Association Between Urinary Triclosan With Bone Mass Density and Osteoporosis in US Adult Women, 2005–2010

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Context: Laboratory studies have demonstrated that triclosan (TCS) can cause significant interstitial collagen accumulation and an increase in trabecular bone. However, little is known about the relationship between TCS exposure and human bone health.

Methods: We used 2005 to 2010 National Health and Nutrition Examination Survey data to examine the association between urinary TCS concentration and bone mineral density (BMD) and osteoporosis in US adult women aged ≥20 years. After inclusion and exclusion, 1848 women were analyzed.

Results: After adjustment for other covariates, we observed significant associations between tertile 3 of TCS concentration and lower BMD in regions of the total femur ($\beta = -0.016$; 95% CI = −0.032, −0.000), intertrochanteric region ($\beta = -0.022$; 95% CI = −0.042, −0.002), and lumbar spine ($\beta = -0.014$; 95% CI = −0.029, 0.001), respectively, relative to tertile 1. Compared with women at tertile 1, those at tertile 3 were more likely to have increased prevalence of osteoporosis in the intertrochanteric region (OR = 2.464; 95% CI = 1.190, 5.105).

Conclusion: This epidemiological study investigated the association between urinary TCS concentration and BMD and osteoporosis in US adult women. We found urinary TCS concentration was negatively associated with BMD and was positively associated with the prevalence of osteoporosis. The evidence was stronger in postmenopausal women than in premenopausal women. Future prospective studies are needed to validate these findings. (***J Clin Endocrinol Metab*** **104: 4531–4538, 2019)**

Osteoporosis is a metabolic bone disease characterized by decreased bone mineral density (BMD) and increased risk for fragility fractures, which result in negative effects on quality of life and increased mortality (1). It is reported that ~30% of postmenopausal women in the United States have osteoporosis, and 40% of them end up with fragility fractures (2). Fracture risk increases with age, and the incidence of hip fractures in US white women is among the highest in the world (3). Multiple factors contribute to reductions in bone mass and quality and lead to higher risk of fracture, including endogenous, environmental, and genetic factors (4). Emerging

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Abbreviations: BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; EDC, endocrine disruptor chemical; NHANES, National Health and Nutrition Examination Survey; TCS, triclosan.

epidemiological evidence indicates a major relationship between environmental xenoestrogens, also known as endocrine disruptor chemicals (EDCs), and bone metabolism and different levels of BMD (5–8).

Triclosan (TCS) is an antimicrobial used in a variety of consumer goods and personal care products including soaps, hand sanitizers, toothpaste, and mouthwash. Environmental exposure usually comes from TCS-containing consumer products or TCS-contaminated water and/or animal/food products (9). Urinary TCS concentrations ranging from 7.9 nM to 13.1 μM were detected in ~75% of the US population between 2003 and 2004 (10). Moreover, in many related studies, females were found to exhibit higher TCS concentrations than males (11, 12).

TCS is characterized as an EDC in multiple species, including humans (9). Some by-products of TCS, such as 2,4-dichlorophenol and 2,4,6-trichlorophenol, have endocrine disruptor activity (13, 14) and the potential to adversely affect levels of BMD. Laboratory studies have demonstrated that TCS can block *MMP-13* expression in parathyroid hormone–stimulated or prostaglandin E_2–stimulated osteoblastic cell lines (15), which can result in substantial interstitial collagen accumulation and an increase in trabecular bone (16, 17). However, little is known about the relationship between TCS and human bone health.

To our knowledge, no study has examined the association between TCS and BMD and osteoporosis. In the current study, we investigated the association of BMD and osteoporosis with urinary TCS concentrations in US adult women.

Material and Methods

Study population

Data analyzed in the current study were obtained from the National Health and Nutrition Examination Survey (NHANES) (http://www.cdc.gov/nchs/nhanes.htm). Information such as demographic, dietary, and health-related data were collected through in-home interviews. Medical examination, physical examination, and laboratory test results from urine and blood samples were conducted by highly trained medical personnel. Detailed information on survey planning and design are described elsewhere (18). All participants provided informed consent at the time of recruitment. The NHANES protocol was reviewed and approved by the National Center for Health Statistics institutional review board.

