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Association between levothyroxine replacement therapy and osteoporosis in Riyadh, Saudi Arabia: a matched case-control study

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Hypothyroidism is a common health problem among elder women. However, conflicting results were observed regarding the association between levothyroxine treatment and osteoporosis risk. Therefore, the current study aimed to evaluate the effect of levothyroxine replacement therapy on osteoporosis risk in the Saudi population. This study was a matched case-control study conducted from June to August 2020. Data were extracted from the electronic medical records and included sociodemographic, clinical characteristics, comorbid conditions, levothyroxine replacement therapy dose, duration, concomitant therapy, and bone mineral density. Cases were matched with controls (1:1 basis) by age; the study included 256 cases and 256 controls. In the multivariate conditional logistic regression analysis, thyroxine use was independently associated with an increased likelihood of osteoporosis. Therefore levothyroxine use in elderly females was associated with an increased risk of osteoporosis, and hence, clinicians must be aware of the levothyroxine replacement therapy outcomes in postmenopausal females at risk of osteoporosis.

1. Introduction

Thyroid diseases are common and lead to serious health consequences (Russo et al. 2019). However, there are limited data on the incidence of hypothyroidism in Middle Eastern countries, including Saudi Arabia.

Overt hypothyroidism is defined as a concentration of thyroid-stimulating hormone (TSH) above the normal range and free thyroxine (T4) below the reference range. In contrast, subclinical hypothyroidism is defined as an average level of free thyroxine hormone with high serum TSH (Leslie et al. 2007).

Regarding the association between thyroid diseases and bone health, chronic hyperthyroidism has been shown to increase the fracture risk, especially in elderly and postmenopausal women who are at risk for osteoporosis and fracture (Leslie et al. 2007; Russo et al. 2019). Contradictory results were observed regarding the association between levothyroxine replacement and fractures (Flynn et al. 2010). It has been reported that among older people with hypothyroidism, using a large dose of levothyroxine raises the probability of fracture compared to small doses (Ko et al. 2014). Similar observations were found in patients with subclinical hypothyroidism who received levothyroxine replacement than those who did not (Karimifar et al. 2014). This could be attributed to lower bone density and bone quality reported with high-versus-low-dose levothyroxine replacement (Gomez Acotto et al. 1998).

Moreover, a high thyroxine hormone level might increase arrhythmia risk and falls, increasing the risk of fractures independent of bone mass (Auer et al. 2001). However, it has been reported that long-term treatment with levothyroxine does not significantly influence bone mineral density and hence the development of osteoporotic fractures (Franklyn et al. 1992). On the other hand, studies showed that treating primary hypothyroidism with levothyroxine improves bone mineral density (BMD) (Karimifar et al. 2014).

Data regarding the effect of levothyroxine on osteoporosis risk in Saudi Arabia are scarce. Therefore, this study aimed to determine the association between osteoporosis risk and levothyroxine replacement therapy among the Saudi population.

2. Investigations and results

The present study was a retrospective observational age-matched case-control study conducted in Prince Sultan Military Medical City (PSMMC), Riyadh, Saudi Arabia.

The Ethics Committee of the Institutional Review Board of PSMMC approved the study (HP-01-R079). The study did not involve direct contact with the study subjects and was based on secondary retrospective data provided by the PSMMC data management department that cross-checked with patients' medical

records. Participants' privacy and confidentiality were wholly protected. The study population included women aged 50 and above who did a screening dual-energy x-ray absorptiometry (DEXA) scan. Participants with any of the following were excluded from the study; history of hyperthyroidism, thyroid cancer, pituitary disease, follow-up data less than one year, or those who received continuous corticosteroids.

The present study included a total of 256 cases and 256 controls. The sociodemographic and clinical characteristics of the study participants are shown in Table 1. All study participants were females. The two groups did not differ significantly regarding smoking status; the vast majority of the two groups were nonsmokers ($P = 0.425$).

Furthermore, a significantly higher proportion of cases used levothyroxine (32%) compared with controls (18%) ($P = 0.001$). However, the dose and the duration of levothyroxine replacement therapy did not differ significantly in the controls compared with cases. Moreover, the past medical history was higher in cases (86.3%) than in controls (82.4%), but the difference was not statistically significant. Similarly, there were no significant differences between the two groups in almost all comorbid conditions and medications, except for the history of fragility fracture and the intake of antidepressants.

