Dyslipidemia in hypothyrodism

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Abstract :

Background: Hypothyroidism is a condition of the deficiency of thyroid hormones, which considered a part in regulating lipid metabolism. Dyslipidemia, or abnormalities in lipid levels, is a common complication of hypothyroidism. This study aims to systematically review and meta-analyze the literature on dyslipidemia in hypothyroidism.

Methods: 50 patients with hypothyroidism and 50 healthy controls. we evaluated from November 2023 to February 2024 for their TFT, RFT and lipid profile. ECG changes and demographic data also reported.

Results: Increased total cholesterol, LDL-C, and TG levels, and decreased HDL-C levels. Increase in urea and creatinine values in hypothyroidism

Conclusion: Dyslipidemia is a common complication of hypothyroidism, It is important for clinicians to monitor lipid levels in patients with hypothyroidism and to consider thyroid hormone replacement therapy to mitigate the risk of cardiovascular disease. These findings suggest that patients with hypothyroidism are at increased risk of cardiovascular disease.

1. Introduction

Dyslipidemia is a condition in which abnormal levels of lipids in the blood occur [1,2]. Lipids are fats or fat-like substances that are important for various bodily functions, such as energy production, cell membrane structure, and hormone production [3]. Dyslipidemia can increase the risk of developing cardiovascular disease, including heart disease and stroke [2,4].

There are several types of dyslipidemia, including [2,3,4,7]:

1. Hypercholesterolemia: High levels of cholesterol in the blood, which can be caused by a high-fat diet, genetic factors, or certain medical conditions.
2. Hypertriglyceridemia: High levels of triglycerides in the blood, which can be caused by a high-carbohydrate diet, obesity, or certain medical conditions.
3. Low HDL cholesterol: Low levels of high-density lipoprotein (HDL) cholesterol, which can increase the risk of cardiovascular disease. HDL cholesterol is often referred to as "good" cholesterol because it helps remove excess cholesterol from the bloodstream and transport it to the liver for excretion.
4. High LDL cholesterol: High levels of low-density lipoprotein (LDL) cholesterol, which can increase the risk of cardiovascular disease. LDL cholesterol is often referred to as "bad" cholesterol because it can build up in the walls of the

arteries, leading to atherosclerosis (hardening of the arteries) and increasing the risk of heart disease and stroke.

5. Mixed dyslipidemia: A combination of high levels of triglycerides, low levels of HDL cholesterol, and high levels of LDL cholesterol.

Dyslipidemia can be caused by a variety of factors, including [5,9]:

1. Genetic predisposition: Certain genetic mutations can affect the metabolism of lipids, leading to dyslipidemia.
2. Poor diet: A diet high in saturated and trans fats, cholesterol, and refined carbohydrates can contribute to dyslipidemia.
3. Excess weight can increase the risk of dyslipidemia, particularly in the form of high triglycerides and low HDL cholesterol.
4. Sedentary lifestyle: Lack of physical activity can contribute to dyslipidemia, particularly in the form of low HDL cholesterol.
5. Certain medical conditions: Certain medical conditions, such as hypothyroidism, Cushing's syndrome, and polycystic ovary syndrome, can increase the risk of dyslipidemia.
6. Medications: Certain medications, such as anabolic steroids, antidepressants, and anti-seizure drugs, can affect lipid levels and contribute to dyslipidemia .

1.2 Pathophysiology

The mechanisms by which hypothyroidism leads to dyslipidemia are not fully understood, but several factors are thought to contribute. Hypothyroidism mean that thyroid gland does not produce enough thyroxine (T4) and triiodothyronine (T3). This hormonal deficiency can lead to various metabolic disturbances, including dyslipidemia, including dyslipidemia, which refers to abnormal lipid levels in the blood. The mechanism of dyslipidemia in hypothyroidism involves several factors :