To increase the sample size, three NHANES surveys conducted between 2005 and 2010 were combined when urinary TCS concentration and BMD values for the lumbar spine and proximal femur were available. We investigated associations between urinary TCS exposure and different levels of BMD in adult women. A total of 8829 women aged ≥20 years participated. Urinary TCS concentrations were measured in only a subsample (n = 2759). Participants with missing values for urinary TCS (n = 106), BMD (n= 612), and other covariates (n = 193) were excluded in the final model. Ultimately, 1848 women aged ≥20 years with complete data of interest were analyzed.

Assessment of urinary triclosan

For each study participant, a single spot urine specimen was collected during a physical examination at a mobile examination center. For laboratory analysis, urine samples were shipped on dry ice to the National Center for Environmental Health and stored at −70°C until analyzed (19). Urinary concentrations of free TCS plus conjugated TCS were measured using automated solid-phase extraction coupled to isotope dilution high-performance liquid chromatography-tandem mass spectrometry (10). The lower limit of detection was 2.3 ng/mL in the three surveys. Samples below the limit were assigned a level of lower limit of detection divided by the square root of 2. The creatinine-corrected urinary TCS values (microgram per gram creatinine) were analyzed to adjust for bias caused by dilution of the urine. Concentration of urine creatinine was measured using the Jaffe rate method (kinetic alkaline picrate) (20).

BMD measurement and osteoporosis

BMD (gram per square centimeter) was measured by dual-energy x-ray absorptiometry (DXA). The scan was conducted using a Hologic QDR-4500A fan-beam densitometer (21). BMD levels in the total femur, femur neck, trochanter, and intertrochanteric region in the femur and lumbar spine were examined separately by the NHANES team. Mean BMD of the lumbar spine was calculated from the first through the fourth lumbar vertebrae (8). The left hip was routinely scanned for regions of proximal femur. If a left-hip replacement or metal objects in the left leg were reported, the right hip was scanned. If participants reported fractures, replacements, or pins in both hips, they were excluded from the DXA scan. Otherwise, if participants were pregnant (positive urine pregnancy test and/or self-report), weighed >300 pounds, or had participated in nuclear medicine studies in the past 3 days, they were also excluded from the DXA scan (22).

We defined osteoporosis according to a diagnostic criterion recommended by the World Health Organization: BMD values <2.5 SDs below the mean values of the young reference group (23). In our study, osteoporosis was assessed separately in the total femur, femur neck, trochanter, intertrochanteric region, and overall. Osteoporosis in any of the four femoral regions was regarded as overall osteoporosis (7). The osteoporosis thresholds were 0.68, 0.59, 0.46, and 0.80 gm/cm^2 for the total femur, femur neck, trochanter and intertrochanteric region, respectively.

Other covariates

Covariates were identified as potential confounders in our analysis as follows: age (years); race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other); education (less than high school, high school or equivalent, more than high school); marital status (married/cohabiting, widowed/divorced/separated, never married); physical activity during recreational time (sedentary, insufficient, moderate, high) (24); and smoking (never, ever, current). Daily calcium intake (tertiles); menopausal status (premenopausal, postmenopausal); and hormone use (yes, no) were recorded using interviewer-administered questionnaires. Body mass index

(kilogram per square meter) (normal, overweight, obesity) and history of diabetes (yes, no) (25) were obtained from physical and medical examinations conducted in the mobile examination center.

Statistical analysis

To account for the complex sampling design and to obtain appropriate SEs, weighted analyses were conducted according to the NHANES Analytic and Reporting Guidelines. Basic characteristics of participants are presented as mean (SE) or frequency (percentage).

Linear regression and logistic regression models were applied to analyze the association of urinary TCS concentration with BMD and osteoporosis, respectively. Linear regression models were constructed to estimate the association between urinary TCS concentration and BMD level with β-coefficients and corresponding 95% CIs. Logistic regression models were constructed to estimate the association between urinary TCS concentration and osteoporosis with ORs and corresponding 95% CIs. Sensitivity analysis was conducted by stratification of menopausal status to explore possible effect modifications.

All analyses were performed using STATA 15.1 (StataCorp LLC), while taking into account sample weights and design variables. $P < 0.05$ was regarded as statistical significant.

