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Dyslipidemia in South African patients with hypothyroidism

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ABSTRACT

Background: Overt hypothyroidism leads to increased cardiovascular risk, primarily through effects the disorder has on lipids. Most studies investigating lipids in the setting of hypothyroidism, have been performed in predominantly Caucasians in North America and Europe. Different patterns and prevalence of dyslipidemia have been described; one study reporting dyslipidemia in 90% of patients with hypothyroidism. The prevalence of dyslipidemia in overt hypothyroidism among the ethnically diverse predominantly black South African population is unknown.

Methodology: A retrospective case-control study evaluating lipid profiles of an ethnically diverse cohort of patients with overt hypothyroidism (TSH > 10 mIU/L) attending two academic hospitals in Johannesburg, South Africa from September 2006–September 2016. Patients with primary or secondary causes for dyslipidemia and those taking lipid-lowering therapy were excluded.

Results: Two hundred and six patients with hypothyroidism were included and compared to 412 euthyroid controls matched for sex, ethnicity, and age. Most hypothyroid patients were female (n = 180;67.5 %). Median TSH was similar across all ethnic groups (p = 0.09). Median TC, TG and LDL-C were higher in hypothyroid patients (p < 0.01). Normal lipid profiles were found in 29.44 % of all hypothyroid patients. However, a greater proportion, 47 of 124 (37.90 %), black African patients with hypothyroidism had a normal lipid profile.

Conclusion: Dyslipidemia is less common in black African patients with hypothyroidism. This is probably due to this population group being in an earlier stage of epidemiologic transition. Those with hypothyroidism were at greater overall cardiovascular risk based on TC/HDL-C ratio but did not reach high risk atherogenic profiles reported in previous studies.

Introduction

Hypothyroidism is the disease state in which there is a deficiency of thyroid hormone or a failure of its action [1,2]. This leads to a variety of non-specific symptoms and signs such as tiredness, dyspnoea, constipation, weight gain, hair loss, dry skin, intolerance to cold and hoarseness of voice [1,3]. As a result, a high index of suspicion is required to make the diagnosis, which is confirmed on biochemical tests [1] . The manifestations of hypothyroidism range from asymptomatic to potentially life-threatening as in the setting of myxoedema coma [1].

Hypothyroidism is common; however, prevalence estimates vary depending on the population being studied. The EPIC-Norfolk study recruited 13 076 participants in the Norfolk region of the UK and reported overt hypothyroidism (defined by a TSH greater than 4 mIU/L and FT4<9 pmol/L) in 0.9 % of men and 2.5 % of women [4]. The National Health and Nutrition Examination Survey (NHANES III) and the Colorado Thyroid Disease Prevalence Study, two large epidemiological studies in the USA, noted overt hypothyroidism in 0.3 % and 0.4 % of the surveyed population respectively [5,6]. Madariaga *et al.* (2014) carried out a *meta*-analysis of seven epidemiological studies performed across Europe [7]. The authors reported prevalence estimates of 4.9 % for hypothyroidism, with 0.8 % of females and 0.3 % of males having overt hypothyroidism [7].

The NHANES study demonstrated ethnic differences in the prevalence of hypothyroidism, with African Americans having a lower prevalence than their Caucasian counterparts [5,8]. A study in Brazil also found a lower prevalence of the disease among black people and showed that mixed-race individuals had an intermediate prevalence [9]. Age

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and sex differences are also well described with hypothyroidism being more common among females [4,5]. Serum TSH tends to rise with age and overt hypothyroidism is more commonly seen in older individuals [5,10].

More than 95 % of cases of hypothyroidism are due to primary hypothyroidism, that is, failure of the thyroid gland to produce thyroid hormone [1]. Common causes for primary hypothyroidism include autoimmune thyroiditis (Hashimoto's thyroiditis), iatrogenic causes (radioactive iodine ablation, thyroidectomy and irradiation to the head and neck) and iodine deficiency or excess (such as amiodarone use) [1]. Rarer causes include infiltrative disorders such as malignancies, haemochromatosis, sarcoidosis and infections [1]. Secondary hypothyroidism (failure of the anterior pituitary to secrete sufficient TSH) and tertiary hypothyroidism (failure of the hypothalamus to secrete thyrotropin-releasing hormone) are uncommon causes [1]. Hypothyroidism due to thyroid hormone resistant states are very rare [2].

Reference ranges for TSH are controversial, but it is generally accepted that a TSH value greater than 10 mIU/L warrants treatment with levothyroxine, particularly in symptomatic patients under the age of 65 years [11–13].

The risk for cardiovascular disease in hypothyroidism have been ascribed to the effects that the disorder has on cardiovascular hemodynamics as well as contributions to the development of atherosclerotic cardiovascular disease as a result of the dyslipidemia that occurs with hypothyroidism [14]. Hypothyroidism leads to a rise in diastolic blood pressure, and a reduction in both heart rate and cardiac output [1,14]. Insulin resistance and oxidative stress are also induced by hypothyroidism and may contribute to increased cardiovascular risk [14]. Furthermore, the dyslipidemia per se has been implicated in the development of insulin resistance and oxidative stress [14].

Abnormalities in lipid profiles among patients with overt hypothyroidism have been well described. A study at the Mayo Clinic noted abnormalities in more than 90 % of 295 patients with overt hypothyroidism [15]. Different patterns have been reported, with raised total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) predominating [15,16]. Triglycerides (TG) may also be elevated [15–17]. High density lipoprotein cholesterol (HDL-C) may be normal, high or low [15,18,19]. The Colorado Thyroid Disease Prevalence Study demonstrated that serum TC and LDL-C levels increase in direct proportion to the severity of hypothyroidism [6].

