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Original Research

Association between Testosterone/Estradiol Ratio and Risk of Cardiometabolic Diseases in Women at Menopause Transition Age

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Abstract

Background: Imbalance of testosterone/estradiol ratio are frequently reported to be associated with the risk of cardiometabolic diseases; however, studies have yet to report the testosterone/estradiol ratio and its relationship to cardiometabolic diseases in women at menopause transition. This study aimed to explore the association between testosterone/estradiol ratio with cardiometabolic diseases in women during their menopausal transition age. **Methods**: 551 women aged from 45 to 55 years old were involved in this study. Their baseline information, disease comorbidity, blood biochemical tests, echocardiography and serum sex hormones were collected. Women were categorized by tertile distribution of testosterone/estradiol ratio. We used binary logistic regression model (for odds ratio) and poisson loglinear model (for prevalence ratio) to evaluate the association between testosterone/estradiol ratio with cardiometabolic diseases. **Results**: The mean age of the study population was 48.6 $\pm$ 3.5 years old. Taking testosterone/estradiol ratio $<$3.9 as reference, the odds ratio with 95% confidence interval across the tertile groups for obesity were: 1.0 (reference), 2.32 (0.96–5.64), 4.70 (1.75–12.67) ($p_{for\ trend}$ = 0.002); for hypertension were: 1.0 (reference), 2.37 (1.45–3.86), 2.02 (1.12–3.62) ($p_{for\ trend}$ = 0.013); for cardiometabolic diseases were: 1.0 (reference), 2.29 (1.47–3.56), 2.34 (1.37–3.99) ($p_{for\ trend}$ = 0.013), compared with the prevalence ratio of 1.0 (reference), 1.64 (1.26–2.15), 1.65 (1.21–2.23) ($p_{for\ trend}$ = 0.001), respectively. **Conclusions**: Higher testosterone/estradiol ratio was associated with elevated prevalence of cardiometabolic diseases in women at menopause transition period.

Keywords: cardiometabolic diseases; testosterone/estradiol ratio; menopause transition; aging

1. Introduction

Cardiometabolic diseases (CMD) are the leading causes of death among women globally [1]. In the past decades, series of campaigns and awareness had helped to ease the impact of CMD on women. Despite these efforts, the overall reduction in the burden of CMD on women has been temporary and stagnant over the last 10 years [2].

The cardio-protective role of estradiol (E2) in women has been a well-established fact [3]. On the other hand, the data regarding the association of testosterone (T) and cardiovascular diseases (CVD) are still conflicting where some showed negative [4,5], positive [6,7], while others no association [8,9]. The testosterone to estradiol (T/E2) ratio may play an important role in the rising cardiometabolic risk throughout the menopausal transition period [10]. A higher T/E2 ratio was reported to be associated with increased risk for CVD, coronary artery diseases (CAD), and heart failure (HF) in older postmenopausal women and hyperlipidemia in CAD [11].

Age and menopause status are the key factors affecting sex hormone level. The previous studies, in their efforts to understand CMD association with T/E2 ratio in women [6,12,13], had not considered the effect of age on hormonal level (wider age gap, younger women vs older women). They had included mostly postmenopausal women in favor of premenopausal women [6,13]. In the quest for establishing an association of CMD risk among women at different ages, change in the balance of T/E2 ratio is more reliable, than T or E2 alone [13]. Currently, there are no available studies that discuss the relationship between T/E2 ratio with CMD in women around menopause transition period [13,14]. This period generally presents at the age between 45 and 55 years old, and also have been linked with increased risk of CMD [13,15–17].

Therefore, we designed this study to generate preliminary findings on the association between T/E2 and CMD to support our hypothesis which states that, "the ratio of T/E2 level in women during their menopausal transition period could be a predictive or diagnostic marker for women who are at risk of CMD." [14].

2. Methods

2.1 Study Population

This study involved women from general population, residents of Chongqing city, China aged between 45 to 55 years old who visited the First Affiliated Hospital of Chongqing Medical University from May 2018 to August 2021 for their annual medical examination.