1. Decreased Lipoprotein Lipase (LPL) Activity: Thyroid hormones play a crucial role in regulating the activity of lipoprotein lipase, an enzyme responsible for the breakdown of triglycerides in circulating lipoproteins. In hypothyroidism, the reduced levels of thyroid hormones lead to decreased LPL activity, resulting in decreased clearance of triglyceride-rich lipoproteins from the blood.
2. Reduced Hepatic Lipase (HL) Activity: Hepatic lipase is another enzyme involved in lipid metabolism, particularly in the liver. In hypothyroidism, there is a decrease in hepatic lipase activity, which impairs the clearance of triglyceride-rich lipoproteins and HDL particles.
3. Altered Lipoprotein Profile: Hypothyroidism is associated with an increase in total cholesterol and LDL cholesterol levels. This is mainly due to decreased LDL receptor activity in the liver, resulting

in reduced uptake and clearance of LDL particles. Furthermore, there is a decrease in the activity of CETP, which normally facilitates the transfer of cholesterol esters from HDL to LDL particles. As a result, there is a decrease in the conversion of LDL to HDL, leading to an accumulation of LDL cholesterol.

4. Impaired Bile Acid Metabolism: Thyroid hormones play a role in the synthesis and metabolism of bile acids, which are essential for the absorption of dietary fats. In hypothyroidism, there is reduced bile acid synthesis and impaired bile flow, which can contribute to the development of dyslipidemia.

1.3 Diagnostic Tests

Thyroid Function Tests: including TSH, FT4, and FT3. They can help diagnose hypothyroidism and also monitor the effectiveness of treatment [2,10,12]. These tests measure the levels of various thyroid hormones in the blood. In hypothyroidism, the thyroid gland does not produce enough thyroid hormones, so the pituitary gland produces more TSH to try to stimulate the thyroid gland [13,14]. Therefore, an elevated TSH level in the blood can indicate hypothyroidism. Other ways include:

1. Free Thyroxine (FT4) Test: This test measures the level of free thyroxine (FT4) in the blood. In hypothyroidism, the level of FT4 is usually low.

2. Free Triiodothyronine (FT3) Test: This test measures the level of free triiodothyronine (FT3) in the blood. In hypothyroidism, the level of FT3 is usually low.
3. Thyroid Antibodies Test: This test measures the level of antibodies against the thyroid gland in the blood. In autoimmune hypothyroidism, the immune system produces antibodies against the thyroid gland, which can damage the gland and lead to hypothyroidism.
4. Thyroid Ultrasound: This test uses sound waves to create images of the thyroid gland. It can help identify any structural abnormalities in the gland, such as nodules or inflammation.
5. Thyroid Scintigraphy: This test uses a small amount of radioactive material to produce images of the thyroid gland. It identify any areas of the gland that are not functioning properly.

It's important to note that these tests are not always 100% accurate, and some people with hypothyroidism may have normal test results. Additionally, some people with hypothyroidism may have symptoms that are not typical of the condition [21,22,23]. Dyslipidemia can be diagnosed through lipid profile [1,2], which measures the levels of various lipids TC, TG, LDL,HDL in the blood. A lipid profile, also known as a lipid panel or lipid profile test, is a blood test that measures the levels of various fats and fatty substances in bloodstream.

A typical lipid profile includes the following :

1. Total cholesterol:measures the total amount of cholesterol (TC), including HDL and LDL
2. High-density lipoprotein cholesterol (HDL)
3. Low-density lipoprotein cholesterol (LDL)
4. Triglycerides (TG): a type of fat that is stored human body.
5. Non-HDL cholesterol: This is calculated by subtracting HDL cholesterol from total cholesterol. Non-HDL cholesterol includes all the cholesterol-containing particles that contribute to plaque formation in the arteries.
6. Ratio of total cholesterol to HDL cholesterol: This ratio is calculated by dividing total cholesterol level by HDL cholesterol level. A higher ratio indicates a higher risk of heart disease

1.4 Complications

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 [4]. Dyslipidemia also has been implicated in the development of insulin resistance and oxidative stress [14]. All these effect of disorder 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].

2 Aim and objective

To identify the prevalence of dyslipidemia in hypothyroidism. And the correlation between them. We also aim to determine whether basic kidney function tests (urea, creatinine, uric acid) were affected in hypothyroid patients.

3 Material and methods

Cross sectional study was conducted and 100 indivisuals , in the period from November 2023 to February 2024 in Baaquba teaching hospital and Alyermok teaching hospital, recording the gender, age, job, urban and rural representation, investigations results and the files of 50 patients with overt hypothyroidism diagnosed in general internal medicine outpatient clinics were retrospectively reviewed. The diagnosis of hypothyroidism was made with increased TSH (>10mlU/Ml), decreased fT3 and fT4 values.