The wide range of effects that thyroid hormones have on metabolism is probably responsible for the lipid abnormalities seen with hypothyroidism [18]. Thyroid hormones play a role in the activity of important enzymes in the cholesterol synthesis and metabolism pathway [16,18,20]. One of the first enzymes in the cholesterol synthesis pathway, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, is induced by thyroid hormones [16,18]. Thus, in the setting of hypothyroidism, the synthesis of cholesterol is impaired [16].

However thyroid hormones, specifically triiodothyronine (T3), upregulate low density lipoprotein receptors expressed on the cell surface in the liver, by controlling LDL receptor gene activation [16,18,20]. This leads to an increase in the uptake of LDL-C [20]. As a result, hypothyroidism will cause a reduction in the clearance of LDL-C from the circulation [16]. While cholesterol synthesis in the liver may be impaired, the disproportionate effect of thyroid hormones on LDL receptor function leads to a rise in serum TC and LDL-C [16]. Lipoprotein lipase (LPL) and hepatic lipase (HL) are both activated by thyroid hormones [20]. LPL hydrolyses TG into very low density lipoproteins while HL breaks down HDL-C and intermediate density lipoproteins [20]. Smoking may also exacerbate the lipid abnormalities in patients with hypothyroidism by impairing the action of thyroid hormones [21].

Lipid abnormalities improve following replacement with thyroxine [18,22]. The Basel Thyroid Study showed that thyroid hormone replacement therapy in patients with subclinical hypothyroidism had a beneficial effect on serum cholesterol and, in particular, LDL-C when TSH was greater than 12 mIU/L [23]. The authors estimated a 9–31 % decrease in risk related to cardiovascular mortality as a direct result of this LDL-C lowering [23].

No study has investigated the effects of overt hypothyroidism on serum lipids in black African individuals. Most studies have been performed in the USA, the United Kingdom and Europe and have characterized dyslipidemia in predominantly Caucasian patients with overt hypothyroidism [4,6,15,24,25]. The aim of this study is to describe the prevalence of dyslipidemia among an ethnically diverse group of hypothyroid South African patients as compared to euthyroid controls.

Methods

This retrospective case-control study involved patients attending two large tertiary academic hospitals in Johannesburg, South Africa, namely the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and the Chris Hani Baragwanath Academic Hospital (CHBAH).

Definitions

Euthyroidism was defined as a serum TSH between 0.35 and 4 mIU/L. Overt hypothyroidism was defined as a thyroid stimulating hormone (TSH) above the normal reference range and a free thyroxine (FT4) below the lower limit of the normal reference range (reference range 12–22 pmol/L). In the setting of overt hypothyroidism, the TSH value is usually greater than 10 mIU/L. For the purpose of this study hypercholesterolemia was defined as a TC $\geq$ 5 mmol/L; hypertriglyceridemia as a TG $\geq$ 1.7 mmol/L; and a raised LDL-C as $\geq$ 3 mmol/L.

Inclusion and exclusion criteria

Adults over the age of 18 years visiting either CMJAH or CHBAH between 1 September 2006 and 1 September 2016 and who had a lipogram done within one month of a TSH greater than 10 mIU/L were considered eligible for the study. Age, gender, ethnicity, TSH and FT4 values and the corresponding lipograms (TC, TG, HDL-C and LDL-C calculated using the Friedewald formula[26]) of eligible participants were recorded.

Euthyroid controls were randomly selected from patients attending CMJAH during the period 2014 – September 2016 and were matched for gender, ethnicity, and age. Two control cases were selected for each case of hypothyroidism. Euthyroid individuals known to have a history of thyroid disease were excluded.

Those with additional, known secondary causes for dyslipidemia, namely diabetes mellitus, chronic kidney disease, nephrotic syndrome, Cushing's syndrome and cholestatic liver disease, were excluded. Patients known to have familial hypercholesterolemia were also excluded. In addition, those taking lipid-lowering therapy, such as statins, ezetimibe or fibrates were excluded. Concomitant medications which may lead to an increase in serum lipids were recorded. Fasting and non-fasting states were not considered as it was not likely to have a meaningful effect on serum lipids [27,28].

Data analysis

Data was analysed using IBM® SPSS® Statistics Version 23. Standard descriptive statistics (mean, median, range and standard deviation) were used to describe the groups and differences between the groups were highlighted. Age, gender, and ethnic differences were compared. A Shapiro-Wilk test found TSH, FT4, TC, TG, HDL-C and LDL-C values to follow a non-normal distribution. Thus, median values, and interquartile ranges (IQR) were reported for these variables. The Mann-Whitney *U* test was used to determine differences between the two groups.

Correlation coefficients between lipid fractions (TC, TG, HDL-C and LDL-C) and TSH and FT4 were determined. A p-value < 0.05 was regarded as statistically significant.

Ethical considerations

Approval to conduct the study was obtained from the University of the Witwatersrand's Human Research Ethics Committee (clearance certificate no. M161111). Institutional approval was obtained from the hospital management of CMJAH and the Medical Advisory Committee at CHBAH.