We recruited 1147 women. In order to eliminate potential confounder, 596 women were excluded due to their conditions known to heavily impacted on sex hormones level. The exclusion criteria are listed as follow: (1) inaccurate report of their last menstrual cycle date (n = 72); (2) diagnoses of oligomenorrhea [18] (n = 147); (3) pregnancy or had breastfed within the past two years (n = 6); (4) sudden weight loss in the last 6 months prior registration [19] (n = 24); (5) diagnoses of any malignant tumors [20] (n = 46); (6) pituitary or adrenal gland diseases (n = 59); (7) or polycystic ovary syndrome [21] (n = 35); (8) history of hysterectomy or oophorectomy [22] (n = 56); (9) an experience of psychological trauma or emotional distress within past 4 weeks (n = 24); (10) the use of oral contraceptive (OCT) pills or hormone replacement therapy (HRT) in the last 3 months (n = 127). In total 551 women were retained for the study.

This study was approved by the ethics committee of the First Affiliated Hospital of Chongqing Medical University. All the participants were informed of the study content and signed informed consent.

2.2 Hormonal and Biochemical Assays

We drew the fasting venous blood samples of the studied group in the morning, 1 to 2 hours after awakening, between 8–9 AM, after approximately 12 hours of overnight fasting, with the subject comfortably seated. The blood samples were centrifuged immediately for 15 min at 4 °C, and the platelet-free serum and plasma were stored at 22 °C to get the most accurate results of hormone levels test. We collected samples from premenopausal women with a normal menstrual cycle from day 19 to 21 of their monthly cycles [23].

The total T, E2, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were analyzed in the hospital lab using an electrochemiluminescence (ECL) system automatically (COBAS 8000 Series, E602 modular analyzer, Roche Diagnostics International Ltd, CH-6343 Rotkreuz, Switzerland). All the Biochemical samples like high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and the total serum cholesterol (TC) were determined by an automated enzymatic procedure (Cobas E602, Roche), using serum samples collected after fasting. The fasting blood glucose was similarly measured. Within a week, we analyzed all samples.

2.3 Assessments and Definitions

The transition to menopause is characterized by the onset of vasomotor symptoms such as hot flashes, night sweats, and other common menopausal symptoms like sleep disturbances, depression, and anxiety [24].

Menopausal status was defined as FSH that is above 25 mIU/mL and E2 below 50 pg/mL after permanent cessation of the menses for 12 consecutive months [25]. T/E2 is the ratio of serum T (pg/mL) to serum E2 (pg/mL). Obesity was defined as body mass index (BMI) $\geq$28 (kg/m^2) according to the Chinese criteria [26]. We considered a participant hypertensive if the average systolic blood pressure (SBP) $\geq$140 mmHg and/or diastolic blood pressure (DBP) $\geq$90 mmHg or based on previous medical history with or without antihypertensive drug use. Type 2 diabetes mellitus (T2DM) was diagnosed based on high oral glucose tolerance test (OGTT) values or confirmation of past medical history with or without medications. A participant was considered hyperlipidemic if she met one or a combination of the lipid panel test as follow: TC $>$5.7 mmol/L, TG $>$1.7 mmol/L and LDL-C $>$3.37 mmol/L. Or if she is on any lipid-lowering medications.

HF was diagnosed when there is an increased B-type natriuretic peptide (BNP) or N-terminal (NT)-prohormone B-type natriuretic peptide (NT-proBNP) profile value accompanied by clinical manifestations or signs of HF. CAD was diagnosed when coronary artery stenosis is $>$50%, confirmed by either computed tomography (CT) or angiography, with or without ischemic manifestations. CVD was either HF or CAD. Metabolic syndrome (MetS) was identified using the AACE 2003 criteria [27].

CMD refers to risk factors such as elevated blood glucose, abdominal obesity, hypertension (HTN), MetS, hyperlipidemia, and elevated triglycerides, resulting in an interrelated set of conditions that include obesity, HTN, T2DM and CVD [28].

2.4 Statistical Analysis

Women were grouped based on the tertiles value of T/E2 ratio, continuous variables with normal distribution were expressed as the mean $\pm$ standard deviation (SD), and the differences between groups were compared using Student's T-test (for two groups), or one-way analysis of variance (ANOVA) test (for three groups), if the variance was uniformed; otherwise, the Kruskal-Wallis test was used. Variables with skewed distributions were expressed as the median and interquartile range (25%–75% quartile) and compared using the Wilcoxon signed-rank test (for two groups) or Kruskal-Wallis test (for three groups).

