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Original Article

The Clinical Implications of Thyroid Dysfunction and its Association with Dyslipidemia and the Geographical Effect: A Comparative Study from Different Altitudes in Saudi Arabia

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ABSTRACT

Background: Thyroid disorder is one of the most prevalent critical issues for public health in clinical practice. Lipid profiles and cardiovascular attenuation are significantly affected by thyroid dysfunction. Thyroid dysfunction related to altitudes (height from sea level) has attracted endocrinologists worldwide. **Objectives:** The current study aimed to investigate the prevalence of thyroid dysfunction and its association with lipid profile among the Saudi population residing at different altitudes and to explore the effect of altitudes on thyroid status. **Materials and Methods:** In this retro cross-sectional study, a large dataset of thyroid hormones and lipid profiles from walk-in patients of both genders doing hormonal and biochemical tests at public labs and government hospital labs from sea level (Jeddah), low altitude (Najran) and high altitude (Asir) were analyzed over the last five years. The data was analyzed using IBM-SPSS version 27. (SPSS Inc., Chicago, IL). **Results:** Subclinical hypothyroidism was the common laboratory finding in all three regions. The overall mean value of TC, LDL-C and TG was significantly high ($p<0.05$) in the hypothyroidism group in all three regions. A significant positive correlation was observed between lipid profile, lipid ratio and TSH. However, there was a negative correlation between lipid profile, lipid ratio and FT4. On the other hand, HDL-C shows a weak but significant negative correlation with FT4. The risk of developing subclinical hypothyroidism was relatively low in the Asir region (high altitude). However, the risk of developing primary hypothyroidism and subclinical hyperthyroidism was significantly high in the Asir region (high altitudes). In the Najran region, the relative risk of developing subclinical hypothyroidism and primary hypothyroidism was high in comparison to sea level. **Conclusion:** The prevalence of subclinical hypothyroidism with High TC and high LDL-C follows the order: Najran>Jeddah (sea level)>Asir (high altitudes). However, the prevalence of subclinical hypothyroidism with high TG follows the order: Jeddah (sea level)>Najran>Asir (high altitudes). The risk for developing primary hypothyroidism and subclinical hyperthyroidism was high at high altitudes.

Keywords: Thyroid dysfunction, Lipid profile, Lipid ratio, High altitudes, Sea level, Hypothyroidism, Hyperthyroidism.

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INTRODUCTION

Nowadays, thyroid dysfunction is one of the most common chronic endocrine problems worldwide and hypothyroidism is the most prevalent among them. After diabetes mellitus, it is the second most pervasive endocrine disorder worldwide.[1] The production of thyroid hormones is predominantly affected by thyroid dysfunction. Thyroid dysfunction is associated with a wide range of generalized symptoms, such as weariness, dyspnea, constipation, obesity (weight gain), baldness, dry skin, cold intolerance and hoarseness of voice.[2]

Thyroid hormones influence key enzymes involved in cholesterol synthesis and metabolism.[3] Thyroid hormones activate 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) reductase, a key enzyme in the production of cholesterol.[2,4] Furthermore, thyroid hormones upregulate the activation of Low-Density Lipoprotein Cholesterol (LDL-C) cholesterol on receptor genes and control the expression of LDL-C receptors on the cellular surface for enhanced uptake of cholesterol.[3,4] Primary hypothyroidism is the most common prevalent thyroid problem and hypothyroid itself is characterized by a high level of serum Thyroid Stimulating Hormones (TSH) and low production of Thyroxine (T4) hormone.[5] Thus, hypothyroidism will result in

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reduced clearance of LDL-C.[2] In addition, hepatic lipase and lipoprotein lipase are stimulated by thyroid hormones. Hepatic lipase is responsible for the lysis of High-Density Lipoprotein Cholesterol (HDL-C) into intermediate-density lipoproteins, while lipoprotein lipase lyses Triglyceride (TG) into LDL.[6] Thus, hypothyroidism results in impaired lipid metabolism, decreased cholesterol clearance and increased blood cholesterol, LDL-C and TG; the opposite happens to HDL-C.[1] Hypothyroidism and dyslipidemia are well-known risk factors for cardiovascular disease. Thyroid hormones facilitate the stimulation of nitric oxide and promote vasodilation.[7] Hypothyroidism affects the cardiovascular system by decreasing cardiac output and increasing systemic vascular resistance as a result of decreased production of nitric oxide.[8] The renin-angiotensin-aldosterone system is also affected by the hypothyroidism and results in sodium sensitive diastolic hypertension.[9,10]

Exposure to high altitudes affects endocrine function, including thyroid hormones.[11] Thyroid function is affected by environmental factors such as high altitudes, temperature, radiation and oxygen saturation.[11,12] Previously it has been reported that habitats from high altitudes experienced elevated thyroid hormones.[11-13] Hyperthyroidism, caused by increased T4, is common in people living at high altitudes. In this study, we have attempted to compare the prevalence of thyroid dysfunction and its association with lipid profile among the Saudi population residing at different altitudes and to explore the effect of altitudes on thyroid status.