Results

Two hundred and six patients with hypothyroidism, 87.4% females (n = 180) and 12.6% males (n = 26), were deemed eligible for inclusion in the study. Black African patients comprised 67.5% (n = 139), with Caucasians (20.4%), Indians (8.3%) and mixed-race individuals (3.9%) making up the remainder –Table 1. All cases of hypothyroidism were due to primary hypothyroidism. Four hundred and twelve euthyroid controls, matched for ethnicity, gender and age range, were deemed eligible.

Of the 206 patients with hypothyroidism, 65 (31.6%) had hypothyroidism due to an iatrogenic cause. Fifty-one patients received radioactive iodine ablation for Graves' disease, 13 had a thyroidectomy and one patient had undergone radiation to the head and neck. The remaining 141 (68.4%) patients were presumed to have hypothyroidism due to autoimmune thyroid disease.

Overall, patients with hypothyroidism had a median TSH of 22.84 mIU/L (13.55–47.69) and median T4 of 9.9 pmol/L (7.15–12.2). There was no difference in TSH between males and females (p = 0.79). Black African patients had a higher median TSH of 24.97 mIU/L (14.14–49.48) as compared to Caucasian patients who had a median TSH of 17.27 mIU/L (12.90–35.60). However, this difference was not statistically significant (p = 0.11). Thyroid function tests for the euthyroid control group and the group with hypothyroidism as they pertain to ethnicity and gender are shown in Table 2.

Median TC, TG and LDL-C levels were greater in all patients with hypothyroidism (p < 0.01). HDL-C was not different between euthyroid and hypothyroid states (p = 0.70). Overall, 32.04% (n = 66) of patients with hypothyroidism had an isolated raised TC, 20.30% (n = 40) had both a raised TC and TG and 10.15% (n = 20) had an isolated hypertriglyceridemia. A normal lipid profile was identified in 29.44% (n = 58) of all patients with hypothyroidism.

Table 1
Demographic and biochemical characteristics of subjects with euthyroidism and hypothyroidism.

	Euthyroidism	Hypothyroidism
Age in years (mean, SD)	54.2 ± 15.9	54.5 ± 15.7
Sex (n, %)	360	180
Female	(87.4)52	(87.4)26
Male	(12.6)	(12.6)
Ethnicity (n, %)	278	139
Black African	(67.5)84	(67.5)42
Caucasian	(20.4)34	(20.4)17
Indian	(8.3)16	(8.3)8
Mixed-race	(3.9)	(3.9)
Thyroid function (median, IQR)	1.65	22.84 (13.54 – 47.69)
TSH	(1.13 – 2.34)13.60	**9.90 (7.15 – 12.2)
FT4	(12.10 – 15.35)	**
Lipogram (median, IQR)	4.56	5.10
TC	(3.98–5.23)1.11	(4.30–6.05)**1.27
TG	(0.81–1.53)1.32	(0.95–1.82)**1.40
HDL-C	(1.08–1.63)2.63	(1.11–1.63)2.97
LDL-C	(2.04–3.16)	(2.32–3.68)**

Data are presented as median and interquartile range; and as percentages (%). *p < 0.05 as compared to euthyroid control **p < 0.01 as compared to euthyroid control

Among black African individuals with hypothyroidism, TC, TG and LDL-C were higher than in their euthyroid counterparts (p < 0.05). HDL-C was not different between the two groups (p = 0.23). Sixty-eight (48.92%) patients had a TC ≥ 5 mmol/L, 25 (18.94%) had both a TC ≥ 5 mmol/L and a TG ≥ 1.70 mmol/L, while 10 (7.58 %) had a raised TG alone. LDL-C ≥ 3 mmol/L was observed in 59 (47.58%) patients. A normal lipogram was seen in 47 of 124 (37.90%) black African patients with hypothyroidism, while normal lipograms were seen in 163 (58.63%) of the euthyroid black African control subjects. Interestingly Black male patients with hypothyroidism (n = 16) had lipids not dissimilar from black male controls with euthyroidism (p = 0.76 for TC; p = 0.76 for TG; p = 0.47 for HDL-C; and p = 0.92 for LDL-C). Lipid profiles of black African patients with and without hypothyroidism are shown in Table 3.

In the black African patients with hypothyroidism, there was a positive correlation between TSH and TC (Spearman's correlation coefficient, ρ = 0.345, n = 139, p < 0.01), as shown in Fig. 1, and between TSH and LDL-C (ρ = 0.291, n = 124, p < 0.01), Fig. 2. Triglyceride (ρ = 0.068, p = 0.44) and HDL-C (ρ = 0.13, p = 0.14) did not have a linear association with TSH. Free T4 had a negative correlation with TC (ρ = -0.344, p < 0.01) and LDL-C (ρ = -0.234, p = 0.02) as seen on Fig. 3. A linear association was not present between FT4 and TG (ρ = -0.160, p = 0.12) or FT4 and HDL-C (ρ = -0.118, p = 0.24).

Caucasian patients with hypothyroidism had a higher TC (p = 0.02) and TG (p = 0.03) than their euthyroid counterparts. HDL-C and LDL-C were not different between the two groups (p = 0.73 and p = 0.09 respectively). A raised, isolated TC was found in 16 (38.10%) of the hypothyroid Caucasian patients. Five (12.20%) had a raised TG alone and 10 (24.39%) had both a raised TC and TG. More than half (56.10%) of hypothyroid Caucasian patients had an LDL-C ≥ 3 mmol/L. Normal lipid profiles were observed in 7 (17.07%) hypothyroid patients compared to 29 (34.52%) euthyroid controls. As with male black African patients with hypothyroidism, Caucasian males with hypothyroidism had lipids that were no different from their matched euthyroid controls. Lipid profiles of Caucasian patients with and without hypothyroidism are shown in Table 4.