Categorical variables were expressed by a number of cases and percentages, and the differences between groups were compared by the Pearson χ^2 test.

To determine the relationship between T/E2 and the parameters of CMD with its components, we calculated odds ratio (OR) and prevalence ratio (PR) and each with

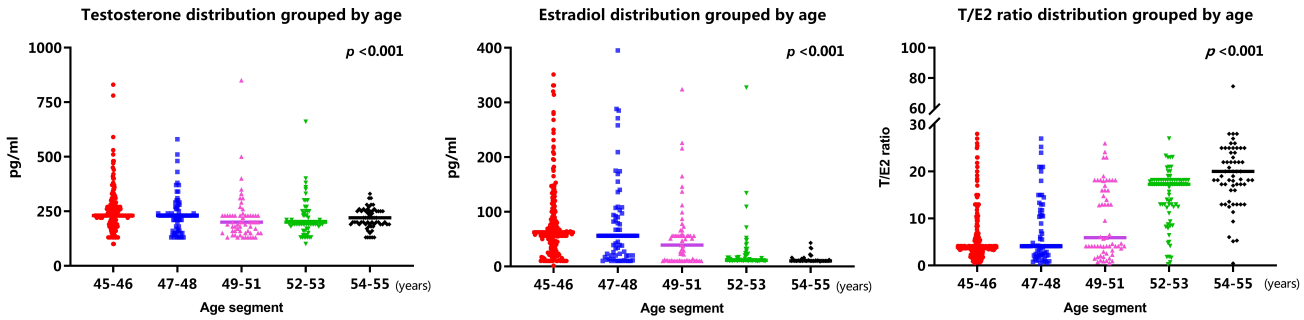

Fig. 1. The distribution of testosterone and estradiol levels, and T/E2 ratio grouped by five age segments.

its 95% confidence interval (CI). Model 1 adjusted for age. Model 2 further adjusted for Han ethnicity, lifestyle variable: married, never smoke and never alcohol; OCT, HRT use. Model 3 further adjusted for number of live births, menopause staus, CAD family history.

We performed the statistical analysis using the SPSS statistical software version 27.0.1 (SPSS Inc., Chicago, IL, USA). We also employed the Graph Pad Prism 9.3.0 (GraphPad Software, Inc., San Diego, CA, USA) for plotting. All the statistical tests were two-tailed, and the significance level was set at $p < 0.05$.

3. Results

3.1 Baseline Characteristics

The baseline characteristics of participants were listed in Table 1. The mean age of the study population was 48.6 $\pm$ 3.5 years. Women with a higher T/E2 ratio value were older, most were in post-menopause, had an older age of menarche and menopause, tend to have higher blood pressure and BMI, a lower level of estimated glomerular filtration rate (eGFR), a thicker interventricular septum (IVS), all $p < 0.05$.

However, women in the three different T/E2 value groups had some similarities such as alcohol consumption, smoking, OCT and HRT, parities and live births, menstruations, CAD family history, heart rate, serum creatinine, fasting glucose and lipid level, heart size and its left ventricular ejection fraction (LVEF).

3.2 Distribution of T, E2 Levels and T/E2 Ratio

The overall distribution of T, E2 and T/E2 ratios were presented in the supplementary materials (see **Supplementary Figs. 1**,**2**). When grouped by age segments, serum T levels had a slight decreasing trend as age increased, while serum E2 levels decreased inversely proportional to age, resulting in T/E2 ratio to be positively correlated with age (Fig. 1).

3.3 T/E2 Ratio and Sex Hormones with CMD

Women with higher level of T/E2 ratio were likely to have obesity, HTN, T2DM, MetS, CVD and CMD all $p < 0.05$ (seen in Table 2).

As displayed in Fig. 2, when grouped by tertiles, after increasing adjustments in binary logistics regressions, women with T/E2 >13.0 were associated with a high risk of obesity, HTN, and CMD (all OR >1, all p and $p_{for\ trend} < 0.05$), however, not associated with T2DM, MetS, or CVD.

