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Hypothyroidism and the risk of coronary artery disease in Saudi patients

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Abstract:

BACKGROUND: Hypothyroidism has been described in the literature as a risk factor for coronary artery disease (CAD). An association between thyroid-stimulating hormone (TSH) levels and CAD has been confirmed. In Saudi Arabia, there has been no study on the relationship between hypothyroidism and CAD. Therefore, the aim of this study was to investigate the prevalence and risk factors of CAD in patients with hypothyroidism.

MATERIALS AND METHODS: This cross-sectional study conducted at King Abdulaziz Medical City in Riyadh (KAMC-R), included 412 adult hypothyroid patients who were followed up between 2013 and 2018. The data was collected on demographics, CAD-related risk factors, and hypothyroidism. In addition, relevant laboratory tests, including thyroid function tests, lipid profile, and hemoglobin A1c, were collected. SPSS version 28.0 was used for data analysis. Categorical data were presented as frequencies and percentages, while mean and standard deviations were computed for the numerical data. Student's *t*-test used to test statistical significance for numerical variables and Chi-square test was performed to test the differences between categorical variables. Multivariate binary logistic regression was used to determine the effects of gender, BMI, family history (CAD), smoking, hypertension, and TSH on CAD.

RESULTS: Of the 412 hypothyroid patients, 21.8% were diagnosed with CAD, with more prevalence in men (44.15%) than in women (15.4%). About 46% had hypertension, 2.2% were smokers, and 2.4% had family history of CAD. Older age was significantly associated with a higher prevalence of CAD compared to younger age groups. The mean of TSH was significantly higher in CAD patients than non-CAD patients before and at diagnosis with CAD ($P < 0.001$). For every 1mIU/L increase in the TSH level, the odds of developing CAD increased significantly by 4.8% ($P = 0.014$). The odds ratios for other CAD risk factors were 3.13 for males, 8.1 for smoking, 2.48 for hypertension, and 9.9 for family history of CAD ($P < 0.05$).

CONCLUSION: The prevalence of CAD in hypothyroid patients was higher than in the general population. TSH level was significantly associated with CAD. Male gender, older age, smoking, hypertension, family history of CAD, and high TSH level increased the likelihood of developing CAD.

Keywords:

Coronary artery disease, hypothyroidism, prevalence, risk

Introduction

The thyroid gland is the largest pure endocrine gland that releases its hormones directly into the bloodstream.

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Thyroid hormones regulate many physiological functions such as heart rate to maintain hemostasis. These hormones also play a fundamental role in different metabolic pathways such as lipid metabolism and cardiovascular physiology. Thyroid hormones affect lipid metabolism

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by increasing the concentration of free fatty acids, the synthesis and utilization of triglycerides (TGs). Thyroid hormones also increase the activity of cholesteryl ester transfer protein, which in turn affects the metabolism of high-density lipoprotein (HDL).^[1] Thyroid hormones increase heart rate by raising the contraction of the heart muscle with increased gene expression of motor proteins in the heart muscle cells. Further, thyroid hormones stimulate the production of nitric oxide, which leads to vasodilation.^[2]

In normal physiology, the pituitary gland controls T3 and T4 levels through a feedback mechanism. When T3 and T4 levels are low, the pituitary gland secretes thyroid-stimulating hormone (TSH) to stimulate the thyroid to produce the hormones. However, in primary hypothyroidism, the thyroid gland produces T3 and T4 less efficiently owing to pathological causes, such as Hashimoto's thyroiditis. The known effects of hypothyroidism include an increase in total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDL-C), very LDL-C, and the TC/HDL ratio, with a decrease in HDL cholesterol (HDL-C).^[3] Hypothyroidism affects the cardiovascular system by decreasing cardiac output and increasing systemic vascular resistance, the result of impaired nitric oxide production.^[4]

Studies have identified hypothyroidism as a risk factor for coronary artery disease (CAD), with a clear association between TSH levels and CAD.^[5,6] In contrast, other studies have found no relation between TSH and cardiovascular diseases or mortality rates.^[7] A meta-analysis has revealed that patients with higher TSH levels have a modest increase in CAD risk.^[8] These contradictory findings can be attributed to the heterogeneity of the populations studied and the multiplicity of risk factors that are not equally controlled in different studies.