TSH had a positive linear correlation with TC (ρ = 0.277, n = 42, p = 0.04) among Caucasian patients with hypothyroidism (Fig. 1). A linear relationship between TSH and LDL-C (Fig. 2) did not achieve statistical significance (ρ = 0.207, p = 0.10), however, FT4 and LDL-C showed a negative linear association which was statistically significant (ρ = -0.336, p = 0.04). FT4 also had a negative linear association with TC (ρ = -0.410, n = 29), the statistical significance of which could not be determined due to the smaller number of patients with a FT4 value available (Fig. 3).

Euthyroid Caucasian controls had higher median TC, HDL-C and LDL-C than euthyroid black African controls (p < 0.01). Caucasians with hypothyroidism had a higher median TC compared to black Africans with hypothyroidism (p = 0.02), while TG, HDL-C and LDL-C were not different (p = 0.13, p = 0.10 and p = 0.24 respectively).

Limited statistical analysis was performed on the Indian and mixed-race groups due to their low sample sizes. Tables showing the lipid values in these groups are included as Appendix 1 and Appendix 2, respectively.

A TC/HDL ratio of 3.83 (3.14–4.52) was obtained for all patients with hypothyroidism where a TC and HDL-C value was available (n = 196). The control group with euthyroidism (n = 412), by comparison, had a lower TC/HDL ratio of 3.40 (2.78–4.24) (p < 0.001).

All female patients with hypothyroidism had a median TC/HDL-C ratio of 3.75 (3.14–4.52), while males had a median TC/HDL-C ratio of 4.04 (3.10–4.62). Black African patients with hypothyroidism had a greater TC/HDL ratio than euthyroid controls (p = 0.005). TC/HDL ratio was not different in black African males with and without hypothyroidism (p = 0.424).

Similarly, Caucasian patients had a greater TC/HDL ratio in the

Table 2
Thyroid function tests in subjects with hypothyroidism and euthyroidism.

	Euthyroidism				Hypothyroidism			
	TSH		FT4		TSH		FT4	
	n	Median	n	Median	n	Median	n	Median
All ethnicities	412	1.65 (1.13–2.34)1.73	165	13.60 (12.1–15.35)13.50	206	22.84 (13.55–47.69)19.05	153	9.9 (7.15–12.2)10.40
Male	52	(1.26–2.23)1.64	23	(11.4–15.4)13.7	26	(11.98–36.89)24.18	20	(8.7–14.48)9.90
Female	360	(1.11–2.34)	142	(12.18–15.33)	180	(14.10–49.18)	133	(6.45–12.15)
Black African, all	278	1.64 (1.12–2.27)1.80	119	13.30 (11.9–15.3)13.30	139	24.97 (14.14–49.48)22.43	108	10.10 (7.03–12.05)10.15
Male	32	(1.21–2.34)1.63	15	(11.2–15.3)13.25	16	(13.18–37.66)26.17	14	(8.23–12.38)10.10
Female	246	(1.11–2.27)	104	(11.9–15.3)	123	(14.23–52.86)	94	(6.48–12.1)
Caucasian, all	84	1.64 (1.18–2.42)1.55	32	14.35 (13.2–15.58)14.10	42	17.27 (12.90–35.60)14.42	29	9.5 (4.7–12.25)11
Male	12	(1.33–2.2)1.68	5	(13.15–16.7)14.50	6	(10.17–44.43)17.27	5	(6.8–17.65)8.95
Female	72	(1.15–2.44)	27	(13.1–15.6)	36	(13.05–33.67)	24	(4.6–11.55)
Indian, all	34	2.01 (0.99–2.67)2.16	10	13.25 (11.58–15.4)	17	27.08 (12.72–34.95)	12	12.15 (9.9–15.68)
Male	6	(1.62–2.57)1.86	2	11.3514.20	3	13.3627.51	1	12.9012.10
Female	28	(0.92–2.68)	8	(12.4–16.8)	14	(12.80–34.35)	11	(9.80–16.60)
Mixed-race	16	1.40 (1.17–1.80)	4	16.4 (14.60–18.58)	8	33.46 (13.43–70.85)	4	6.60 (1.13–14.25)
Male	2	1.411.40	1	17.0015.8	1	12.1137.89	-	-6.60
Female	14	(1.15–1.89)	3	(14.20–15.80)	7	(16.80–75.80)	4	(1.13–14.25)

Data presented as medians and interquartile ranges.

Table 3
Lipid profiles in black African subjects with euthyroidism and hypothyroidism

	Euthyroidism					Hypothyroidism				
	n	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	n	TC	TG	HDL-C	LDL-C
All	278	4.37 (3.83-5.13)	1.03 (0.77-1.46)	1.27 (1.06-1.55)	2.53 (1.98-3.07)	139	4.93 (4.17-5.82) **	1.20 (0.92-1.80)*	1.38 (1.11-1.60)	2.95 (2.27-3.60) **
Males	32	4.39 (3.65-4.99)	1.02 (0.84-1.41)	1.13 (0.96-1.39)	2.49 (1.94-2.97)	16	4.49 (3.53-6.04)	1.16 (0.71-1.54)	1.19 (1.02-1.43)	2.49 (1.74-3.09)
Females	246	4.37 (3.88-5.13)	1.03 (0.76-1.48)	1.31 (1.08-1.56)	2.53 (1.98-3.10)	123	5.04 (4.23-5.80) **	1.21 (0.93-1.83)*	1.39 (1.12-1.61)	3.02 (2.40-3.60) **

Data are presented as medians and interquartile ranges.
*$p<0.05$ as compared to euthyroid control **$p<0.01$ as compared to euthyroid control

setting of hypothyroidism ($p = 0.029$). However, the difference seen in males did not reach statistical significance ($p = 0.341$), probably due to small sample size.