In detail, after multivariate analysis, the OR (95% CI) across the tertile groups for obesity were: 1.0 (reference), 2.32 (0.96–5.64), 4.70 (1.75–12.67) ($p_{for\ trend} = 0.002$); for HTN were: 1.0 (reference), 2.37 (1.45–3.86), 2.02 (1.12–3.62) ($p_{for\ trend} = 0.013$); for CMD were: 1.0 (reference), 2.29 (1.47–3.56), 2.34 (1.37–3.99) ($p_{for\ trend} = 0.013$).

In comparison, PR (95% CI) for obesity were: 1.0 (reference), 2.16 (0.93–5.03), 4.01 (1.59–10.11) ($p_{for\ trend} = 0.002$); for HTN were: 1.0 (reference), 1.86 (1.30–2.66), 1.67 (1.10–2.53) ($p_{for\ trend} = 0.010$); for CMD were: 1.0 (reference), 1.64 (1.26–2.15), 1.65 (1.21–2.23) ($p_{for\ trend} = 0.001$) (see **Supplementary Table 1**).

As for hyperlipidemia, multivariate regression analysis indicated that women with T/E2 >13.0 seemed to have a lower risk with OR (95% CI) 0.19 (0.04–0.80) ($p = 0.023$), but none of model 1 or 2 regression significantly revealed this result (all p and $p_{for\ trend} > 0.05$) (see **Supplementary Table 2**).

4. Discussion

This study objective was to evaluate the relationship between T/E2 ratio with cardiometabolic risk of Chinese women at menopause transition age (generally between 45 to 55 years old). Our results revealed that (1) despite the short enrollment age range, both T and E2 level varied differently through age segments, this had resulted to significant differences in T/E2 among age groups; and that (2) women with high T/E2 ratio had a higher prevalence risk of CMD such as obesity and HTN.

4.1 The Association of Sex Hormones with Age

Erratic changes in E2 levels in women happened long before menopause [18]. And when they are near menopause, E2, and progesterone level decrease but FSH increases [29]. Women may be exposed to higher estrogenic activity before the drastic decline, because of early drop-in ovary activity in anticipation of menopause tran-

Table 1. Baseline data grouped by tertiles of T/E2 ratio.