MATERIALS AND METHODS

This study was designed and conducted following the guidelines of the Helsinki principles. Ethical approval and subject consent waiver were obtained from the research ethics committee at King Khalid University (HAPO-06-B-001) (approval number ECM#2021-4405).

In this retrospective cross-sectional study, the lab reports were collected and screened over five years (2018-2022)) from the public, government hospital labs and the medical clinics serving chronic patients located in the Jeddah (Sea level), Najran (1293 m above the sea level) and Asir (2200 m above the sea level) region. Lab reports were screened for thyroid hormones and lipid profiles. Exclusion lab criteria were used to rule out any pre-existing medical problems. Laboratory reports with abnormal kidney, liver and pulmonary diseases were excluded from the study. Inclusion criteria consist of laboratory investigation with normal liver and kidney function values.

Statistical Analysis

The statistical analysis in this study was carried out using IBM® SPSS, version 27 (SPSS Inc., Chicago, USA). The categorical variables were analyzed using Chi-square ($\chi 2$) and the results were presented as frequency and percentage. The Kolmogorov-Smirnov test or Shapiro-Wilk test was employed to determine the normality of data. Student's *t*-test or Kruskal-Wallis test was used to analyze the difference between groups based on the normality report. A partial correlation test was used to examine the correlation between lipid profile and lipid ratio to thyroid hormones. Multiple regression analysis was used to predict lipid profile and lipid ratio association with thyroid hormones. Multinomial regression analysis was performed to analyze the risk of thyroid disorder at different altitudes.

RESULTS

General Characteristics and laboratory data of the study population are presented in Table 1. In the current investigation, a total of 79856 from Jeddah with 44147 (55.3%) females and 35709 (44.7%) males, 11237 from Najran with 6567 (58.4%) females and 4670 (41.6%) males and 15790 laboratory reports from Asir region with 8906 (56.4%) female and 6884 (43.6%) males were included in the final analysis. In all three regions, more than half were female. Gender was statistically significant ($p<0.001$) between the three regions. The mean age of the study subject from Jeddah was 43.53±16.39 years, from Najran were 40.83±15.69 years and the Asir region was 41.45±15.86 years, respectively. The mean age of the study population stratified by gender in three different regions is presented in Table 1. Age showed a statistically significant difference ($p=0.000$) between the region. The mean value of TC, LDL-C, TG, HDL-C, lipid ratio, TSH and FT4 shows a statistically significant difference ($p<0.05$) between the region.

The overall prevalence of subclinical hypothyroidism from the three regions was found to be 31% (33180), among which there was 16.9% ($n=18075$) female and 14.1% ($n=15105$) male. The overall prevalence of subclinical hyperthyroidism from three regions was found to be 0.6% ($n=648$), with 0.4% female ($n=380$) and 0.2% male ($n=268$). The overall prevalence of primary hypothyroidism in three regions was found to be 2.2% (2303), with 1.2% female ($n=1245$) and 1% male ($n=1058$). The overall prevalence of primary hyperthyroidism in all three regions was found to be 0.9% ($n=1013$), with 0.6% female ($n=615$) and 0.3% male ($n=398$). The overall prevalence of euthyroidism in all three regions was 65.5%, with 36.8% female ($n=39305$) and 285% male ($n=30434$).

The prevalence of thyroid disorders and euthyroidism in three different regions stratified by gender is presented in Table 2. The prevalence of subclinical hypothyroidism was significantly high ($p<0.01$) in all three regions. Overall, the prevalence of subclinical hypothyroidism was significantly high ($p<0.01$) among females in the male in Jeddah, Najran and Asir regions, respectively. The prevalence of subclinical hypothyroidism in the Jeddah region ($n=26426$) was 33.1%, $n=26426$ (17.7% female, $n=14171$ and 15.4% male, $n=12255$). The prevalence of subclinical hypothyroidism in the Najran region was 33.1%, $n=3723$ (19% female, $n=2139$ and 14.1% male, $n=1584$). The prevalence of

Table 1: General Characteristics and laboratory data of the study population.

Variables	Jeddah (*n*=79856)		Najran (*n*=11237)		Asir (*n*=15790)		*p**
Gender (n, %)	Female	Male	Female	Male	Female	Male	
Female	44147 (55.3%)	35709 (44.7%)	6567 (58.4%)	4670 (41.6%)	8906 (56.4%)	6884 (43.6%)	<0.001†
Age (years) Mean±SD)	42.42±16.07	44.92±16.67	39.95±14.99	42.07±16.54	40.56±15.32	42.59±16.46	0.000‡
TC (mg/dL) (mean±SD)	190.80±39.29	189.17±40.06	192.52±38.77	193.13±38.20	194.51±39.44	193.48±39.90	0.000‡
LDL-C (mg/dL) (mean±SD)	122.06±35.68	122.89±36.76	124.49±34.69	126.08±34.77	122.54±34.30	122.44±34.37	<0.001‡
TG (mg/dL) (mean±SD)	137.78±71.01	141.12±73.31	125.11±75.32	127.02±78.13	123.28±78.06	126.21±70.05	0.000‡
HDL-C (mg/dL) (mean±SD)	53.56±14.22	49.77±14.22	48.72±12.18	47.59±11.94	46.88±11.40	45.70±11.41	0.000‡
TC/HDL-C (mean±SD)	3.80±1.31	4.06±1.41	4.18±1.36	4.30±1.40	4.35±1.29	4.45±1.29	0.000‡
LDL-C/ HDL-C (mean±SD)	9.84±2.90	10.61±3.19	10.72±2.94	10.99±3.11	11.10±2.95	11.40±2.96	0.000‡
TG/HDL-C (mean±SD)	2.85±2.08	3.15±2.25	2.88±2.35	3.02±2.73	2.93±3.21	3.07±2.47	0.000‡
TSH (µIU/mL (mean±SD)	3.40±2.02	3.44±2.04	3.66±3.93	3.69±3.77	3.57±3.53	3.51±3.22	0.000‡
FT4 (ng/dL) (mean±SD)	1.01±0.22	1.01±0.20	1.01±1.63	1.01±0.15	0.91±0.30	0.90±0.31	0.000‡