Discussion

Dyslipidemia is a common finding in hypothyroidism and is one of the main reasons why hypothyroidism is a risk factor for atherosclerotic cardiovascular disease [29,30]. One study reported dyslipidemia in more than 90% of individuals with overt hypothyroidism [15]. Many black African patients have, anecdotally, been found to have normal lipids in the setting of hypothyroidism. The majority of studies have been performed in predominantly Caucasian populations of North America, the UK and Europe [4,6,15,24].

This study sought to describe the prevalence of dyslipidemia in an ethnically diverse cohort of patients with hypothyroidism and to assess whether ethnic differences could account for an anecdotal absence of dyslipidemia seen in black African patients with hypothyroidism.

Dyslipidemia was common across all ethnic groups with hypothyroidism. Overall, 71% of patients with hypothyroidism had some form of dyslipidemia; 32% had an isolated hypercholesterolemia, 10% had an isolated hypertriglyceridemia and 20% had both a raised TC and a raised TG.

The prevalence of dyslipidemia among the euthyroid Caucasian controls was more generalizable to the large scale prevalence studies performed in populations elsewhere [31]. Half of euthyroid Caucasian control subjects had a TC greater than 5 mmol/L, 39% had an LDL-C greater than 3 mmol/L and 21 % had a TG level greater than 1.7 mmol/L. Dyslipidemia was also more common among the Indian and mixed-race control populations, more than 30 % of which had a TC greater than 5 mmol/L.

In the present study, euthyroid black African control subjects had a lower TC than their Caucasian counterparts, which may be indicative of a population group in the earlier stages of an epidemiological transition [32]. Indeed, 28 of euthyroid black African control subjects had a TC greater than 5 mmol/L. When adjusted for comparison with the Heart of Soweto study, only 14% of euthyroid black African subjects had a TC greater than 5.5 mmol/L. These prevalence estimates for dyslipidemia are predicted to rise in accordance with other countries on the African continent where dyslipidemia is a growing problem [33].

A gradual rise in the prevalence of non-communicable diseases in South Africa has occurred over the last few decades [34]. Shifts in the diet of black African people over the last 50 years has led to a 60% relative increase in fat intake [34]. Urbanization leads to diets higher in saturated fats, calories and sugar, but also a reduction in energy expenditure and the adoption of a more sedentary lifestyle [35].

Most of the hypothyroid patients with normal lipids in our study were black African. Indeed, 38 % of black African patients with hypothyroidism had a normal lipogram. To the best of our knowledge, the only other larger study evaluating serum lipids in the setting of overt hypothyroidism, described normal serum lipids in only 8.6% of patients [15]. The Caucasian subjects with hypothyroidism in our study more closely resembled the results reported in their study with only 17% having a normal lipogram.

Despite a reasonable proportion of black African subjects with hypothyroidism having normal lipids, scatter plots showing associations between TSH and TC and TSH and LDL-C have linear fit lines which are very similar between Caucasian and black African subjects with

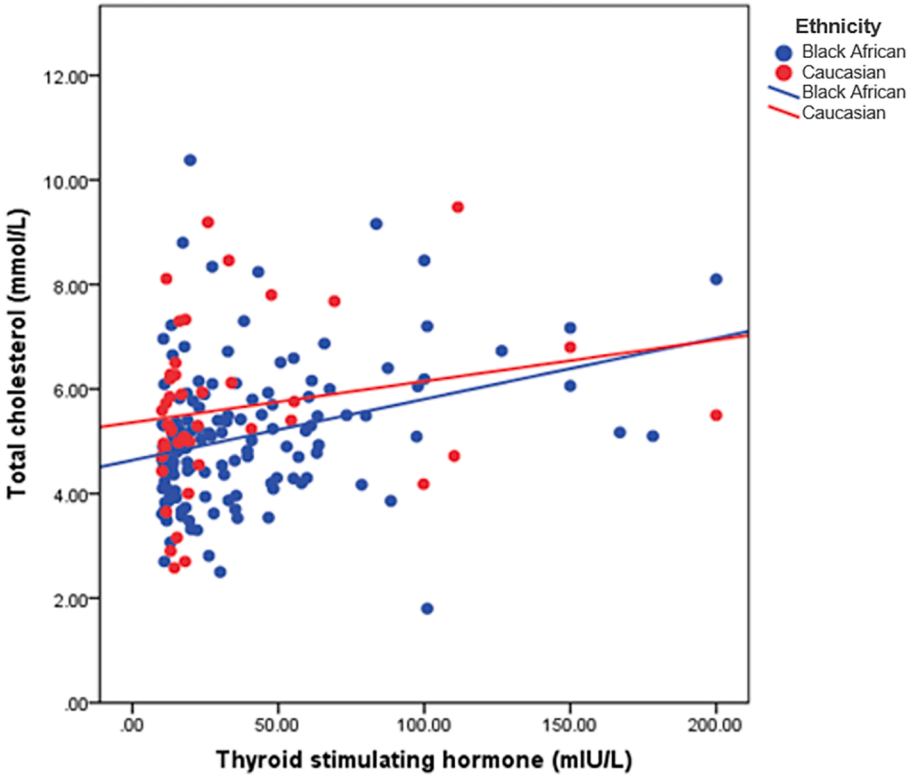

Fig. 1. Scatter plot with fit lines showing the positive relationship between TSH and TC in black African ($\rho = 0.345$, $n = 139$, $p < 0.01$) and Caucasian patients ($\rho = 0.277$, $n = 42$, $p = 0.04$) with hypothyroidism.