Characteristics	Overall (N = 551)	Tertiles of testosterone to estradiol (T/E2) ratio			*p*
		T1 <3.9	T2 = 3.9–13.0	T3 >13.0	
		n = 183	n = 198	n = 170	
Age, yrs	48.6 ± 3.5	46.5 ± 2.1	48.0 ± 3.0	51.5 ± 3.3	<0.001
Age ≥50 yrs, n%	207 (37.6)	22 (12.0)	56 (28.3)	129 (75.9)	<0.001
Han race, n%	537 (97.5)	179 (97.8)	195 (98.5)	163 (95.9)	0.267
Married, n%	540 (98.0)	180 (98.4)	190 (96.0)	170 (100.0)	0.020
Chongqing natives, n%	469 (85.1)	158 (86.3)	166 (83.8)	145 (85.3)	0.788
Never smoke, n%	521 (94.6)	172 (94.0)	187 (94.4)	162 (95.3)	0.861
Never alcohol, n%	519 (94.2)	171 (93.4)	188 (94.9)	160 (94.1)	0.820
Never OCT, n%	523 (94.9)	171 (93.4)	189 (95.5)	163 (95.9)	0.529
Never HRT, n%	529 (96.0)	176 (96.2)	190 (96.0)	163 (95.9)	0.989
Number of parities	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	3.0 (2.0, 4.0)	0.966
Number of livebirths	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.157
Number of abortions	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	0.852
Age of menarche, yrs	14.0 ± 1.6	13.7 ± 1.3	14.0 ± 1.6	14.1 ± 1.8	0.028
*Days of menstrual period	4.9 ± 1.3	5.0 ± 1.3	4.9 ± 1.4	4.8 ± 1.2	0.218
*Days of menstrual circle	28.1 ± 2.8	28.0 ± 2.8	27.9 ± 3.0	28.5 ± 2.5	0.055
*Irregular menstrual circle, n%	28 (5.1)	15 (8.2)	7 (3.5)	6 (3.5)	0.064
Menopause status, n%	168 (30.5)	14 (7.7)	51 (25.8)	103 (60.6)	<0.001
Age of menopause, yrs	49.0 (46.0, 51.0)	46.0 (45.0, 50.0)	47.0 (45.0, 50.0)	50.0 (47.8, 51.0)	0.001
Months since menopause	36.0 (11.0, 72.0)	6.0 (2.0, 17.3)	36.0 (11.0, 60.0)	36.0 (24.0, 78.0)	<0.001
Menopause ≤1 year, n%	48 (8.7)	11 (6.0)	18 (9.1)	19 (11.2)	<0.001
Menopause >1 year, n%	120 (21.8)	3 (1.6)	33 (16.7)	84 (49.4)	<0.001
Dysmenorrhea, n%	119 (21.6)	48 (26.2)	42 (21.2)	29 (17.1)	0.111
Hypermenorrhea, n%	193 (35.0)	70 (38.3)	63 (31.8)	60 (35.3)	0.420
CAD family history, n%	96 (17.4)	32 (17.5)	31 (15.7)	33 (19.4)	0.638
Heart rate, bpm	85.4 ± 12.4	84.8 ± 10.8	86.5 ± 12.9	84.8 ± 13.3	0.293
SBP, mmHg	125.5 ± 17.4	121.7 ± 15.1	125.7 ± 16.9	129.4 ± 19.4	<0.001
DBP, mmHg	77.5 ± 11.5	74.2 ± 10.5	78.1 ± 11.3	80.3 ± 11.9	<0.001
Weight, kg	58.9 ± 8.0	57.9 ± 6.5	59.5 ± 8.4	59.4 ± 8.7	0.083
Height, cm	157.1 ± 4.9	157.3 ± 4.7	157.1 ± 5.0	157.0 ± 4.9	0.875
BMI, kg/m^2	23.9 ± 3.0	23.4 ± 2.7	24.1 ± 3.1	24.1 ± 3.3	0.045
Hemoglobin, g/L	118.3 ± 12.4	117.5 ± 11.0	117.7 ± 13.1	119.9 ± 13.0	0.150
Albumin, g/L	40.3 ± 5.2	40.1 ± 5.0	40.4 ± 5.2	40.3 ± 5.4	0.862
Serum creatinine, mmol/L	59.1 ± 15.8	58.2 ± 14.4	59.0 ± 17.9	60.1 ± 14.6	0.531
Serum calcium, mmol/L	2.3 ± 0.2	2.3 ± 0.1	2.3 ± 0.2	2.3 ± 0.2	0.007
eGFR, mL/(min × 1.73 cm^2)	105.2 ± 13.7	108.6 ± 10.3	106.2 ± 14.5	100.5 ± 14.7	<0.001
Total cholesterol, mmol/L	4.5 ± 1.1	4.3 ± 0.8	4.6 ± 1.4	4.6 ± 0.9	0.359
Triglyceride, mmol/L	1.1 (0.9, 1.7)	1.1 (0.8, 1.9)	1.2 (1.0, 1.6)	1.2 (0.9, 1.9)	0.766
LDL-C, mmol/L	2.8 ± 0.8	2.6 ± 0.8	2.9 ± 0.7	2.9 ± 0.9	0.118
HDL-C, mmol/L	1.4 ± 0.5	1.4 ± 0.3	1.4 ± 0.3	1.3 ± 0.7	0.991
HDL-C/LDL-C	0.5 ± 0.3	0.6 ± 0.2	0.5 ± 0.2	0.5 ± 0.6	0.659
Fasting glucose, mmol/L	5.4 ± 1.2	5.3 ± 1.0	5.4 ± 1.2	5.6 ± 1.4	0.074
LVDD, mm	45.9 ± 3.8	45.9 ± 4.0	46.0 ± 3.2	45.8 ± 4.1	0.898
RV, mm	18.4 ± 1.9	18.3 ± 1.6	18.2 ± 1.2	18.5 ± 2.7	0.646
IVS, mm	9.6 ± 0.9	9.4 ± 1.0	9.5 ± 0.7	9.9 ± 1.0	<0.001
LVEF, %	67.4 ± 3.9	67.7 ± 4.7	67.4 ± 3.2	67.1 ± 3.8	0.598

*Postmenopausal women data from previous periods.