In Saudi Arabia, hypothyroidism is a common condition with a prevalence of 32.26% in women and 18.2% in men.^[9]

However, few local studies have investigated the association of thyroid function tests with cardiac mortality. One local study concluded that there was no significant association between hypothyroidism and CAD.^[10]

Our study's aim was to determine whether there is a relationship between hypothyroidism and CAD and investigate the risk factors of CAD in patients with hypothyroidism.

Materials and Methods

This cross-sectional study was conducted at King Abdulaziz Medical City in Riyadh (KAMC-R), Health Affairs, Ministry of the National Guard, Saudi Arabia. Ethical approval was obtained from the Institutional Review Board vide Letter No. SP19/352/R dated 07/07/2019, with a waiver of written consent since data were only collected from medical records of patients.

The study sample consisted of adult patients (age >18) with hypothyroidism and TSH above the normal range (i.e., above 4.94 mIU/l), who attended KAMC-R between 2013 and 2018. The calculation of the sample size was based on the confidence level of 95% and margin of error of 5%. Since the prevalence of CAD in hypothyroidism patients in Saudi Arabia is unknown, it was set at 50%. Based on these variables, the estimated minimum needed sample size was 377. Convenience sampling was used to collect the study sample.

Data were collected from patients' medical records using a structured data collection sheet. The following were collected: patient demographics, including gender, age, and body mass index (BMI). Other data collected included hypothyroidism-related laboratory tests (TSH, FT4, and FT3) and thyroid hormone treatment in terms of thyroid hormone replacement and dose, lipid profile (HDL-C, LDL-C, TG, and TC), and hemoglobin A1c (HbA1c) before, at, and after the diagnosis of CAD. We also collected the medical history of patients with or without CAD. CAD was defined as hospital admission with confirmed acute coronary syndrome (i.e., ST-elevation myocardial infarction, non-ST elevation myocardial infarction, and unstable angina). We also included CAD-related variables: smoking history for any period, reported family history of CAD, and statin use.

We used Microsoft Excel for data entry and SPSS software version 28.0 for data analysis. Categorical data were presented as frequencies and percentages, while numerical data, such as age, were presented as mean and standard deviation. An independent *t*-test was used to compare the means of numerical data. Differences between categorical variables were compared using a Chi-square test or Fisher's exact test as appropriate. Multivariate binary logistic regression was used to investigate the effects of gender, BMI, family history (CAD), smoking, hypertension, and TSH on CAD. In this model, females, ≥ 70 years, obese patients, negative family history, nonsmoker, and nonhypertensive were the reference group for gender, age, BMI, family history (CAD), smoking, and hypertension, respectively. A test was considered significant if $P < 0.05$.

Results

Our study comprised 412 patients with hypothyroidism, 90 (21.8%) of whom were diagnosed with CAD. Ninety-three (22.6%) were males, and 319 (77.4%) were females. Participants were divided into four groups of nearly 25% each of the sample: 38 years or younger ($n = 106$), 39–52 years ($n = 102$), 53–69 years ($n = 103$), and 70 years or older ($n = 101$). A positive family history of CAD was present in 2.4% ($n = 10$) of the study population. The prevalence of obesity, overweight, and underweight in all age groups with hypothyroidism was 51% ($n = 210$), 28.2% ($n = 116$), and 3.9% ($n = 16$), respectively, while those of normal weight made up 17% ($n = 70$). We also found that the prevalence of smoking was 2.2% ($n = 9$). About 45.6% ($n = 188$) of the sample had hypertension. Of the

Table 1: Demographic characteristics, coronary artery disease risk factors, and use of thyroid replacement therapy and statins among Saudi hypothyroidism patients at King Abdulaziz Medical City in Riyadh ($n=412$)