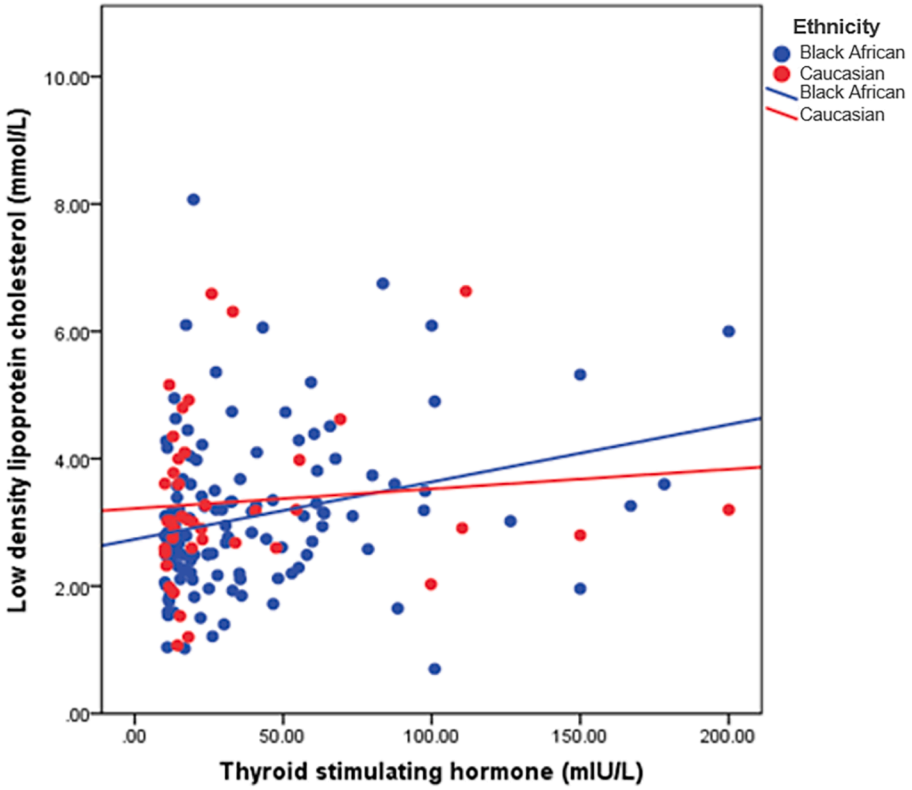

Fig. 2. Scatter plot with fit lines showing the positive relationship between TSH and LDL-C in black African ($\rho = 0.291$, $n = 124$, $p < 0.01$) and Caucasian patients ($\rho = 0.207$, $n = 42$, $p = 0.10$) with hypothyroidism.

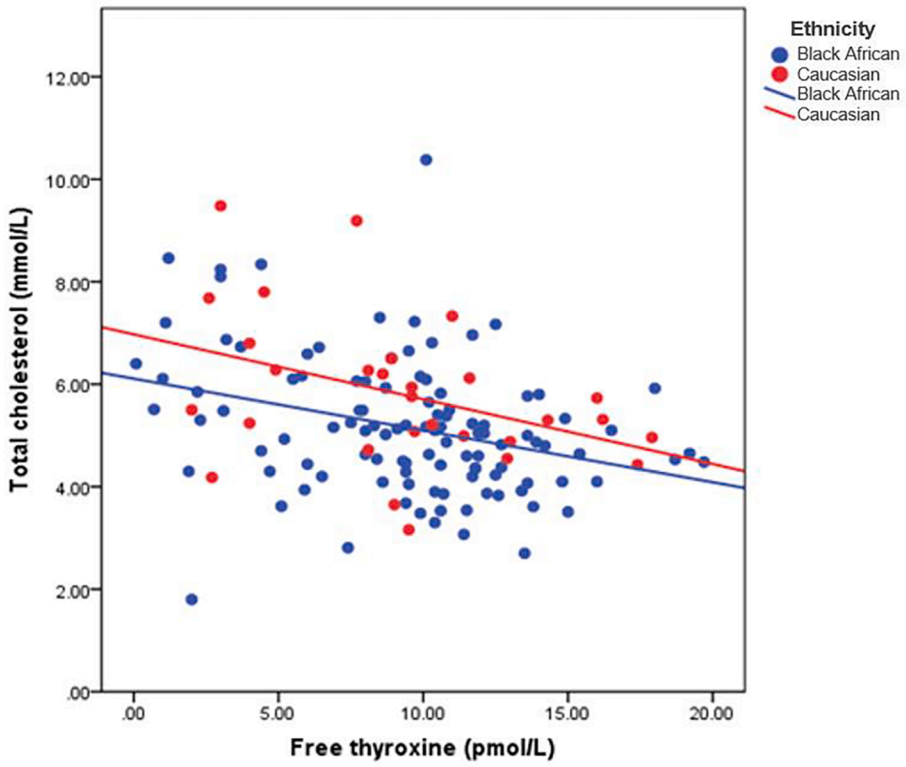

Fig. 3. Scatter plot with fit lines showing the negative relationship between FT4 and TC in black African ($\rho = -0.344$, $p < 0.01$) and Caucasian patients ($\rho = -0.410$, $n = 29$, p-value indeterminate due to small sample size) with hypothyroidism.