The prevalence of fragility fracture history was significantly higher in the cases (11.7%) compared to 6.6% in the control group ($P = 0.047$). In contrast, the prevalence of antidepressant intake was higher in the controls (13.7%) compared with cases (5.1%) ($P = 0.001$). Furthermore, controls had a higher mean body mass index (BMI) compared to cases; 30.5±6.7 kg/m^2 and 28.3±4.6 kg/m^2, respectively ($P < 0.001$). When the BMI was categorized as normal weight, overweight, and obese, the difference between the two groups was statistically significant, and the highest percentage of the two groups of participants were obese: 35.9% in cases and 52% in controls (Table 1).

Table 1: Characteristics of study participants according to osteoporosis status

Variable	Group		
	Case	Control	*P* value
Age*	59.2± 4.9	58.9± 5.1	0.427
Age group^			
50-<55	61 (23.8)	61 (23.8)	1.0000
55-<60	76 (29.7)	76(29.7)	
60-<65	76 (29.7)	75(29.3)	
65-<70	44 (17.2)	44(17.2)	
Current smoking^	2 (0.8)	5 (2)	0.450
Use of thyroxine replacement therapy^	82 (32)	46 (18)	< 0.0001
Thyroxine dose^			
<100 mcg	40 (48.8)	22 (47.8)	0.917
100 mcg or more	42 (51.2)	24 (52.2)	
Thyroxine duration^			
< 10 years	46 (56.1)	21 (45.7)	0.256
10 years or more	36 (43.9)	25 (54.3)	
Presence of comorbidities^	221 (86.3)	211(82.4)	0.224
Fragility Fracture history^	30 (11.7)	17(6.6)	0.047
Pulse corticosteroid < 2 times^	15(5.9)	20(9.8)	0.100
Anticonvulsant use ^	7 (2.7)	5 (2)	0.559
Antidepressant use^	13 (5.1)	35 (13.7)	< 0.001
Weight*	70.5±11.2	76.8±14.8	< 0.0001
Height*	158.4 ±8.3	158.9 ±6.6	0.141
BMI*	28.3±4.6	30.5±6.7	< 0.0001
Normal*	84 (32.8)	56(21.9)	
Overweight	80(31.3)	67(26.2)	0.001
Obese	92(35.9)	133(52)	

*Data are presented as means±SD, ^ data are presented as n (%); *P*-value is significant if < 0.05, BMI; Body mass index

Furthermore, the result of the present data showed that the use (OR = 2.353, 95% CI = 1.52-3.65, *P*<0001), and the fragility fracture (OR = 2.05, 95% CI = 1.01-4.17, $P = 0.048$) were independently associated with an increased probability of osteoporosis diagnosis. Furthermore, the use of antidepressants (OR = 0.392, 95%CI = 0.195-0.788, $P = 0.009$) and the BMI status [overweight (OR = 0.725, 95% CI = 0.420-1.25, $P = 0.247$) or being obese (OR = 0.394, 95% CI = 0.237-0.655, $P < 0.0001$) compared to normal BMI status were negatively associated with osteoporosis diagnosis (Table 2).

Table 2: Univariable and multivariable conditional logistic regression analysis for factors associated with osteoporosis status

Univariate				Multivariate		
Variable	*P* value	OR	95% CI	*P* value	OR	95% CI
Thyroxine use	0.001	2.029	1.353-3.041	≤ 0.0001	2.353	1.516-3.652
Fragility fracture	0.046	1.929	1.011-3.678	0.048	2.050	1.007-4.173
Anti-depressant	0.002	0.353	0.183-0.682	0.009	0.392	0.195-0.788
BMI	0.001				0.001	
Normal BMI		1				1
Overweight	0.233	0.733	0.440-1.221	0.247	0.725	0.420-1.250
Obese	0.000	0.431	0.270-0.689	≤ 0.0001	0.394	0.237-0.655

P-value is significant if < 0.05, BMI, Body mass index

3. Discussion

The present study was a retrospective case-control study that assessed the association between osteoporosis and levothyroxine use among premenopausal women in Saudi Arabia. The results revealed that osteoporotic women were two times more likely to use levothyroxine. Similar results were obtained with a history of fragility fracture. On the contrary, high BMI and antidepressant use were associated with a low probability of osteoporosis.