Significant $p<0.05$, †Analyzed by Chi-square test, ‡ Analyzed by Kruskal-Wallis Test.

subclinical hypothyroidism in the Asir region was 19.2%, *n*=3031 (11.2% female, *n*=1765 and 8% male, *n*=1266). The prevalence of thyroid disorders and euthyroidism in three different regions stratified by age group is presented in Table 3. The overall prevalence of subclinical hypothyroidism was significantly high ($p=0.002$) in the age group of 21-40 years, followed by 41-60 years ($p=0.003$).

The mean value of lipid profile and lipid ratio among different thyroids groups stratified by three different regions is presented in Table 4.

The overall mean value of TC, LDL-C and TG was significantly high ($p<0.05$) in the hypothyroidism group (subclinical hypothyroidism and primary hypothyroidism compared to subclinical hyperthyroidism, primary hyperthyroidism and euthyroidism groups in all three regions. Furthermore, the mean value of TC and TG from all three-region in different thyroidism groups were statistically significant ($p<0.05$). The mean value of LDL-C in all three-region demonstrated a statistically significant difference ($p<0.05$) in all thyroid disorder groups except primary hyperthyroidism ($p=0.520$). A statistically significant difference ($p<0.05$) was observed in the mean value of LDL-C/HDL-C and TG/HDL-C ratio in thyroidism groups between the three regions. No significant difference was observed in the mean value of TC/HDL-C ratio in primary hyperthyroidism between the three regions. However, the mean value of TC/HDL-C ratio in subclinical hypothyroidism, subclinical hyperthyroidism, primary hypothyroidism and euthyroidism groups between the three regions was statistically significant ($p<0.05$).

Multiple regression analysis was used to predict lipid profile and lipid ratio association with thyroid hormones (Table 5).

With 1 µIU/mL level increase in TSH correlated with a 6.278 mg/dL increase in TC (B=6.278; 95% CI=6.189-6.367; $p=0.000$) and each one ng/dL increase in FT4, there is a decrease in TC of 1.374 mg/dL (B=-1.374, 95% CI=-2.342--0.406, $p=0.005$). For LDL-C, with 1 µIU/mL level increase in TSH correlated with a 6.501 mg/dL increase in LDL-C (B=6.501; 95% CI=6.423-6.578; $p=0.000$) and each one ng/dL increase in FT4, there is a decrease in LDL-C of 4.8 mg/dL (B=-4.8; 95%CI=-5.646--3.954; $p<0.001$). Similarly,

Table 2: Prevalence of thyroid disorder in three different regions stratified by gender.

	Jeddah (*n*=79856)		Najran (*n*=11237)		Asir (*n*=15790)		*p**
	Female (*n*=44147)	Male (*n*=35709)	Female (*n*=6567)	Male (*n*=4670)	Female (*n*=8906)	Male (*n*=6884)	
Subclinical Hypothyroidism (n, %)	14171 (17.7%)	12255 (15.4%)	2139 (19.0%)	1584 (14.1%)	1765 (11.2%)	1266 (8.0%)	<0.01†
Subclinical Hyperthyroidism (n, %)	66 (0.1%)	55 (0.1%)	146 (1.3%)	101 (0.9%)	168 (1.1%)	112 (0.7%)	0.585†
Primary Hypothyroidism (n, %)	185 (0.2%)	143 (0.2%)	52 (0.5%)	35 (0.3%)	1008 (6.4%)	880 (5.6%)	0.031†
Primary Hyperthyroidism (n, %)	528 (0.7%)	356 (0.4%)	65 (0.6%)	37 (0.3%)	22 (0.1%)	5 (0.01%)	0.60†
Euthyroidism (n, %)	29197 (36.6)	22900 (28.6%)	4165 (37.1%)	2913 (25.9%)	5943 (37.6%)	4621 (29.3%)	<0.01†

*Significant $p<0.05$, †Analyzed by Chi-square test.