Table 4
Lipid profiles in Caucasian subjects with euthyroidism and hypothyroidism

	Euthyroidism					Hypothyroidism				
	n	TC	TG	HDL-C	LDL-C	n	TC	TG	HDL-C	LDL-C
All	84	5.01 (4.51-5.58)	1.13 (0.87-1.61)	1.43 (1.16-1.78)	2.87 (2.39-3.26)	42	5.45 (4.72-6.34) *	1.41 (1.00-2.04) *	1.41 (1.23-1.84)	3.02 (2.60-3.99)
Males	12	4.11 (3.46-5.25)	0.90 (0.78-2.07)	1.15 (0.98-1.20)	2.62 (1.83-3.49)	6	5.42 (4.83-6.15)	1.58 (1.24-2.14)	1.36 (1.22-1.49)	3.40 (2.47-4.22)
Females	72	5.06 (4.69-5.68)	1.15 (0.92-1.59)	1.56 (1.29-1.80)	2.89 (2.44-3.26)	36	5.45 (4.71-6.45)	1.37 (1.00-2.06)	1.45 (1.23-1.86)	3.02 (2.60-4.00)

Data are presented as medians and interquartile ranges
*p<0.05 as compared to euthyroid control **p<0.01 as compared to euthyroid control.

hypothyroidism.

O'Brien *et al* also reported on atherogenic TC/HDL-C ratios among subjects with hypothyroidism with ratio values of 6.4 in males and 4.7 in females [15]. Females tend to have higher HDL-C and, as a result, lower TC/HDL-C ratios.

In this study, euthyroid subjects had median TC/HDL-C ratios of 3.4, a value below average risk for cardiovascular disease [36]. By comparison, hypothyroid patients had a higher median TC/HDL-C ratio of 3.83, but did not reach the highly atherogenic ratios reported by O'Brien *et al.* [15] Similar to other reported studies, females had lower TC/HDL-C ratios [15,36]. All values obtained for TC/HDL-C in our study fall below the average risk for cardiovascular disease. Indeed, they would follow the first tertile of the Kaplan-Meier curve showing survival time without coronary heart disease from the Framingham Heart Study [37].

There were some limitations in this study. Estimation of cardiovascular risk based on cholesterol alone is difficult without also knowing other traditional cardiovascular risk factors such as body mass index, hypertension and smoking history. The control group was randomly chosen from a "hospital-going population" and, while efforts were made to exclude subjects with known secondary causes of dyslipidemia, a euthyroid group without co-morbid illness, obtained from the general population may have had an even lower prevalence of dyslipidemia.