Results

Characteristics of participants

Table 1 shows the basic characteristics and urinary TCS level by menopausal status in the US adult women studied. The majority of subjects were non-Hispanic whites (72.23%), had an educational level greater than high school (57.84%), were married/cohabiting (62.19%), were normal weight (39.53%), were sedentary during recreational time (43.08%), were nonsmokers (56.51%), were without diabetes (91.43%), and did not use hormones (77.40%). Among 939 premenopausal women and 909 postmenopausal women, the mean age at interview and distributions of race/ethnicity, education, marital status, smoking status, body mass index, physical activity, calcium intake, diabetes, and hormone use were all statistically different ($P < 0.001$). Geometric means of urinary TCS concentration were similar in different menopausal status groups ($P = 0.625$).

Among all 1848 women included, the weighted percentages of osteoporosis in the total femur, femur neck, trochanter, intertrochanteric region, and overall were 3.93% (n = 91), 4.82% (n = 111), 2.17% (n = 60), 4.09% (n = 91), and 6.36% (n = 143), respectively [see (26)].

Associations between urinary TCS and BMD

Table 2 presents associations between urinary TCS concentration and BMD in the femur and lumbar spine. In tertile analyses, after adjustment for other covariates, significant associations were found between tertile 3 for TCS concentration and lower BMD in regions of the total femur ($\beta = -0.016$; 95% CI = -0.032, -0.000), intertrochanteric region ($\beta = -0.022$; 95% CI = -0.042, -0.002), and lumbar spine ($\beta = -0.014$; 95% CI = -0.029, 0.001), respectively, relative to tertile 1. These negative associations strengthened among postmenopausal women. However, they disappeared among premenopausal women; that is, except for BMD in the trochanter, lower BMD in all other regions was significantly associated with tertile 2 ($\beta = -0.024$; 95% CI = -0.045, -0.002 in the total femur; $\beta = -0.029$; 95% CI = -0.051, -0.006 in the femur neck; $\beta = -0.025$; 95% CI = -0.051, -0.000 in the intertrochanteric region; and $\beta = -0.023$; 95% CI = -0.044, -0.003 in the lumbar spine) and with tertile 3 ($\beta = -0.028$; 95% CI = -0.052, -0.005 in the total femur; $\beta = -0.029$; 95% CI = -0.049, -0.008 in the femur neck; $\beta = -0.036$; 95% CI = -0.065, -0.008 in the intertrochanteric region; and $\beta = -0.027$; 95% CI = -0.049, -0.005 in the lumbar spine) compared with tertile 1 in postmenopausal women.

Associations between urinary TCS and osteoporosis

Tertiles of urinary TCS concentration in participants with or without osteoporosis are presented in an online repository (26). We further explored the associations between urinary TCS concentration and osteoporosis in different bone sites as shown in Table 3. Compared with women at tertile 1, those at tertile 3 were more likely to have increased prevalence of osteoporosis in the intertrochanteric region (OR = 2.464; 95% CI = 1.190, 5.105). We did not observe statistically significant associations for different levels of urinary TCS with osteoporosis in the other three regions or overall. As shown in the online repository (26), the numbers of osteoporosis cases in the total femur, femur neck, trochanter, intertrochanteric region, and overall were only three, five, two, four, and seven, respectively, in premenopausal women. Further analysis for osteoporosis was conducted only in postmenopausal women. The result was similar to that in all adult women (OR = 2.250; 95% CI = 1.059, 4.782).

Discussion

Our epidemiological study investigated the association between urinary TCS concentration and BMD and osteoporosis in US adult women. We found urinary TCS concentration was negatively associated with BMD and positively associated with prevalence of osteoporosis. The evidence was stronger in postmenopausal women than in premenopausal women.