1 µIU/mL level increase in TSH correlated with a 7.678 mg/dL level increase in TG (B=7.678; 95%CI=7.507-7.850; $p=0.000$) and each one ng/dL increase in FT4, there is a decrease in TG by 1.262 mg/dL (B=-1.262; 95%CI=-3.148--0.625; $p=0.190$). However, HDL-C shows a negative association with TSH and a positive association with FT4. One µIU/mL level increase in TSH correlated with a 0.127 mg/dL decrease in HDL-C (B=-0.127; 95%CI=-0.161--0.095; $p<0.001$) and each one ng/dL increase in FT4, there is an increase in 3.643 mg/dL of HDL-C (B=3.643; 95%CI=3.277-4.008; $p<0.001$). TSH level was also associated with elevated TC/HDL-C (B=0.141; 95%CI=0.138-0.144; $p=0.000$), LDL-C/HDL-C (B=0.014; 95%CI=(0.007-0.022; $p<0.001$) and TG/HDL-C (B=0.169; 95%CI=0.162-0.174; $p=0.000$) ratios. However, FT4 shows negative association with TC/HDL-C (B=-0.33; 95%CI=-0.37--0.30; $p<0.001$), LDL-C/HDL-C (B=-0.691; 95%CI=-0.773--0.609; $p<0.001$) and TG/HDL-C (B=-0.361; 95%CI=-0.422-- 0.300; <0.001) ratios.

Partial correlation was used to determine the correlation of lipid profile and lipid ratio to thyroid hormones in study subjects by controlling age, gender and height from sea level (Table 6). There is a significant positive correlation between TC (r=0.402); LDL-C (r=0.465); TG (r=0.269); TC/HDL ratio (r=0.271); LDL-C/HDL-ratio (r=0.020) and TG/HDL- ratio (r=0.191) with TSH. However, there is negative correlation between TC (r=-0.092); LDL-C (r=-0.132); TG (r=-0.073; TC/HDL-C ratio (r=--0.095); LDL-C/HDL-C ratio (r=-0.036); TG/HDL-ratio (r=0.075). On the other hand, HDL shows a weak but significant negative correlation (r=-0.033) with TSH and a positive correlation (r=0.045) with FT4 levels.

Multinomial regression analysis was performed to analyze the risk of thyroid disorder at different altitudes (Table 7). At high altitudes (Asir region), relative to sea level (Jeddah region), the relative risk for subclinical hypothyroidism compared to euthyroidism is expected to decrease by a factor of 0.566. For Najran Region ($p<0.001$), relative to sea level (Jeddah region), the relative risk for subclinical hypothyroidism compared to euthyroidism is expected to increase by a factor of 1.037 ($p=0.093$).

For subclinical hyperthyroidism at high altitudes (Asir region), relative to sea level (Jeddah region), the relative risk for subclinical hyperthyroidism compared to euthyroidism is expected to increase by a factor of 11.412 ($p<0.001$), for Najran region it was expected to increase by a factor of 15.025 ($p<0.001$).

For primary hypothyroidism, at high altitudes (Asir region), relative to sea level (Jeddah region), the relative risk for primary hypothyroidism compared to euthyroidism is expected to increase by a factor 28.387 ($p=0.001$), for Najran region it was expected to increase by a factor of 1.952 ($p<0.001$).

For primary hyperthyroidism, at high altitudes (Asir region), relative to sea level (Jeddah region), the relative risk for primary hyperthyroidism compared to euthyroidism is expected to decrease by a factor of 0.151 ($p<0.001$), for Najran region it was expected to decrease by a factor of 0.849 ($p=0.121$).

DISCUSSION

Saudi Arabia is a high-risk population concerning thyroid dysfunction and cardiovascular diseases and the numbers are steadily increasing.[5,14-16] This is a cross-sectional, retrospective study collecting data on lipid profiles and thyroid tests from

Table 3: Prevalence of thyroid disorder in three different regions stratified by age group.

Region		Thyroidism					
		Subclinical Hypothyroidism	Subclinical Hyperthyroidism	Primary Hypothyroidism	Primary Hyperthyroidism	Euthyroidism	*p*-value*
Jeddah	Below 20	1506 (1.9%)	10 (0.013%)	12 (0.01%)	49 (0.06%)	3073 (3.8%)	0.300
	21-40	11141 (14.0%)	43 (0.1%)	140 (0.2%)	348 (0.4%)	22162 (27.8%)	<0.001
	41-60	10056 (12.6%)	53 (0.1%)	126 (0.2%)	300 (0.4%)	18074 (22.6%)	0.010
	Above 60	3723 (4.7%)	15 (0.01%)	50 (0.1%)	187 (0.2%)	8788 (11.0%)	<0.001
Najran	Below 20	26 (2.4%)7	18 (0.2%)	3 (0.03%)	5 (0.04%)	544 (4.8%)	0.054
	21-40	1781 (15.8%)	111 (1.0%)	47 (0.4%)	54 (0.5%)	3410 (30.3%)	0.845
	41-60	1238 (11.0%)	92 (0.8%)	30 (0.3%)	37 (0.32%)	2310 (20.6%)	0.191
	Above 60	437 (3.9%)	26 (0.2%)	7 (0.1%)	6 (0.1%)	814 (7.2%)	0.960
Asir	Below 20	231 (1.5%)	19 (0.1%)	136 (0.9%)	1 (0.01%)	717 (4.5%	0.099
	21-40	1514 (9.6%)	121 (0.8%)	813 (5.1%)	14 (0.1%)	4881 (30.9%)	0.586
	41-60	975 (6.2%)	104 (0.7%)	672 (4.3%)	7 (0.04%)	3645 (23.1%)	0.058
	Above 60	311 (2.0%)	36 (0.2%)	267 (1.7%)	5 (0.03%)	1321 (8.4%)	<0.001
Total	Below 20	2004 (1.9%)	47 (0.04%)	151 (0.1%)	55 (0.1%)	4334 (4.1%)	0.028
	21-40	14436 (13.5%)	275 (0.3%)	1000 (0.9%)	416 (0.4%)	30453 (28.5%)	0.002
	41-60	12269 (11.5%)	249 (0.2%)	828 (0.8%)	344 (0.3%)	24029 (22.5%)	0.003
	Above 60	4471 (4.2%)	77 (0.1%)	324 (0.3%)	198 (0.2%)	10923 (10.2%)	<0.001