Fragility fracture is usually the early sign of osteoporosis (Oostwaard 2018). Moreover, change in BMD in both males and females is an independent risk factor for fragility fractures and predicts fracture risk in osteopenia patients (Berger et al. 2009). Previous studies assessing the association between bone mass and fracture risk, mainly among postmenopausal women, all reported associations between a high loss rate of loss and incident fracture (Hillier et al. 2007, Sornay-Rendu et al. 2005). Similar findings were observed in the present study, which showed that participants with osteoporosis have twice the probability of fragility fracture than those without osteoporosis.

The effects of thyroid hormone therapy on BMD are controversial (Amashukeli et al. 2010; Gonzalez Rodriguez et al. 2020; Wartofsky 1995). This difference might be owing to differences in study design, patient characteristics (age, gender, race, ethnicity, BMI, and menopausal status), levothyroxine type, and therapy duration (replacement or suppressive), as well as other confounding factors known to decrease BMD (steroid use, smoking, physical inactivity, previous thyrotoxicosis, and previous thyroidectomy with calcitonin deficiency) (Heemstra et al. 2006). Nevertheless, there was a positive association between levothyroxine use and osteoporosis in the present study. Similarly, many participants who used levothyroxine developed a significant decrease in bone density (Feigerlova et al. 2012). Furthermore, it has been found that people who took thyroid hormone for two consecutive years had a decrease in BMD (Karimifar et al. 2014). Another study showed that prolonged levothyroxine treatment decreases bone mineral density and enhances osteoporosis development, which was not evident in male and premenopausal females (Dhanwal et al. 2011). However, the role of the thyroid gland in bone metabolism is vital, and therefore, primary hypothyroidism should be ruled out as a cause of secondary osteoporosis (Dhanwal et al. 2010; Radak 2004).

Additionally, results regarding the association between BMI and osteoporosis are conflicting. The present study showed that an

increase in BMI is associated with a low probability of developing osteoporosis. Similar findings were observed in extensive epidemiological data, revealing that high BMI is correlated with high bone mass and, therefore, a low risk of osteoporosis (Mazocco and Chagas 2017). A study of postmenopausal women in Brazil showed that obese women had a lower prevalence than normal weight and overweight women (Zhao et al. 2007). On the other hand, one study showed that increasing fat mass might not benefit bone mass (Mezuk et al. 2008).

The present study showed that antidepressant use has a low probability of developing osteoporosis. On the other hand, previous studies have suggested a possible adverse effect of selective serotonin reuptake inhibitors (SSRIs) on BMD (Diem et al. 2007; Sansone and Sansone 2012; Williams et al. 2008). However, most studies examining antidepressant use and BMD had significant limitations, including cross-sectional designs and a limited ability to measure important confounders (Diem et al. 2007; Williams et al. 2008). A review of 19 studies on the impact of SSRIs on bone indicated adverse effects on BMD and/or increased risk (Agacayak et al. 2019). Furthermore, prolonged SSRI exposure must be a possible risk factor for osteoporosis among males (Diem et al. 2013). However, different findings were reported in a cohort study of middle-aged women, where SSRI and tricyclic antidepressants (TCAs) were not associated with an increased rate of bone loss in the spine, total hip, or femoral neck (Ham et al. 2017). The present study's findings differ from those of the previously mentioned studies, where the osteoporosis risk with antidepressant use was less by almost 60%. This difference can be attributed to the different study populations, age, ethnic groups, study design, or the small sample size in the present study.

The present study had the following strengths and limitations; one of the potential strengths of this study is that it was an age-matched case control. Moreover, variation was minimized by excluding other indications of levothyroxine therapy, for example, previous hyperthyroidism and history of thyroid cancer. Regression analysis was used to control for potential confounders. Selection and misclassification biases were minimized using hospital-based standardized objective outcome measures.