It has been demonstrated that thyroid hormone signaling is important for normal skeletal development and

Table 1. Basic Characteristics and Urinary Triclosan Level by Menopausal Status in US Adult Women, NHANES 2005–2010

Characteristics	All Women (n = 1848)	Premenopausal Women (n = 939)	Postmenopausal Women (n = 909)	*P* Value[a]
Age, mean ±SE	47.71 ±0.48	36.20 ±0.41	62.44 ±0.48	<0.001[b]
Race/ethnicity, n (%)				
Non-Hispanic white	924 (72.23)	430 (67.08)	494 (78.83)	<0.001
Non-Hispanic black	354 (10.80)	179 (11.57)	175 (9.83)	
Mexican American	331 (6.88)	187 (8.55)	144 (4.74)	
Other	239 (10.09)	143 (12.81)	96 (6.60)	
Education, n (%)				
Less than high school	479 (16.90)	204 (14.40)	275 (20.08)	<0.001
High school or equivalent	458 (25.26)	211 (22.15)	247 (29.26)	
More than high school	911 (57.84)	524 (63.45)	387 (50.66)	
Marital status, n (%)				
Married/cohabiting	1032 (62.19)	556 (64.20)	476 (59.60)	<0.001
Widowed/divorced/separated	511 (22.50)	135 (12.84)	376 (34.86)	
Never married	305 (15.31)	248 (22.95)	57 (5.54)	
Smoking status, n (%)				
Never	1102 (56.51)	587 (59.30)	515 (52.94)	<0.001
Ever	356 (21.88)	110 (14.69)	246 (31.07)	
Current	390 (21.61)	242 (26.01)	148 (15.99)	
BMI, n (%)				
Normal	626 (39.53)	367 (43.89)	259 (33.96)	<0.001
Overweight	586 (29.91)	274 (29.04)	312 (31.03)	
Obese	636 (30.56)	298 (27.08)	338 (35.01)	
Physical activity during recreational time, n (%)				
Sedentary	948 (43.08)	416 (37.77)	532 (49.89)	<0.001
Insufficient	310 (18.72)	164 (19.16)	146 (18.16)	
Moderate	221 (14.03)	111 (13.33)	110 (14.93)	
High	369 (24.16)	248 (29.75)	121 (17.01)	
Calcium, n (%)				
Tertile 1	618 (31.40)	297 (30.02)	321 (33.16)	<0.001
Tertile 2	632 (34.11)	287 (31.16)	345 (37.88)	
Tertile 3	598 (34.50)	355 (38.82)	243 (28.97)	
Diabetes, n (%)				
Yes	215 (8.57)	901 (96.71)	732 (84.67)	<0.001
No	1633 (91.43)	38 (3.29)	177 (15.33)	
Hormone use, n (%)				
Yes	400 (22.60)	30 (4.83)	370 (45.36)	<0.001
No	1448 (77.40)	909 (95.17)	539 (54.64)	
Triclosan, GM (95% CI)	17.58 (16.15, 19.14)	17.95 (15.96, 20.20)	17.21 (15.23, 19.44)	0.625[c]

Triclosan, urinary triclosan (microgram per gram creatinine).

Abbreviations: BMI, body mass index; GM, geometric mean; n, numbers of subjects; NHANES, National Health and Nutrition Examination Survey; %, weighted proportion.

[a] χ^2 test was used to compare proportions between premenopausal and postmenopausal women.

[b] A linear regression model was constructed with age as the dependent variable and menopause status as an independent variable.

[c] A linear regression model was constructed with log-transformed triclosan levels as dependent variables and menopausal status as an independent variable.

adult bone maintenance (27). Thyrotoxicosis is considered an important reason for secondary osteoporosis and increased risk of fracture in adults (28). Alteration of thyroid function has been associated with lower BMD and higher risk of fracture in postmenopausal women (29). As a halogenated biphenyl ether, TCS can cause several modifications in the thyroid axis of adult zebrafish by sharing structural similarity with T4 (30, 31), including thyroid tissue inactivation, increased level of pituitary TSH, and thyroid tissue hyperplasia (32). Therefore, we speculated that disruption in the thyroid axis caused by exogenous compounds such as TCS could lead to lower BMD and increased prevalence of osteoporosis in US adult women.

