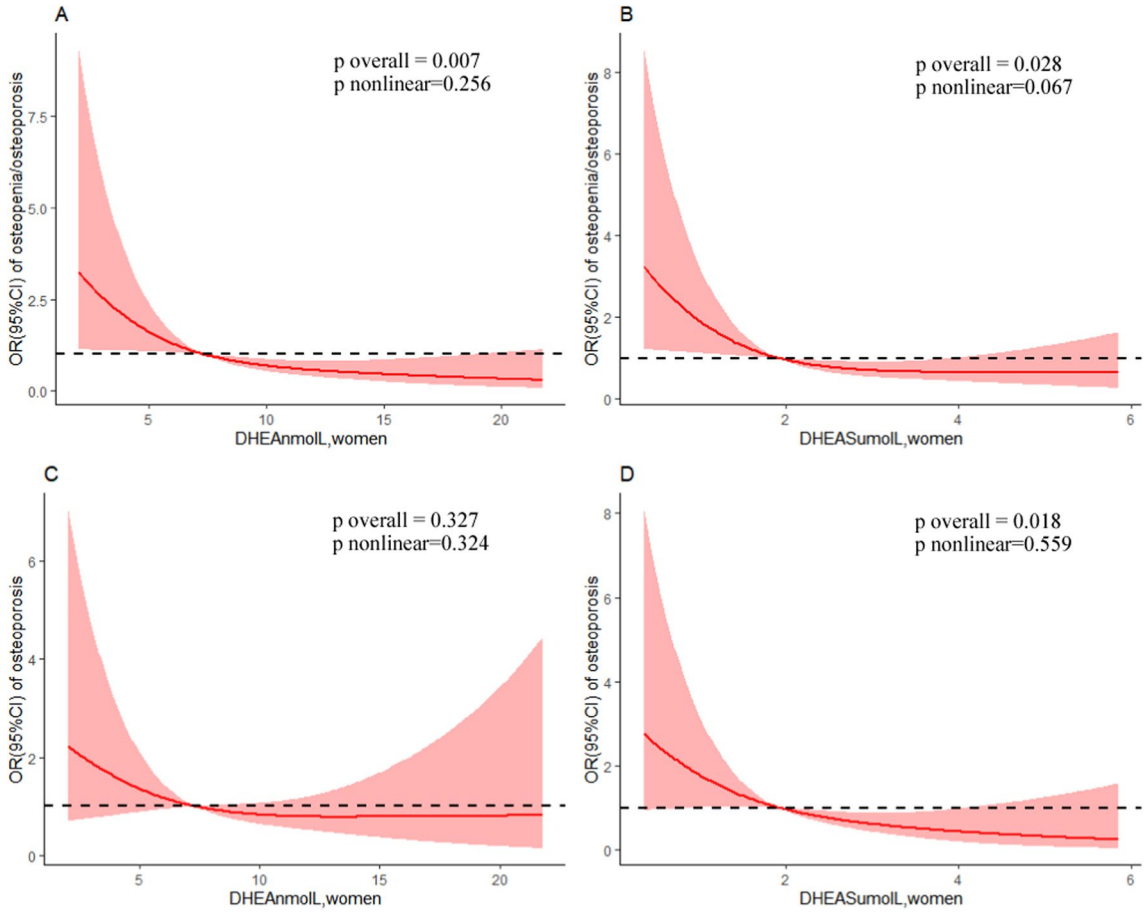

Fig. 3 The overall dose−response association of DHEA and DHEAS with osteopenia and/or osteoporosis shown by the restricted cubic spline (RCS). The line indicates the adjusted OR, and the 95% CI is shown by shaded portions. The overall dose−response association of DHEA(**A**) and DHEAS(**B**) with osteopenia/osteoporosis in postmenopausal women with T2DM. The overall dose−response association of DHEA(**C**) and DHEAS(**D**) with osteoporosis in postmenopausal women with T2DM. Adjusted for adjusted age, BMI, duration of T2DM, HbA1c, FBG, metformin, hypertension, dyslipidemia, eGFR, serum uric acid, serum calcium, serum phosphorus, cortisol, testosterone, estradiol, ACTH and PTH

BMD but had no significant effect on femoral neck BMD [33]. It is essential to note, however, that the aforementioned studies were conducted on the general population, and DHEA and DHEAS measurements were not consistently performed using mass spectrometry.

In the findings of this study within the T2DM cohort revealed a positive correlation between DHEA and DHEAS levels and BMD in postmenopausal women. Even after adjusting for various confounding factors, DHEA remained significantly positively correlated with lumbar BMD, and DHEAS exhibited positive correlations with BMD at different sites: femoral neck, total hip, and lumbar spine. As such, it was hypothesized that DHEA may exert a more pronounced influence on lumbar spine BMD, primarily composed of trabecular bone, as opposed to femoral neck BMD, which mainly consists of cortical bone. However, DHEAS may exert influence on both trabecular and cortical bone in postmenopausal women with T2DM.