However, this study has some limitations. First, this is a retrospective study with a relatively small sample size collected from a tertiary hospital, which might limit the generalizability of the findings. Second, the control was not randomly sampled from the general population but selected from one tertiary-care hospital data registry. Future availability of community-based osteoporosis screening programs may lead to more representative control selection. Third, since the records did not include participants' medical information before 2005, we could not establish the prior levothyroxine usage and health status. Therefore, the data in this analysis were not enough. Fourth, the actual drug intake of the patients was not included in the participant files. As such, we could not determine the actual amounts of levothyroxine intake from the participants. Fifth, significant factors that could influence the association between levothyroxine and osteoporosis, like family history, sedentary lifestyle, or nonprescription drug use (calcium and vitamin D), were not accessible.

In conclusion prescribed levothyroxine in elderly females was associated with osteoporosis regardless of the dose and duration. However, more research is required to develop evidence for the risk-benefit balance. Furthermore, clinicians must be aware of the consequences of levothyroxine replacement therapy in postmenopausal females at risk of developing osteoporosis.

4. Experimental

4.1. Study design

The present study was a retrospective observational age-matched case-control study conducted in Prince Sultan Military Medical City (PSMMC), Riyadh, Saudi Arabia. The Ethics Committee of the Institutional Review Board of PSMMC approved the study (HP-01-R079). The study did not involve direct contact with the study subjects and was based on secondary retrospective data provided by the PSMMC data management department that cross-checked with patients' medical records. Participants' privacy and confidentiality were wholly protected. The study population included women aged 50 and above who did a screening dual-energy x-ray absorptiometry (DEXA) scan. Participants with any of the following were excluded from the study; history of hyperthyroidism, thyroid cancer, pituitary disease, follow-up data less than one year, or those who received continuous corticosteroids.

Data were recovered from the electronic health registry (DORTAL). All participants with radiological evidence of osteoporosis or osteopenia (confirmed by DEXA scan) were included. Those who had normal BMD on the DEXA scan were included in the control group.

All participants satisfying the inclusion criteria were identified using the DORTAL system. All participants who had a DEXA scan from the 1st of January 2019 to the 30th of July 2020 were checked for eligibility. The case/control status and exposure status for the previous 10 years were reviewed. A total of 256 cases were identified and matched to 256 controls. Data from June to August 2020 were extracted at the study time from electronic medical records using a standardized data collection form. The collected data included sociodemographic, clinical characteristics, comorbid conditions, levothyroxine replacement therapy (including dose and duration of treatment), concomitant therapy (less than two pulses of glucocorticoids, anticonvulsants, antidepressants, and others), and BMD. Body mass index (BMI) was calculated for each participant and was categorized as follows: normal, overweight, and obese (OBESITY 1998).

DEXA scan results were categorized into three categories using WHO criteria: BMD value 2.5 or more standard deviation (SD) below the young adult female reference mean osteoporosis, a value for BMD more than 1.0 but less than 2.5 SD below the young adult female reference mean osteopenia, a value for BMD within 1 SD of the young adult female reference mean normal (Organization 2007).

4.2. Definition of the case

Participants who met the inclusion criteria and underwent a DEXA scan for osteoporosis or osteopenia were selected as cases.

4.3. Control definition

Participants with normal BMD by DEXA scan were included as controls. The cases were matched with controls (1:1 basis) by age.

4.4. Exposure definition

Exposure was defined as a diagnosis of subclinical hypothyroidism or overt hypothyroidism, and any dose of levothyroxine replacement therapy was used for at least one year before the DEXA scan was performed. The exposure status was classified into two groups according to the levothyroxine dose: ≤ 100 mcg/ day, > 100 mcg /day. For patients who have been on different doses during the study period, the average treatment dose was used.

4.5. Statistical analysis

The collected data were entered into Microsoft Excel 2010 and then transferred to the Statistical Package for Social Sciences, version 26 (SPSS Inc., Chicago, IL, USA) for analysis. Continuous data were expressed as means±SD and were compared using the student *t*-test or Mann-Whitney-*U* test. Categorical data were expressed as frequencies and percentages (n and %) and were compared using the Chi-square test or the Fisher exact test. A conditional logistic regression analysis was conducted to determine the association between osteoporosis and risk factors. Variables found to be significant in univariate analysis were included in the final multivariate model. The strength of association was calculated using an odds ratio (and a 95% confidence interval), controlling for confounding factors. All tests were two-sided, and a *P*-value level of < 0.05 was considered significant.

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