Demographics	N (%)
Gender	
Male	93 (22.6)
Female	319 (77.4)
Age group (years)	
≤ 38	106 (25.7)
39-52	102 (24.8)
53-69	103 (25)
≥ 70	101 (24.5)
BMI	
Underweight	16 (3.9)
Normal weight	70 (17.0)
Overweight	116 (28.2)
Obese	210 (51.0)
Coronary artery disease	
Yes	90 (21.8)
No	322 (78.2)
CAD risk factors	
Smoking	
Smoker	9 (2.2)
Nonsmoker	403 (97.8)
Hypertension	
Yes	188 (45.6)
No	224 (54.4)
Family history	
Positive	10 (2.4)
Negative	402 (97.6)
Medications	
Thyroid hormone therapy	
Yes	308 (74.8)
No	104 (25.2)
Dyslipidemia on treatment	
Yes	154 (37.4)
No	258 (62.6)

CAD=Coronary artery disease, BMI=Body mass index

412 hypothyroid patients, 308 (74.8%) were on thyroid hormone replacement therapy, and 154 (37.4%) were on a statin [Table 1].

Table 2 shows that the prevalence of CAD in men and women with hypothyroidism was 44.4% (41/93) and 15.4% (49/319), respectively ($P < 0.001$). Older age was significantly associated with a higher prevalence of CAD ($P < 0.001$): 70 years or older, 43.6%; 53–69, 34%; 39–52, 9.8%; and younger than 39, 0.9%. In obese, overweight, and patients with normal weight, the prevalence of CAD was 21%, 23.3%, and 15.7%, respectively. Eight (50%) of the 16 underweight patients had CAD and six of them (75%) were 70 years or older. The majority (66.7%) of the patients who were smokers had CAD. More than one-third of the patients with hypertension (38.8%) had CAD. Approximately 60% of the patients with a family history of CAD developed the disease. Obesity, smoking, hypertension, and a family history of CAD were significantly associated

Table 2: The relationship between coronary artery disease and various risk factors among Saudi hypothyroidism patients at King Abdulaziz Medical City in Riyadh ($n=412$)

Variables	Coronary artery disease		P-value
	Yes N (%)	No N (%)	
Gender			
Male	41 (44.1)	52 (55.9)	<0.001
Female	49 (15.4)	270 (84.6)	
Age group (years)			
≤ 38	1 (0.9)	105 (99.1)	<0.001
39-52	10 (9.8)	92 (90.2)	
53-69	35 (34.0)	68 (66.0)	
≥ 70	44 (43.6)	57 (56.4)	
BMI			
Underweight	8 (50.0)	8 (50.0)	0.027
Normal weight	11 (15.7)	59 (84.3)	
Overweight	27 (23.3)	89 (76.7)	
Obese	44 (21.0)	166 (79.0)	
Smoking			
Smoker	6 (66.7)	3 (33.3)	0.004
Nonsmoker	84 (20.8)	319 (79.2)	
Hypertension			
Yes	73 (38.8)	115 (61.2)	<0.001
No	17 (7.6)	207 (92.4)	
Family history			
Positive	6 (60.0)	4 (40.0)	0.009
Negative	84 (20.9)	318 (79.1)	
Thyroid replacement therapy			
Yes	69 (22.4)	239 (77.6)	0.22
No	21 (20.2)	83 (79.8)	
Dyslipidemia on treatment			
Yes	65 (42.2)	89 (57.8)	<0.001
No	25 (9.70)	233 (90.3)	

Chi-squared test for all comparisons except smoking and family history with Fisher's exact test. BMI=Body mass index

with CAD ($P = 0.027$, $P = 0.004$, $P < 0.001$, and $P = 0.009$, respectively).

Around 22.4% of the patients with hypothyroidism who had thyroid replacement therapy developed CAD. In comparison to patients without CAD, patients who developed the disease had significantly higher TSH levels before and at the time of diagnosis of CAD (8.4 [9.34] vs. 4.73 [5.11] mIU/L, $P < 0.001$, and 8.73 [14.64] vs. 4.68 [5.66] mIU/L, $P < 0.001$, respectively). After diagnosis, the TSH level was higher in the CAD group, but the difference was not statistically significant ($P = 0.429$). The overall mean TSH of the three intervals, before, at, and after the diagnosis, was significantly higher in the CAD group (7.43 [9.42] vs. 4.66 [5.21] mIU/L, $P < 0.001$). Free triiodothyronine (FT3) levels were significantly lower in CAD patients before, at, and after the diagnosis (3.19 [0.93] vs. 4.04 [1.10] pmol/L, $P < 0.001$, 2.97 [0.93] vs. 3.81 [1.10] pmol/L, $P < 0.001$, and 2.78 (0.63) vs. 3.74 (0.92) pmol/L, $P < 0.001$, respectively). The overall mean FT3 was lower in CAD patients (2.97 [0.77] vs. 3.82 [1.05] pmol/L, $P < 0.001$). Free thyroxine (FT4) was significantly lower only in patients with CAD at diagnosis (12.32 [3.02] vs. 13.24 [2.77] pmol/L, $P = 0.016$). Before and after the diagnosis, FT4 levels were lower in the CAD group but did not reach statistical significance ($P = 0.33$ and $P = 0.581$, respectively) [Table 3].