*Significant $p<0.05$, †Analyzed by Chi-square test.

public labs in Jeddah, Najran and Asir, three Saudi Arabian cities located at sea level, 1293 meters and 2200 meters above sea level, respectively. The overall prevalence of thyroid dysfunction was significantly high ($p<0.001$) in the Najran region (37.0%), followed by Jeddah (34.8%), then the Asir region (33.1%). In the Jeddah region, the prevalence of subclinical hypothyroidism was significantly high in the age group of 21-40 (14.0%) years, followed by 41-60 years (12.6%). In the Najran region, it was 15.8% for 21-40 years and 11% for 41-60 years. In the Asir region, the prevalence of subclinical hypothyroidism was 9.6% for the 21-40 age group and 6.2% for the 41-60 age group. Furthermore, subclinical hypothyroidism was significantly high ($p<0.01$) in females in all regions (Table 2) compared to males (with female to male ratio: 1.23:1 in Jeddah, 1.4:1 in Najran and 1.29:1 in Asir region. Our results are in agreement with other recent reports.[17] Al Jabri and colleague. (2019), in their investigation, reported the case of hypothyroidism in 85.7% of females and 14.3% of males ($p<0.0001$) with male to female ratio of 1 to 6.[15] Similarly, Alqahtiani and colleague reported that 18.7% of the study population had hypothyroidism, most of whom (86.3%) were females.[16]

Another crucial part of the current study is the lipid profiles evaluation which showed a mean value of TC, LDL-C and TG and lipid ratio were significantly high ($p<0.05$) in the hypothyroidism group (both subclinical hypothyroidism and primary hypothyroidism) compared to euthyroid and hyperthyroidism groups (both subclinical hyperthyroidism and primary hyperthyroidism). Subsequently, high TC, LDL-C and TG prevalence were significantly high in subclinical hypothyroidism, followed by primary hypothyroidism in all studied regions (among the thyroid dysfunction group).

In our study, the mean cholesterol level in the subclinical hypothyroidism group was 213.10±37.28 mg/dL, 222.12±34.44 mg/dL and 230.20±37.15 mg/dL in Jeddah, Najran and Asir region, respectively ($p=0.000$), while in primary hypothyroidism group, it was 226.62±40.34 mg/dL; 213.01±45.87 mg/dL; 209.99±41.83 mg/dL in Jeddah, Najran and Asir region, respectively ($p=0.001$). Our results are in agreement with the other studies. Desai and

Table 4: Mean±SD of lipid profile in thyroid disorder group stratified by three different region.