Conclusion

Dyslipidemia is less common in black African patients with hypothyroidism when compared to other ethnic groups with hypothyroidism. However, this occurs in the context of a population group in an earlier stage of epidemiologic transition where the prevalence of dyslipidemia is less among euthyroid individuals. Although set at a lower level, a linear, positive correlation between TSH and TC as well as TSH and LDL-C is similar between Caucasian and black African patients with hypothyroidism. The TC/HDL-C ratio, a measure of cardiovascular risk, is increased in the setting of hypothyroidism. The ratio was similar between Caucasian and black African patients. The TC/HDL-C ratio did not, however, reach the markedly atherogenic levels reported in previous studies and placed individuals only at an average cardiovascular risk.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet 2017;6736 (17):4–8.
[2] Refetoff S, Weiss R, Usala S. The syndromes of resistance to thyroid hormone. Endocr Rev 1993;14(3):348–99.
[3] Carlé A, Pedersen IB, Knudsen N, et al. Hypothyroid symptoms fail to predict thyroid insufficiency in old people: a population-based case-control study. Am J Med 2016;129(10):1082–92.
[4] Boekholdt SM, Titan SM, Wiersinga WM, et al. Initial thyroid status and cardiovascular risk factors: The EPIC-Norfolk prospective population study. Clin Endocrinol (Oxf) 2010;72(3):404–10.
[5] Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): national health and nutrition examination survey (NHANES III). J Clin Endocrinol Metab 2002;87: 489–99.
[6] Canaris G, Manowitz N, Mayor G, Ridgway C. The colorado thyroid disease prevalence study. Arch Intern Med 2000;160:526–34.
[7] Madariaga AG, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab 2014;99(3):923–31.
[8] Aoki Y, Belin RM, Clickner R, Jeffries R, Phillips L, Mahaffey KR. Serum TSH and total T_4 in the United States population and their association with participant characteristics: national health and nutrition examination survey (NHANES 1999–2002). Thyroid 2007;17(12):1211–23.
[9] Sichieri R, Baima J, Marante T, De Vasconcellos MTL, Moura AS, Vaisman M. Low prevalence of hypothyroidism among black and Mulatto people in a population-based study of Brazilian women. Clin Endocrinol (Oxf) 2007;66(6):803–7.
[10] Tunbridge WMG, Evered DC, Hall R, et al. the spectrum of thyroid disease in a community: the whickham survey. Clin Endocrinol (Oxf) 1977;7(6):481–93.
[11] Pearce SHS, Brabant G, Duntas LH, et al. 2013 ETA guideline: management of subclinical hypothyroidism. Eur Thyroid J 2013;2(4):215–28.
[12] Dave JA, Klisiewicz A, Bayat Z, et al. SEMDSA/ACE-SA guideline for the management of hypothyroidism in adults. J Endocrinol Metab Diabetes South Africa 2015;20(2):18–26.
[13] Okosieme O, Gilbert J, Abraham P, et al. Management of primary hypothyroidism: statement by the British Thyroid association executive committee. Clin Endocrinol (Oxf) 2016;84(6):799–808.
[14] M. Peppa G. Betsi G. Dimitriadis Lipid abnormalities and cardiometabolic risk in patients with overt and subclinical thyroid disease J Lipids. 2011;2011(Vldl): 575840.
[15] O'Brien T, Dineen SF, O'Brien PC, Palumbo PJ. Hyperlipidemia in patients with primary and secondary hypothyroidism. Mayo Clin Proc 1993;68(9):860–6.
[16] Pearce EN. Hypothyroidism and dyslipidemia: modern concepts and approaches. Curr Cardiol Rep 2004;6(6):451–6.
[17] Nikkilä EA, Kekki M. Plasma triglyceride metabolism in thyroid disease. J Clin Invest 1972;51(8):2103–14.
[18] Rizos CV, Elisaf MS, Liberopoulos EN. Effects of thyroid dysfunction on lipid profile. Open Cardiovasc Med J 2011;5:76–84.
[19] Agdeppa D, Macaron C, Mallik T, Schnuda ND. Plasma high density lipoprotein cholesterol in thyroid disease. J Clin Endocrinol Metab 1979;49(5):726–9.
[20] Liberopoulos EN, Elisaf MS. Dyslipidemia in patients with thyroid disorders. Hormones (Athens) 2002;1(4):218–23.
[21] Eat B, Üller M, Enryk H, et al. Impaired action of thyroid hormone associated with smoking in women with hypothyroidism. N Engl J Med 1995;333:964–9.
[22] Triguero MLM, Hernández-Mijares A, Nguyen TT, et al. Effect of thyroid hormone replacement on lipoprotein(a), lipids, and apolipoproteins in subjects with hypothyroidism. Mayo Clin Proc 1998;73(9):837–41.
[23] Meier C, Staub JJ, Roth CB, et al. TSH-controlled 1-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (Basel Thyroid Study). J Clin Endocrinol Metab 2001;86:4860–6.
[24] Tunbridge WMG, Evered DC, Hall R, et al. Lipid profiles and cardiovascular disease in the whickham area with particular reference to thyroid failure. Clin Endocrinol (Oxf) 1977;7(6):495–508.
[25] Tsimihodimos V, Bairaktari E, Tzallas C, Miltiadus G, Liberopoulos E, Elisaf M. The incidence of thyroid function abnormalities in patients attending an outpatient lipid clinic. Thyroid 1999;9(4):365–8.
[26] Friedewald W, Levy R, Fredrickson D. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18(6):499–502.
[27] Davis HE. Fasting time and lipid levels in a community-based population. Cardiol Rev 2013;29(1):1707–10.
[28] Nordestgaard BG, Langsted A, Mora S, et al. Fasting is not routinely required for determination of a lipid profile: Clinical and laboratory implications including flagging at desirable concentration cut-points – A joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. Eur Heart J 2016;37(25):1944–58.
[29] Biondi B, Klein I. Hypothyroidism as a risk factor for cardiovascular disease. Endocrine 2004;24(1):1–13.
[30] Ning Y, Cheng YJ, Liu LJ, et al. What is the association of hypothyroidism with risks of cardiovascular events and mortality? A meta-analysis of 55 cohort studies involving 1,898,314 participants. BMC Med 2017;15(1):21.
[31] Goff DC, Bertoni AG, Kramer H, et al. Dyslipidemia prevalence, treatment, and control in the Multi-Ethnic Study of Atherosclerosis (MESA): Gender, ethnicity, and coronary artery calcium. Circulation 2006;113(5):647–56.
[32] Sliwa K, Wilkinson D, Hansen C, et al. Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study. Lancet 2008;371(9616):915–22.
[33] Noubiap JJ, Bigna JJ, Nansseu JR, et al. Prevalence of dyslipidaemia among adults in Africa: a systematic review and meta-analysis. Lancet Glob Heal 2018;6(9): e998–1007.
[34] Mayosi BM, Flisher AJ, Lalloo UG, Sitas F, Tollman SM, Bradshaw D. The burden of non-communicable diseases in South Africa. Lancet 2009;374(9693):934–47.
[35] Goryakin Y, Rocco L, Suhrcke M. The contribution of urbanization to non-communicable diseases: Evidence from 173 countries from 1980 to 2008. Econ Hum Biol 2017;26:151–63.
[36] Ridker PM, Cook NR, Bradwin G, Buring JE. Lipid ratios, and CRP as risk factors for cardiovascular disease. J Am Med Assoc 2005;294(3):326–33.
[37] Castelli WP, Anderson K, Wilson PWF, Levy D. Lipids and risk of coronary heart disease. The Framingham Study. Ann Epidemiol 1992;2(1/2):23–8.