LDL-C levels were significantly lower in CAD patients compared to non-CAD patients before, at, and after diagnosis (2.50 [0.86] vs. 2.97 [1.04] mmol/L, $P = 0.001$, 2.32 [0.83] vs. 2.85^[1] mmol/L, $P < 0.001$, and 2.25 [0.9] vs. 2.86 [1.04] mmol/L, $P < 0.001$, respectively). In addition, the overall mean LDL was significantly lower in CAD patients ($P < 0.001$). Before, at, and after diagnosis of CAD, HDL-C levels were significantly lower in CAD patients than in non-CAD patients (0.88 [0.22] vs. 1.12 [0.31] mmol/L, $P < 0.001$, 0.85 [0.25] vs. 1.14 [0.36] mmol/L, $P < 0.001$, and 0.94 [0.22] vs. 1.13 [0.31] mmol/L, $P < 0.001$, respectively). Mean total HDL-C levels were significantly lower in CAD patients (0.89 [0.21] vs. 1.13 [0.30] mmol/L, $P < 0.001$). TC was significantly lower before, at, and after diagnosis in the CAD group ($P < 0.001$, $P < 0.001$, and $P = 0.002$, respectively). TG was significantly higher in CAD patients before, at, and after the diagnosis ($P < 0.001$, $P < 0.001$, and $P = 0.002$, respectively). In addition, HbA1C levels were significantly higher in patients with CAD before, and at diagnosis (7.94% [1.94%] vs. 7.10% [2.14%], $P = 0.01$, and 7.58% [1.89%] vs. 6.87% [2.14%], $P = 0.007$, respectively). After diagnosis, HbA1C was higher in CAD patients, but the difference was not statistically significant ($P = 0.093$). The overall mean of TG and HbA1C was higher in CAD patients ($P = 0.008$ and $P < 0.001$, respectively) [Table 3].

Table 3: Comparison of thyroid hormones levels, lipid profile, and hemoglobin A1C between hypothyroidism patients with coronary artery disease and hypothyroidism patients without coronary artery disease at King Abdulaziz Medical City in Riyadh