Lipid profile	Thyroid dysfunction	Jeddah	Najran	Asir	*p**
TC (mg/dL) (mean±SD)	Subclinical Hypothyroidism	213.10±37.28	222.12±34.44	230.20±37.15	0.000 ‡
	Subclinical Hyperthyroidism	166.07±27.76	186.88±36.47	194.75±15.06	0.000 ‡
	Primary Hypothyroidism	226.62±40.34	213.01±45.87	209.99±41.83	0.001 ‡
	Primary Hyperthyroidism	181.36±41.08	179.19±41.29	155.11±31.54	0.007 ‡
	Euthyroidism	178.37±35.31	177.49±30.68	180.93±32.18	0.000‡
LDL-C (mg/dL) (mean±SD)	Subclinical hypothyroidism	145.69±33.71	153.25±30.25	159.70±22.19	0.000‡
	Subclinical Hyperthyroidism	100.12±20.85	119.90±32.68	110.18±30.93	<0.001‡
	Primary Hypothyroidism	154.91±35.78	143.19±38.20	160.77±26.78	<0.001‡
	Primary Hyperthyroidism	112.37±36.08	111.50±36.46	101.45±33.71	0.520‡
	Euthyroidism	110.65±31.23	110.53±22.51	105.36±22.51	0.000‡
TG (mg/dL) (mean±SD)	Subclinical hypothyroidism	176.78±73.27	156.79±68.39	107.37±62.82	0.000‡
	Subclinical Hyperthyroidism	97.47±21.82	125.76±63.69	116.80±55.93	0.002‡
	Primary Hypothyroidism	175.70±75.38	140.73±66.50	206.54±79.65	0.000‡
	Primary Hyperthyroidism	154.27±69.24	144.34±71.41	122.92±47.52	<0.001‡
	Euthyroidism	119.87±636.36	109.21±73.69	115.05±67.87	0.000‡
HDL-C	Subclinical hypothyroidism	51.06±13.65	46.03±10.73	51.32±12.33	0.000‡
	Subclinical Hyperthyroidism	51.04±12.94	47.84±12.58	45.71±11.70	<0.001‡
	Primary Hypothyroidism	50.91±14.18	48.39±12.53	40.78±9.74	0.000‡
	Primary Hyperthyroidism	51.42±15.21	47.25±15.35	45.37±10.80	0.003‡
	Euthyroidism	52.29±14.29	49.45±12.53	45.96±10.85	0.000‡
TC/HDL-C (mean±SD)	Subclinical hypothyroidism	4.44±1.38	5.06±1.37	4.75±1.48	0.000‡
	Subclinical Hyperthyroidism	3.39±0.82	4.14±1.26	4.55±1.29	0.000‡
	Primary Hypothyroidism	4.78±1.56	4.64±1.35	5.35±1.41	<0.001‡
	Primary Hyperthyroidism	3.80±1.52	4.16±1.96	3.50±0.83	0.188‡
	Euthyroidism	3.64±1.27	3.79±1.15	4.12±1.10	0.000‡
LDL-C/HDL-C (mean±SD)	Subclinical hypothyroidism	10.28±2.83	11.22±2.72	4.75±1.48	0.000‡
	Subclinical Hyperthyroidism	10.37±3.53	10.97±2.96	11.48±3.26	<0.001‡
	Primary Hypothyroidism	10.43±3.16	10.82±2.90	12.69±3.06	0.000‡
	Primary Hyperthyroidism	10.52±4.03	11.55±4.25	11.46±3.05	0.003‡
	Euthyroidism	10.13±3.14	10.61±3.12	11.27±2.82	0.000‡

Lipid profile	Thyroid dysfunction	Jeddah	Najran	Asir	*p**
TG/HDL-C (mean±SD)	Subclinical hypothyroidism	3.79±2.23	3.71±2.35	2.27±1.71	0.000‡
	Subclinical Hyperthyroidism	2.06±0.81	2.94±2.11	2.84±2.50	<0.001‡
	Primary Hypothyroidism	3.87±2.31	3.29±2.28	5.51±3.25	0.000‡
	Primary Hyperthyroidism	3.37±2.35	4.01±7.51	2.92±1.51	0.004‡
	Euthyroidism	2.57±2.01	2.51±2.37	2.75±2.91	0.000‡

Table 5: **Multiple regression analysis to predict the association of lipid profile and lipid ratio with thyroid hormones.**

Dependent variables	Independent variables			
	TSH		FT4	
	B (95%CI	*p*	B (95%CI	*p*
TC	6.278 (6.189-6.367)	0.000	-1.374 (-2.342--0.406	0.005
LDL-C	6.501 (6.423-6.578)	0.000	-4.800 (-5.646--3.954)	<0.001
TG	7.678 (7.507-7.850)	0.000	-1.262 (-3.148--0.625)	0.190
HDL-C	-0.127 (-0.161--0.095)	<0.001	3.643 (3.277-4.008)	<0.001
TC/HDL-C	0.141 (0.138-0.144)	0.000	-0.33 (-0.37--0.30)	<0.001
LDL-C/HDL-C	0.014 (0.007-0.022)	<0.001	-0.691 (-0.773--0.609)	<0.001
TG/HDL-C	0.169 (0.163-0.174)	0.000	-0.361 (-0.422-- 0.300)	<0.001

*Significant $p<0.05$; ‡Analyzed by Kruskal-Wallis Test.

Table 6: **Partial correlation by controlling the age, gender and height from sea level.**

Variables	TSH		FT4	
	Correlation (r)	*p*	Correlation (r)	*p*
TC	0.402	0.000	-0.092	0.000
HDL-C	-0.033	0.000	0.045	0.000
LDL-C	0.465	0.000	-0.132	0.000
TG	0.269	0.000	-0.073	0.000
TC/HDL-C ratio	0.271	0.000	-0.095	0.000
LDL-C/HDL-C ratio	0.020	0.000	-0.036	0.000
TG/HDL-C ratio	0.191	0.000	-0.075	0.000

Table 7: **Risk analysis for thyroid disorder.**

Thyroid disorder	Region	B	Exp(B)	95%CI	*p*-value
Subclinical Hypothyroidism	Asir	-0.570	0.566	0.542-0.590	<0.001
	Najran	0.036	1.037	0.994-1.082	0.093
Subclinical Hyperthyroidism	Asir	2.435	11.412	9.211-14.139	<0.001
	Najran	2.710	15.025	12.071-18.702	<0.001
Primary hypothyroidism	Asir	3.346	28.387	25.199-31.977	0.000
	Najran	0.669	1.952	1.539-2.476	<0.001
Primary hyperthyroidism	Asir	-1.893	0.151	0.103-0.221	<0.001
	Najran	0.163	0.849	0.691-1.044	0.121

colleague.[18] reported a mean TC value of 241.96±32.24 mg/dL. Hueston and colleague.[19] found a mean total TC value of 226±44.2 mg/dL in the subclinical hypothyroidism group. Jiffri and colleague.[20] reported a mean TC value of 232.64±37.15 mg/dL in patients with hypothyroid function in the Jeddah region.