OCT, oral contraceptive therapy; HRT, hormone replacement therapy; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; LVDD, left ventricular diastolic diameter; RV, Right ventricle size; IVS, interventricular septum; LVEF, left ventricular ejection fraction.

Table 2. Comorbidity grouped by tertiles of T/E2 ratio in women.

Diseases	Overall (N = 551)	Tertiles of T/E2 ratio			*p*
		T/E2 <3.9	T/E2 = 3.9–13.0	T/E2 >13.0	
		n = 183	n = 198	n = 170	
Obesity	48 (8.7%)	8 (4.4%)	18 (9.1%)	22 (12.9%)	0.017
Hypertension	164 (29.8%)	35 (19.1%)	70 (35.4%)	59 (34.7%)	0.001
T2DM	44 (8.0%)	8 (4.4%)	16 (8.1%)	20 (11.8%)	0.038
Hyperlipidemia	21 (3.8%)	9 (4.9%)	6 (3.0%)	6 (3.0%)	0.613
MetS	74 (13.4%)	18 (9.8%)	24 (12.1%)	32 (18.8%)	0.037
CVD	53 (9.6%)	11 (6.0%)	14 (7.1%)	28 (16.5%)	0.001
CAD	48 (8.7%)	10 (5.5%)	13 (6.6%)	25 (14.7%)	0.004
HF	6 (1.1%)	1 (0.5%)	1 (0.5%)	4 (2.4%)	0.161
CMD	246 (44.6%)	54 (29.5%)	99 (50.0%)	93 (54.7%)	<0.001

T2DM, type 2 diabetes mellitus; T/E2 ratio, testosterone/estradiol ratio; MetS, metabolic syndrome; CVD, cardiovascular diseases; CAD, coronary artery diseases; HF, heart failure; CMD, cardiometabolic diseases.