Variables	Coronary artery disease		P-value
	Yes Mean±SD	No Mean±SD	
TSH (mIU/L)			
Pre-CAD diagnosis	8.04±9.34	4.73±5.11	<0.001
At CAD diagnosis	8.73±14.64	4.68±5.66	<0.001
Post-CAD diagnosis	4.83±5.93	4.22±6.08	0.429
Overall mean TSH	7.43±9.42	4.66±5.21	<0.001
FT3 (pmol/L)			
Pre-CAD diagnosis	3.19±0.93	4.04±1.10	<0.001
At CAD diagnosis	2.97±0.95	3.81±1.05	<0.001
Post-CAD diagnosis	2.78±0.63	3.74±0.92	<0.001
Overall mean FT3	2.97±0.77	3.82±1.05	<0.001
FT4 (pmol/L)			
Pre-CAD diagnosis	12.77±3.17	13.21±3.15	0.33
At CAD diagnosis	12.32±3.02	13.24±2.77	0.016
Post-CAD diagnosis	12.48±2.98	12.74±3.10	0.581
Overall mean FT4	12.44±2.73	13.01±2.38	0.06
LDL-C (mmol/L)			
Pre-CAD diagnosis	2.50±0.86	2.97±1.04	0.001
At CAD diagnosis	2.32±0.83	2.85±1.00	<0.001
Post-CAD diagnosis	2.25±0.90	2.86±1.04	<0.001
Overall mean LDL-C	2.39±0.71	2.90±0.96	<0.001
HDL-C (mmol/L)			
Pre-CAD diagnosis	0.88±0.22	1.12±0.31	<0.001
At CAD diagnosis	0.85±0.25	1.14±0.36	<0.001
Post-CAD diagnosis	0.94±0.22	1.13±0.31	<0.001
Overall mean HDL-C	0.89±0.21	1.13±0.30	<0.001
TG (mmol/L)			
Pre-CAD diagnosis	1.81±1.11	1.43±0.80	0.002
At CAD diagnosis	1.70±1.02	1.42±0.77	0.012
Post-CAD diagnosis	1.77±1.22	1.45±0.98	0.027
Overall mean TG	1.78±1.06	1.47±0.91	0.008
TC (mmol/L)			
Pre-CAD diagnosis	4.15±1.05	4.79±1.20	<0.001
At CAD diagnosis	3.96±1.15	4.67±1.21	<0.001
Post-CAD diagnosis	4.01±1.31	4.55±1.19	0.002
Overall mean TC	4.05±0.98	4.67±1.06	<0.001
HbA1C (mmol/mol)			
Pre-CAD diagnosis	7.94±1.94	7.10±2.14	0.01
At CAD diagnosis	7.58±1.89	6.87±1.95	0.007
Post-CAD diagnosis	7.41±1.74	6.90±2.17	0.093
Overall mean TG	7.56±1.78	6.67±1.78	<0.001

Data are mean (SD). CAD=Coronary artery disease, TSH=Thyroid-stimulating hormone, FT3=Free triiodothyronine, FT4=Free thyroxine, DL-C=Density lipoprotein cholesterol, LDL-C=Low-DL-C, HDL-C=High-DL-C, TG=Triglyceride, TC=Total cholesterol, HbA1C=Hemoglobin A1c, SD=Standard deviation

In multivariate analysis, men had a 3.13-fold higher risk of developing CAD than women (odds ratio [OR]: 3.13, 95% confidence interval [CI]: 1.6–6.1, $P < 0.001$). Patients aged ≥ 70 years had an odds ratio of 36.60 (95% CI: 4.33–309.26, $P = 0.001$) compared to the ≤ 38 years' age group. The 53–69 years' age group had an odds ratio of 30.67 (95%

CI: 3.73–252.22, $P = 0.001$) compared to the ≤ 38 years' age group. There was no significant difference in the odds of having CAD between the 39–52 years' age group and the ≤ 38 years' age group ($P = 0.126$). Obese patients had 4.19 odds of developing CAD (95% CI: 1.58–11.08, $P = 0.004$) than patients with normal weight. Smokers had an odds ratio of 8.1 (95% CI: 1.54–43.4, $P = 0.014$). Hypertensive patients were 2.48 times (OR: 2.48, CI: 1.16–5.3, $P = 0.019$) more likely to develop CAD than nonhypertensive patients. We also found that patients with a positive family history had a 9.9-fold higher risk of developing CAD (OR: 9.9, 95% CI: 1.6–61.2, $P = 0.014$) than patients with a negative family history. Furthermore, the odds of developing CAD increased by 4.8% for every 1 mIU/L increase in TSH level (OR: 1.048, CI: 1.009–1.09, $P = 0.014$) [Table 4].

Discussion

Although the association between hypothyroidism and CAD is known,^[11-14] the local data on this problem are limited.

In our study, the prevalence of CAD in hypothyroid patients was 21.8% higher than was reported previously

Table 4: Binary logistic regression analysis for the association between coronary artery disease and various independent variables among patients with hypothyroidism at King Abdulaziz Medical City in Riyadh