Estrogens play crucial roles in regulating osteoblast activity and differentiation by enhancing the process of osteogenic differentiation, stimulating differentiation from preosteoblasts to osteoblasts, and prolonging osteoblast and osteocyte life span by suppressing apoptosis in cultured mesenchymal stem cells (33). In addition,

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Table 2. Association Between Urinary Triclosan Level and BMD Among US Adult Women by Menopausal Status, NHANES 2005–2010

	BMD				
Triclosan	**Total Femur β (95% CI)**	**Femur Neck β (95% CI)**	**Trochanter β (95% CI)**	**Intertrochanteric Region β (95% CI)**	**Lumbar Spine β (95% CI)**
Total women[a]					
Tertile 1	Reference	Reference	Reference	Reference	Reference
Tertile 2	−0.011 (−0.028, 0.007)	−0.010 (−0.028, 0.008)	−0.006 (−0.022, 0.010)	−0.012 (−0.032, 0.008)	−0.010 (−0.027, 0.007)
Tertile 3	−0.016 (−0.032, −0.000)[b]	−0.010 (−0.024, 0.004)	−0.009 (−0.023, 0.006)	−0.022 (−0.042, −0.002)[b]	−0.014 (−0.029, 0.001)[b]
Premenopausal women[c]					
Tertile 1	Reference	Reference	Reference	Reference	Reference
Tertile 2	−0.002 (−0.027, 0.023)	0.004 (−0.021, 0.028)	0.000 (−0.021, 0.022)	−0.003 (−0.034, 0.028)	−0.000 (−0.025, 0.024)
Tertile 3	−0.008 (−0.032, 0.015)	0.004 (−0.021, 0.028)	−0.005 (−0.026, 0.016)	−0.012 (−0.040, 0.016)	−0.005 (−0.029, 0.018)
Postmenopausal women[c]					
Tertile 1	Reference	Reference	Reference	Reference	Reference
Tertile 2	−0.024 (−0.045, −0.002)[b]	−0.029 (−0.051, −0.006)[b]	−0.016 (−0.036, 0.004)	−0.025 (−0.051, −0.000)[b]	−0.023 (−0.044, −0.003)[b]
Tertile 3	−0.028 (−0.052, −0.005)[b]	−0.029 (-−0.049, −0.008)[b]	−0.015 (−0.035, 0.006)	−0.036 (−0.065, −0.008)[b]	−0.027 (−0.049, −0.005)[b]

Abbreviations: NHANES, National Health and Nutrition Examination Survey; β, coefficient.

[a]Linear regression adjusted for age (5-year intervals); race (non-Hispanic white, non-Hispanic black, Mexican American, other); educational level (less than high school, high school, more than high school); marital status (married/cohabiting, widowed/divorced/separated, never married); smoking (never, ever, current); body mass index (normal weight, overweight, obese); physical activity (sedentary, insufficient, moderate, high); calcium intake (tertile 1, tertile 2, tertile 3); diabetes (yes, no); hormone use (yes, no); and menopause (yes, no).

[b]$P < 0.05$.

[c]Linear regression was adjusted for the same covariates except for menopausal status.

Table 3. Association Between Urinary Triclosan Level and Osteoporosis Among US Adult Women by Menopausal Status, NHANES 2005–2010

	Osteoporosis				
Triclosan	Total femur OR (95% CI)	Femur neck OR (95% CI)	Trochanter OR (95% CI)	Intertrochanteric region OR (95% CI)	Overall[a] OR (95% CI)
Total women[b]					
Tertile 1	Reference	Reference	Reference	Reference	Reference
Tertile 2	0.891 (0.407, 1.951)	1.112 (0.577, 2.141)	0.724 (0.293, 1.793)	1.298 (0.590, 2.859)	1.206 (0.659, 2.206)
Tertile 3	1.607 (0.794, 3.252)	1.287 (0.706, 2.347)	1.551 (0.727, 3.307)	2.464 (1.190, 5.105)[c]	1.656 (0.950, 2.885)
Postmenopausal women[d]					
Tertile 1	Reference	Reference	Reference	Reference	Reference
Tertile 2	0.870 (0.395, 1.919)	1.099 (0.537, 2.250)	0.700 (0.274, 1.788)	1.328 (0.592, 2.978)	1.238 (0.658, 2.328)
Tertile 3	1.376 (0.669, 2.833)	1.135 (0.584, 2.205)	1.267 (0.560, 2.866)	2.250 (1.059, 4.782)[c]	1.555 (0.841, 2.875)

Abbreviation: NHANES, National Health and Nutrition Examination Survey.