In the current investigation, the mean LDL-C value in the case with subclinical hypothyroidism was 145.69±33.71 mg/dL, 153.25±30.25 mg/dL and 159.70±22.19 (p=0.000) in Jeddah, Najran and Asir region, respectively, while in primary hypothyroidism group, it was found to be 154.91±35.78 mg/dL; 143.19±38.20 mg/dL and 160.77±26.78 mg/dL (p<0.001) in Jeddah, Najran and Asir region respectively. Our results are consistent with other investigations in Saudi Arabia and other parts of the world. For example, Jiffri and colleague.[20] reported a mean LDL-C of 165.19±28.3 mg/dL (p<0.05) in patients with low thyroid dysfunction in Jeddah. Similarly, Desai and colleague reported a mean LDL-C of 157.71±30.60 mg/dL (p<0.001) in the hypothyroidism group.[18] In another study, Ghosh and colleague reported the mean total LDL-C of 208.69±1.665 mg/dL in the subclinical hypothyroidism group.[21]

In this study, the mean total TG level in a case with subclinical hypothyroidism was 176.78±73.27 mg/dL; 156.79±68.39 mg/dL and 107.37±62.82 (p=0.000) from Jeddah, Najran and Asir region, respectively. In the primary hypothyroidism group, it was found to be 175.70±75.38 mg/dL, 140.73±66.50 mg/dL and 206.54±79.65 mg/dL (p=0.000) from Jeddah, Najran and Asir region, respectively. Jiffri and colleague.[20] reported a mean value of 179.45±32.16 mg/dL in the hypothyroidism group from the Jeddah region. Similarly, Desai and colleague reported a mean TG value of 155.18±39.22 mg/dL in the hypothyroidism group.[18] In another study, Hueston and colleague found a total mean TG value of 178.1±99.7 mg/dL in patients with subclinical hypothyroidism.[19]

In our study, the prevalence of subclinical hypothyroidism with High TC was significantly high in Najran (25.9%, n=2908) followed by Jeddah (22.2%, n=17736 and Asir (19.2%, n=3031) region respectively (p=0.000). The same pattern was observed with the prevalence of subclinical hypothyroidism with a high value of LDL-C among all three regions. However, the prevalence of subclinical hypothyroidism with high TG was significantly high in the Jeddah region (22.5%, n=17932), followed by Najran (14.6%, n=1636), then Asir (6.1%, n=967) region. We also observed the high prevalence of primary hypothyroidism with high TG from the Asir region (11.3%, n=1790). Qasim and colleague[22] reported that dyslipidemia was much more prevalent in patients with subclinical hypothyroidism. Similarly, Mensfield and colleague reported that median TC, LDL-C and TG were higher in hypothyroid patients (p<0.01).[2] Alarcon-Gonzalez and colleague found 96.1% of the patients with dyslipidemia in the subclinical hypothyroidism group compared to 87.3% in the control group.[23] Similarly, many studies have documented the association between thyroid disorder and dyslipidemia.[24-28]

Our findings suggest that imbalanced TSH and FT4 levels are independent risk factors for dyslipidemia in study subjects. Our results agree with similar studies conducted in Saudi Arabia and other parts of the world.[8,20,29,30] A retrospective case-control study suggests hypothyroidism was associated with greater cardiovascular risk based on TC/HDL-C ratio. Desai and colleague found an association between hypothyroidism with dyslipidemia.[18] Suggesting a possible association with an increased risk of coronary artery disease. Furthermore, a case-control study by Alarcon-Gonzalez showed that hypothyroidism is a risk factor for developing dyslipidemia.[23]

Similarly, Tawfik and colleague.[31] reported that increased levels of TSH have been associated with rises in TC, LDL-C and TG. Recently, Gao and colleague[32] reported that subclinical hypothyroidism directly correlates with the level of TSH and the risk of hyper triglyceridemic significantly increases with the rise in TSH level itself. Another study reported an increase in TC and a decrease in HDL-C in hypothyroidism patients.[1] Similarly, Rastgooye Haghi *et al.*[33] reported that subclinical hypothyroidism had a significant positive correlation with LDL-C.