Variable	OR (95% CI)	P-value
Gender		
Male	3.13 (1.6-6.1)	<0.001
Female	Reference group	
Age group (years)		
≥ 70	36.6 (4.33-309.26)	0.001
53-69	30.67 (3.73-252.22)	0.001
39-52	5.61 (0.62-51.12)	0.126
≤ 38	Reference group	
BMI		
Obese	4.19 (1.58-11.01)	0.004
Overweight	3.56 (3.01-74.37)	0.014
Underweight	14.96 (0.42-1.7)	0.001
Normal weight	Reference group	
Smoking		
Smoker	8.1 (1.54-43.4)	0.014
Nonsmoker	Reference group	
Hypertension		
Yes	2.48 (1.16-5.3)	0.019
No	Reference group	
Family history (CAD)		
Positive	9.9 (1.6-61.2)	0.014
Negative	Reference group	
Overall TSH mean	1.048 (1.009-1.090)	0.014

OR=Odds ratio, CI=Confidence interval, CAD=Coronary artery diseases, TSH=Thyroid hormone-stimulating hormone, BMI=Body mass index

in the general population (5.5%).^[15] Hypothyroidism was more common in female patients, which is consistent with the findings in the literature.^[9,14] However, the prevalence of CAD was more common in males than females, as male gender is a well-known risk factor for CAD.

Our study also found a high prevalence of obesity (51.6%) and hypertension (45.6%) in patients with hypothyroidism. Obese and overweight patients had significantly higher odds of developing CAD. The odds were also higher for underweight patients to develop CAD than individuals of normal weight. However, most underweight patients (75%) were 70 years or older, which most likely had influenced the prevalence of high CAD in this patient group. As in the general population, there was a clear association between CAD and common CAD risk factors, including smoking, hypertension, positive family history of CAD, diabetes control, and older age. The effect of thyroid status, particularly hypothyroidism, on known CAD-related risk factors is well established.^[1,3,6]

Consistent with our findings, a cross-sectional study documented a high prevalence of hypertension in hypothyroid patients.^[16] Similarly, many studies have documented the association between hypothyroidism and diabetes mellitus.^[17]

LDL-C was significantly lower in CAD patients. This can be attributed to the fact that 72.2% of the CAD patients were taking statin medications, compared to 27.6% of the non-CAD patients who took statins. In contrast, HDL-C, which has a cardioprotective role, was significantly higher in the non-CAD group.^[18] Derangement in LDL oxidation is one of the possible mechanisms by which hypothyroidism causes CAD.^[19,20] Furthermore, hypothyroidism is associated with atherosclerotic risk factors, such as hypercholesterolemia and low HDL.^[21,22]

Our findings suggest that higher TSH level is an independent risk factor for CAD. This finding is like what has been reported in the literature. A case-control study found that a high TSH level was associated with higher CAD prevalence.^[23] Auer *et al.*, found that a high TSH level was an independent predictor of the severity of CAD, despite adjustment for the CAD risk factor, while a low FT3 level was significantly associated with advanced CAD.^[24] Moreover, a 2010 meta-analysis by Rodondi *et al.*, covering 11 prospective cohort studies, showed that the risk of CAD events and mortality increased with higher TSH levels.^[5] This association between hypothyroidism and CAD is possibly partly due to the higher prevalence of CAD risk factors in our population. However, several studies have found

a significant association between hypothyroidism and CAD after adjustment for traditional CAD risk factors, indicating that hypothyroidism may affect CAD risk through pathways other than traditional risk factors.^[5,25,26] In one study, for example, patients with high TSH levels had significantly impaired flow-mediated endothelium-dependent vasodilation, which may explain the increased CAD risk associated with hypothyroidism.^[27]

The strengths of our study include our relatively large sample size, detailed documentation of thyroid-related variables, and other classic CAD risk factors before, at, and after CAD diagnosis.

Although our study suggested hypothyroidism as a risk factor, the cross-sectional design cannot confirm this hypothesis. Therefore, future cohort studies are recommended to assess the association between hypothyroidism and CAD.

Conclusion

The prevalence of CAD seems to be higher in patients with hypothyroidism than in the general population in Saudi Arabia. CAD patients had significantly higher TSH levels before and at diagnosis of CAD. In addition, an increase in TSH levels raises the likelihood of developing CAD. Male gender, older age, hypertension, smoking, dyslipidemia, diabetes, and positive family history were risk factors in hypothyroid patients for developing CAD. Thus, our study is of the opinion that hypothyroidism is a risk factor for CAD, but this merits further investigation.

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Conflicts of interest

There are no conflicts of interest.

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