[a]Overall osteoporosis was defined as osteoporosis in any femoral region of interest.

[b]Logistic regression was adjusted for age (5-year intervals); race (non-Hispanic white, non-Hispanic black, Mexican American, other); educational level (less than high school, high school, more than high school); marital status (married/cohabiting, widowed/divorced/separated, never married); smoking (never, ever, current); body mass index (normal weight, overweight, obese); physical activity (sedentary, insufficient, moderate, high); calcium intake (tertile 1, tertile 2, tertile 3); diabetes (yes, no); hormone use (yes, no); and menopause (yes, no).

[c]$P < 0.05$.

[d]Logistic regression was adjusted for the same covariates except for menopausal status.

estrogens promote insulin-like growth factor 1 and transforming growth factor-β production by osteoblasts as well as procollagen synthesis (34). TCS is one of the suspected EDCs with potential estrogenic activity (35, 36). Several *in vitro* studies demonstrated that TCS had antiestrogenic effects in transactivation and proliferative assays in human cells (37, 38). Thus, in US adult women, TCS exposure may adversely influence BMD and osteoporosis through its antiestrogenic effect.

Nojiri *et al.* (39) found that cytoplasmic superoxide could distinctly reduce bone stiffness and decrease BMD *in vivo*. They also showed that intracellular oxidative stress could induce cell apoptosis and reduce cell proliferation in primary osteoblasts but not in osteoclasts in *in vitro* experiments. Impaired osteoblast viability reduced osteoblast number and suppressed receptor activator of nuclear factor-κ ß ligand and recombinant human macrophage colony stimulating factor (RANKL/M-CSF) osteoclastogenic signaling in bone. It was reported that TCS at sublethal concentrations could induce oxidative stress, decreasing cellular thiol content and increasing intracellular Zn^{2+} concentration by Zn^{2+} release from intracellular stores in rat thymocytes (40). Cellular analysis suggested that TCS can inhibit the nuclear localization of SKN-1/Nrf2 and the expression of its target genes, which have been associated with oxidative stress response in human mesenchymal stem cells. Moreover, TCS-induced toxicity could be significantly reduced either by antioxidant treatment or constitutive SKN-1/Nrf2 activation (41). Therefore, TCS-related oxidative stress may have an effect on decreased BMD levels and osteoporosis.

Postmenopausal osteoporosis is the most common type of osteoporosis, resulting mainly from estrogen deficiency. After menopause, rapid bone loss appears, with an annual bone loss rate of 3% to 5% for 5 to 10 years because of reduced ovarian production of estrogens in women, affecting primarily trabecular bone (42). On the other hand, significantly increased alterations in oxidative balance occur during the menopausal transition. Changes in oxidative balance may be related to endocrine menopausal changes along with aging (43). These may partly explain the phenomenon that the association between TCS concentration and BMD and osteoporosis was more pronounced in postmenopausal women than in all adult women.

There are several limitations to this study. First, we used a cross-sectional design, which was not suitable for establishing cause-and-effect relationships. Second, because TCS is usually rapidly metabolized and excreted (44), TCS measurement in spot urine samples may not represent intraindividual variability and average long-term exposure. Moreover, repeated measurements and long-time observation of BMD are needed to capture the health status of bone because bone maintenance is a continuous process. In addition, there may have been errors in measurement of BMD and other confounding variables. Finally, we found a significantly elevated prevalence of osteoporosis (tertile 3 vs tertile 1) only in the intertrochanteric region, which correlates with the fact that maximal reduction in BMD (tertile 3 vs tertile 1) occurred in the intertrochanteric region. This may indicate that TCS exposure has more influence on the intertrochanteric region than on other regions of the femur;

however, no mechanistic studies supporting our hypothesis have been found.

In summary, we provide evidence that urinary TCS concentration was significantly associated with BMD and osteoporosis in US adult women. Higher TCS exposure was associated with lower BMD in the total femur, intertrochanteric region, and lumbar spine and with a higher prevalence of osteoporosis in the intertrochanteric region. The association was more pronounced in postmenopausal women. Future prospective studies are needed to validate the findings.

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