Many physiological processes, including heart rate, lipid metabolism and cardiovascular physiology, are regulated by thyroid hormones.[8] Increased levels of thyroid hormones are associated with changes in lipid metabolism, including elevated levels of free fatty acids and increased synthesis and utilization of TGs.[8] Thyroid hormones also influence HDL-C metabolism by increasing the activity of cholesteryl ester transfer protein.[34] Furthermore, thyroid hormones promote vasodilation by increasing nitric oxide synthesis.[7] Due to decreased nitric oxide production, hypothyroidism impacts the cardiovascular system by lowering cardiac output and raising systemic vascular resistance.[8]

Hypothyroidism is associated with elevated TC, LDL-C and TG serum levels. Thyroid hormone influences lipid production, clearance and transformation, but a new study indicates that TSH also plays a critical role in lipid metabolism independently of thyroid hormones.[35] Furthermore, dyslipidemia in hypothyroidism has been linked to a number of recently identified regulatory factors, like proprotein convertase subtilisin/kexin type 9, angiogenin-related proteins and fibroblast growth factors.[36,37] Hypothyroidism is commonly associated with obesity, decreased basal metabolic rate, thermogenesis and higher body mass index.[38] Thus, biochemical testing for thyroid dysfunction should be performed on all patients with dyslipidemia whose lipid profile changes unexpectedly or worsens. In this circumstance, underlying thyroid problems should be identified and addressed. Various factors, including wind, temperature and radiation, may influence specific endocrine parameters at high

altitudes. It has been reported that temperature, environment and altitude significantly impact the thyroid glands function and the production of thyroid hormones.[39] In our study, risk analysis using multinomial regression analysis, we observed the effect of altitudes on the risk of developing a thyroid disorder. At high altitudes (Asir region), the risk for subclinical hypothyroidism was relatively low compared to the sea level. However, the risk of developing subclinical hyperthyroidism was significantly high in the Asir region (High altitudes). In the Najran region, the relative risk of developing subclinical hypothyroidism and primary hypothyroidism was high compared to sea level. At high altitudes, hyperthyroidism is a common phenomenon to withstand hypoxia. Since thyroid hormone stimulates the RBC to release 2,3-diphosphoglycerate, which is responsible for releasing oxygen to the tissue.[40]

CONCLUSION

The thyroid hormone is one of the known critical factors influencing lipid metabolism and its utilization. Hypothyroidism associated with dyslipidemia is a well-known independent risk factor for the development of cardiovascular disease. A strong correlation was observed between hypothyroidism and lipid profiles. Hypothyroidism is positively associated with TC, LDL-C and TG in the Saudi population. Hypothyroidism generally tends to increase the LDL-C, TG and TC levels because the regulating factors counterbalance each other, while the HDL-C level is compromised. The mean value of TC, LDL-C and TG and lipid ratio were significantly high in the hypothyroidism group (subclinical hypothyroidism and primary hypothyroidism) compared to the euthyroid and hyperthyroidism groups in all three regions. In our study, the overall thyroid dysfunction was significantly high in the Najran region, followed by Jeddah and Asir regions. Furthermore, subclinical hypothyroidism in all regions was significantly higher in females than males. Here, we observed the different types of association between hypothyroidism and lipid profiles among the people living at different altitudes, for example, the prevalence of subclinical hypothyroidism with High TC and high LDL-C follow the order: Najran>Jeddah (sea level)>Asir (high altitudes). However, the prevalence of subclinical hypothyroidism with high TG follows the order: Jeddah (sea level)> Najran>Asir (high altitudes).

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ABBREVIATIONS

LDL-C: Low-Density Lipoprotein Cholesterol; **HDL-C:** High-Density Lipoprotein Cholesterol; **TG:** Triglyceride.

ETHICAL APPROVAL

Ethical approval and subject consent waiver were obtained from the research ethics committee at King Khalid University (HAPO-06-B-001) (approval number ECM#2021-4405).

SUMMARY

The thyroid hormone plays a crucial role in influencing lipid metabolism and utilization. Hypothyroidism, characterized by insufficient thyroid hormone levels, is a recognized independent risk factor for cardiovascular disease due to its association with abnormal lipid profiles. Studies have shown a significant positive correlation between hypothyroidism and levels of Total Cholesterol (TC), Low-Density Lipoprotein Cholesterol (LDL-C) and Triglycerides (TG) in the Saudi population. Hypothyroidism tends to elevate levels of LDL-C, TG and TC, as the regulatory mechanisms involved counterbalance each other, leading to compromised levels of High-Density Lipoprotein Cholesterol (HDL-C). In a comprehensive analysis, it was observed that individuals with hypothyroidism, including both subclinical and primary hypothyroidism, exhibited significantly higher mean values of TC, LDL-C, TG and lipid ratios compared to those with euthyroidism or hyperthyroidism across all three regions studied. The prevalence of thyroid dysfunction was found to be highest in the Najran region, followed by Jeddah and Asir regions. Additionally, subclinical hypothyroidism was more prevalent in females than males across all regions. Interestingly, the study revealed distinct associations between hypothyroidism and lipid profiles in populations residing at different altitudes. For instance, the prevalence of subclinical hypothyroidism with elevated TC and LDL-C followed the order: Najran>Jeddah (sea level)>Asir (high altitudes). In contrast, the prevalence of subclinical hypothyroidism with high TG levels followed a different order: Jeddah (sea level)>Najran>Asir (high altitudes). These findings highlight the complex interplay between thyroid function and lipid metabolism, influenced by both geographical factors and gender disparities.

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