A control group consisting of 50 healthy individuals were included in the study and selected with same numbers, gender, age , job and areas distribution to be more significant in realizing the prevalence of dyslipidemia in hypothyroidism and ensure the results by excluding other risk factors. The healthy control group, which was matched in same parameters of the patient group among the

healthcare professionals who had their routine labrotary examinations done for general control.

The criteria for patient selection:

1. Patients with overt hypothyroidism and subclinical hypothyroidism diagnosed in general internal medicine outpatient clinics
2. Confirmed by tests, all patients included in the study had TSH, fT4, fT3, TC , TG ,LDL , HDL , urea, creatine and uric acid values.
3. Exclude other medical condition or drugs using that may affect the results

The criteria for patients Exclusion

1. Pregnant ladies
2. Patients with hepatic or renal dysfunction, heart failure , sick thyroid syndrome.
3. Patients with essential and chronic hypertension
4. Patients who have used lithium or amiodarone, methimazole or propylthiuracil due to hyperthyroidism
5. Patients who have used contrast material in the last month
7. Having other and other inflammatory conditions that can alter their CBC,TFT , RFT

Statistical analysis:

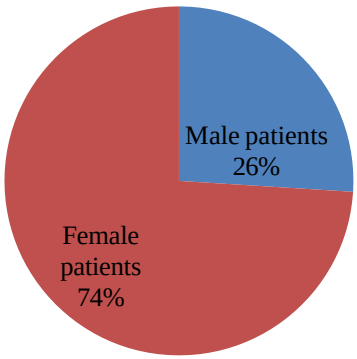
The data was collected in a Proforma and analyzed manualy using Kruskal Wallis test that used to compare between the means, Chi square analysis was done for statistical confirmation of the data

Mean, median, standard deviation, minimum , maximum values and interquartile range in summarizing numerical parameters; and percentage values were used for categorical variables.The statistical significance limit (p) was determined as 0.05.

4 Results

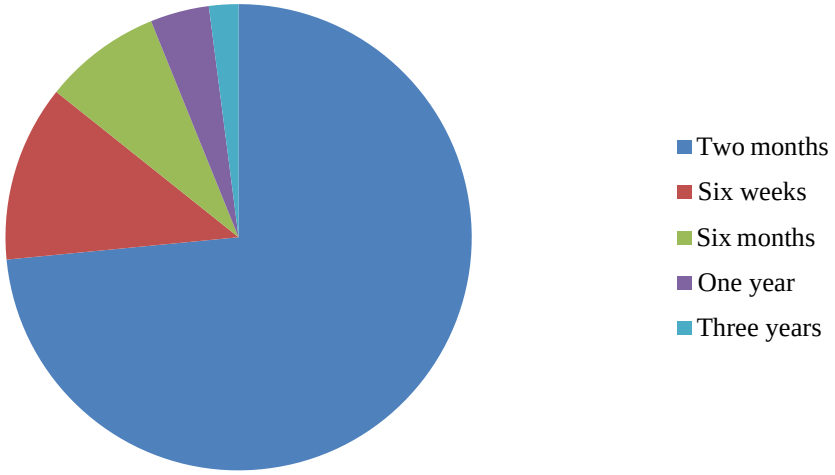
Fifty patients with hypothyroidism were included and compared to fifty thyroid controls. Most hypothyroid patients were female (n = 37) ,while were male (n= 13) .

Figure 1 : Distribution of thyroid disorder according to sex



72% suffer from hypothyroid symtoms for 2 months , 12% for 6 weeks , 8% for six months , 2% for one year 4% for 3 years

Figure 2 : Duration of thyroid disorder



36 (72%) of them in teenage range of age (11→ 20) , 12 ,24%of them aged (21 →30) , 2 aged more than thirty (4%).