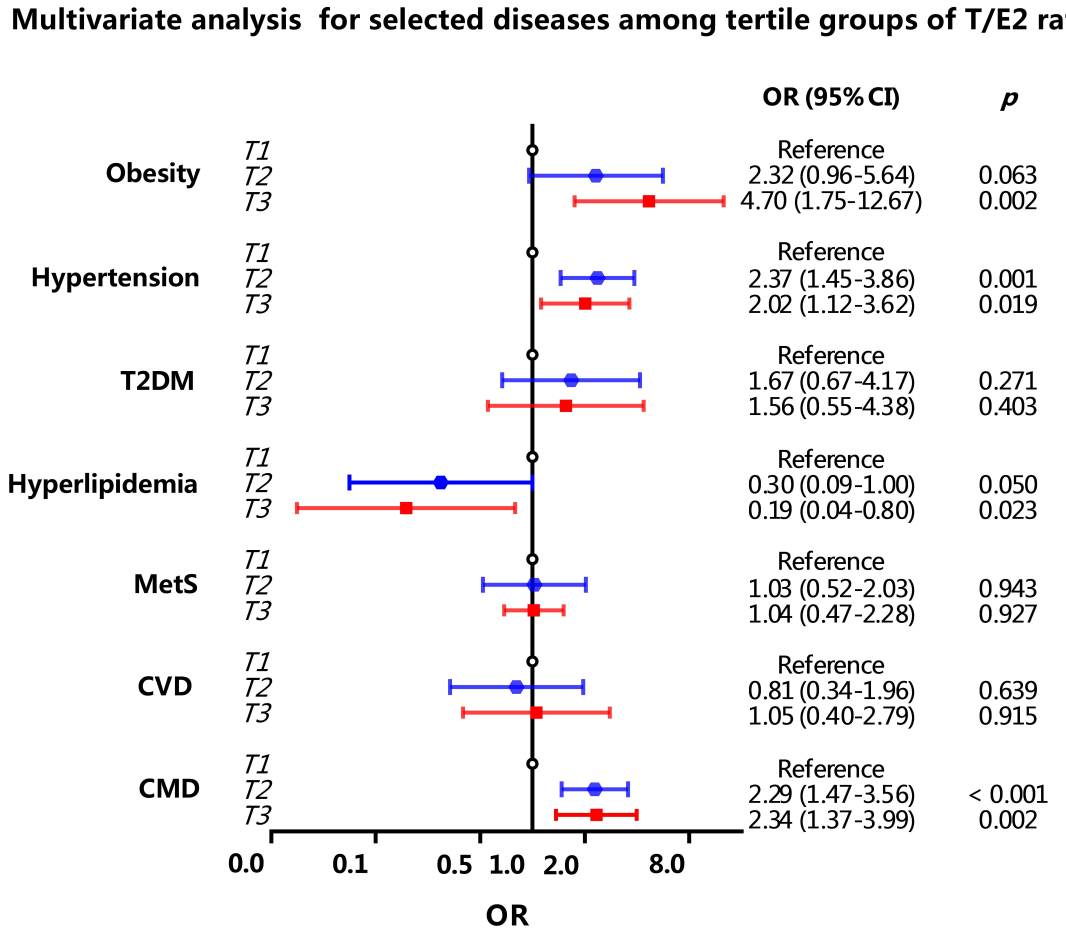

Fig. 2. Odds ratio between T/E2 ratio with CMD and its components. Groups were the tertiles of T/E2 ratio, and were set with T1 < 3.9, T2 = 3.9–13.0, T3 >13.0. Binary logistics regression was performed, and was adjusted by age (continuous variable), Han ethnicity, married, never smoke, never alcohol, never OCT, never HRT, number of live births (continuous variable), menopause staus, CAD family history. T2DM, type 2 diabetes mellitus; OR, odds ratio; CI, confidence interval; CVD, cardiovascular diseases; MetS, metabolic syndrome; CMD, cardiometabolic diseases.

sition period [30]. This hormonal alteration is generally translated to early menopausal symptoms such as infrequent menstruation (oligomenorrhea), night sweating, sleep disturbance and hot flashes (vasomotor symptoms) [31].

Following early sign of menopause comes the amenorrhea periods, which is the period during which women ovarian function slowly decline along with the decrease level of E2. As women progress through this time, they completely loss the ovarian function and the permanent cessation of menses at which after 12 months they are considered postmenopausal. Consequently, women permanently remain in low hypoestrogenic state as the E2 and progesterone level also remained low after menopause. Studies on T in women have shown that there is either increase or stable T level during menopause [32]. However, more evidence suggest that the decline is due to age instead of menopause [33]. Most importantly, owing to the steep decline of E2 at menopause transition, T/E2 increases in post-menopausal women, which may involve endothelial and cardiovascular health [34].

4.2 The Association of Testosterone with CMD

Data regarding T and its relationship with CMD are mixed. While Lambrinoudaki *et al*. [35] have claimed that T is positively correlated with CVD-related risk in postmenopausal women, Mudali and colleagues pointed to its deleterious effects on lipid profiles [36]. The latter consequently lead to the occurrence of atherosclerosis formation, specifically in carotid arteries [37], therefore, cardiometabolic related risk factors [38] such as HTN, obesity, and insulin resistance in postmenopausal women escalate [39]. It is important to consider that studies have been contradictory despite the potential pathological linkage between CVD events and T levels.

In addition, a cohort study claimed that higher testosterone levels were associated with an increased risk of CAD in a study with 30 years follow-up [7], which contradicted the finding from the Laughlin and colleagues [40], that lower T levels were associated with increased CVD events in post-menopausal women. Furthermore, another cohort study in Germany involving 2129 middle-aged women [8] and the Women's Health Study [41] have both concluded a null association between T with CVD incidents.

4.3 The Association of Estradiol with CMD

The protective effects of estrogens on cardiometabolic physiology works through several mechanisms. One of these mechanisms is its through increasing the synthesis of nitric oxide, which in turn causes vasodilation [31]. Another mechanism involves its regulatory effect on serum lipids which further decreases the risk of plaque formation; thus, ensuring a normal blood flow.