DHEA and DHEAS are the main sources of androgens and estrogens in postmenopausal women [13]. DHEAS, the sulfated form of DHEA, has a longer half-life of about 10–20 h compared to DHEA, which has a half-life of approximately 1–3 h [34]. And in female, DHEAS concentration is about 250 times higher than that of DHEA, while in male, it is approximately 500 times higher [34]. This may explain the significance of DHEAS as a reservoir for DHEA and its implications for BMD abnormalities. Low level of DHEAS, the storage form of DHEA, may better reflect the decline in BMD and the risk of osteoporosis. Therefore, supplementation of adrenal-derived hormones (DHEA and DHEAS) becomes crucial, especially in postmenopausal women with T2DM experiencing estrogen deficiency.

Previous research regarding the impact of DHEA and DHEAS levels on BMD in men has yielded inconsistent results. Some studies have shown that DHEA and DHEAS is positively correlated with BMD in men [23, 35, 36]. A

cohort study involving 2,568 older men in Sweden discovered that serum DHEAS levels were inversely associated with the risk of accidental fractures and suggested potential benefits of DHEA treatment for older men with serum DHEAS levels below 0.60 mg/mL [37]. However, the majority of studies have reported no significant correlations [38–40], and DHEA treatment in men did not demonstrate substantial beneficial effects on BMD [28–32, 41]. Nevertheless, the specific relation between DHEA, DHEAS and BMD in men with T2DM remains relatively unexplored. In our study, it was observed that there was no significant correlation between DHEA, DHEAS levels and BMD in men with T2DM. The reason may be that DHEA and DHEAS are the primary sources of estrogen and androgen in postmenopausal women, while they account for only 40% in men [42].

Our comprehensive cross-sectional study provides valuable insights for future strategies addressing osteopenia/osteoporosis in T2DM. Testing DHEA and DHEAS concentrations in the population of T2DM is necessary. Moreover, elevating the levels of DHEA and DHEAS may serve as a therapeutic target for treating osteoporosis in postmenopausal women with T2DM. Adequate supplementation of DHEA could be beneficial for maintaining BMD in postmenopausal women with T2DM. what is more, it has been suggested that DHEA therapy may be safer than estrogen or testosterone therapy. Because of DHEA and DHEAS, as precursors of estrogen and testosterone, could exert their effects in a tissue-specific manner [43]. The doses of DHEA were 50 to 75 mg/day in some Clinical Trials [33], which can increase levels of DHEAS and BMD. Is there a similar effect of these doses of DHEA on BMD in postmenopausal women with T2DM? Moreover, whether supplementing estrogen and adrenal-derived hormones (DHEA and DHEAS) together is necessary for postmenopausal women with T2DM and osteoporosis warrants further investigation.

There are some limitations in this study. First, the causal relation between DHEA(S) levels and BMD cannot be established due to the retrospective nature of the study, so future prospective cohort studies are still needed to elucidate the relation. Second, the study was conducted within a single center and focused on the Chinese population and we didn't perform fracture assessment, necessitating further verification in diverse ethnic groups and across multiple centers to enhance its generalizability. Third, we adjusted for a sufficient number of variables, but we still cannot exclude the possibility of residual confounding factors, such as sclerostin, bone formation marker, AGEs, sex hormone-binding globulin and insulin-like growth factor 1. Last but not least, we did not account for participants' levels of physical activity and aerobic exercise in our analysis. Consequently, additional research involving larger and more diverse populations is warranted to further validate our findings in the future.

In conclusion, our study provides evidence that elevated levels of DHEA and DHEAS are associated with increased BMD and a reduced risk of osteoporosis/osteopenia in postmenopausal women with T2DM, independent of estradiol and testosterone levels. As a result, DHEA and DHEAS can serve as a predictive indicator for osteoporosis in postmenopausal women with T2DM and elevating the levels of DHEA and DHEAS may serve as a therapeutic target for treating osteoporosis in postmenopausal women with T2DM. Therefore, adequate supplementation of DHEA could be beneficial for maintaining BMD in postmenopausal women with T2DM, however, further confirmation is needed through prospective trials.

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Author Contributions SL performed the study, did statistical analysis, and wrote the manuscript. WL and LC did statistical analysis, and wrote the manuscript. JW and SC participated in the study data collection. XZ performed the study, did statistical analysis. QH and ML provided funding support, designed the study, and reviewed the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

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Declarations

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This study was approved by the institutional Review Board of Tianjin Medical University General Hospital (approval number: IRB2020-YX-027-01).

Informed consent Due to the extraction of all patient data from the hospital's electronic medical records and the anonymization of participants' identities, the study waived the requirement for informed consent.

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