Beside these main effects, estrogens further contribute to endothelial vasodilation through regulating regulate specific inflammatory markers and cytokines [42]. Conversely, literature has shown that decreased E2 levels could increase the risk of CAD in women [7]. When studying the menopausal transition, it was observed that women with higher premenopausal E2 levels had lower risk of developing carotid plaque after menopause, compared to those that had a lower premenopausal E2 level [43]. This evidences that the decrease of E2 may associate with increased risks of CMD.

In contrast, other studies argued that high exposure to estrogen in premenopausal women, such as in pregnancy [13], is associated with disadvantageous metabolic profiles, including high blood pressure or hyperglycemia, which led to an increased risk of HTN and T2DM later in life [44]. High estrogenic exposure was also reported to be associated with the risk of CAD and stroke among older postmenopausal women [45].

While the aforementioned studies revealed that high E2 exerted possible benefits on the cardiometabolic health, other data suggested its detrimental effects. However, these studies converge with the "timing hypothesis", in which estradiol has an undesirable vascular effect in older women, while it has neutral or positive effects in younger women [46].

4.4 The Association of T/E2 Ratio with CMD

During the menopausal transitioning, the increasing T/E2 ratio coincides with an increased incidence of CVD, T2DM, and other metabolic risk factors including HTN, dyslipidemia, impaired glucose metabolism, and obesity [43]. The dysregulated serum T levels association with aging and/or the diminishing cardio-protective E2 levels [47] could be the reasons for the increased risk of CMD [11].

In the present study, we found an association between a higher T/E2 ratio and increased incidence of CMD. We previously assumed that the imbalance in the T/E2 ratio among these women was a result of decreased E2 as they experience a swift decline of E2 during the menopausal transition age compared to the gradual decline of T level. Therefore, we evaluated the association of T/E2 ratio with CMD-related risk factors. The results indicated that higher T/E2 ratio was associated with CMD and its components such as obesity and HTN. This suggest that a balance level of T/E2 ratio may play a reliable key role in CMD-related risk in women around the menopause transition period.

Our study is intended to provide preliminary data on T/E2 ratio association with CMD in women transitioning into menopause.

Treatment with an appropriate of T/E2 ratio appeared to attenuate injury to the endothelium and also reduced inflammation in cell and animal models [48]. This finding suggested that a combined therapy of T and E2 based on their ratio would prove to be more efficient compared to the exclusive replacement therapy of T or E2.

Based on our results, we suggest further prospective studies assessing women transitioning into menopause with intended purpose of proving the importance of the T/E2 ratio diagnosis in women transitioning into menopause.

5. Limitations

Though our study has many strengths, such as the inclusion of only women transiting to menopause, between the ages of 45 and 55 years, articulated exclusion criteria, and well-diagnosed comorbidities, we observed few limitations.

This is a single-center cross-sectional study with a small sample size due to strict exclusion criteria for enrollment and regional confinement of southwestern Chinese women. Therefore, we recommend a large-scale multicenter cohort study across race/ethnicity among women within the age bracket of 45–55 years in the future.

We also acknowledge that we did not use fertility monitors for to appropriately account menstrual cycle phase among premenopausal women. While obesity is a quantifiable measure emphasizing the stratification parameters associated to the BMI and waist circumference, adiposity refers to the distribution of body fat. In our study, we did not calculate the amount of visceral fat presented. However we found that BMI was statistically significant with T/E2 ratio.

6. Conclusions

Our study indicates that a higher T/E2 ratio is associated with a high prevalence of CMD in women at menopause transition age. From our findings, we suggest further prospective research to confirm the sensitivity of the T/E2 ratio in predicting the possibility of CMD in women around their menopause transition period.

Availability of Data and Materials

The dataset used and analyzed in this study is available from the corresponding author [GL] upon reasonable request.

Author Contributions

FBA—Investigation, Data collection, Visualization, Writing - Original Draft, Conceptualization; YX—Investigation, Data collection; BH, BRS—Supervision, Resources; AC, SCO—Writing - Review & Editing; AS—Visualization; GL—Writing - Review & Editing, Methodology, Software, Formal analysis, Project administration, Funding acquisition; SL—Project administration, Supervision. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of the First Affiliated Hospital of Chongqing Medical University, No. 2020-23. All the participants were informed of the study content and signed informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.ceog4912260.

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