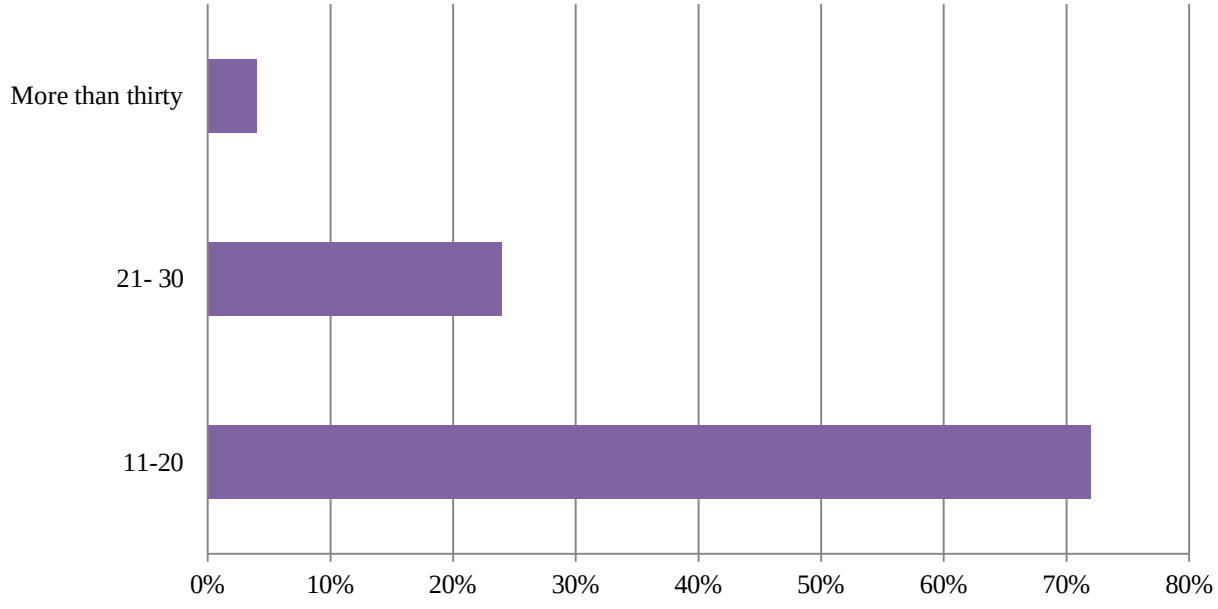
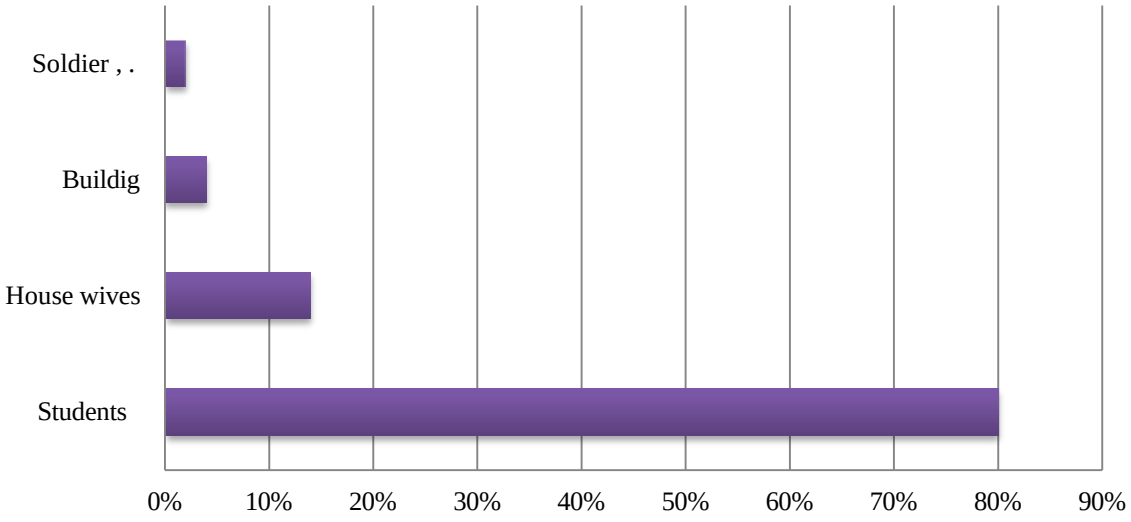


Figure 3 :Distribution of thyroid disorder according to age groups…

40 of them were students (80%) , 7 are house wives (14%), 2 buildig worker 4% , one is soldier ,2% .

Figure 4 : Distribution of thyroid disorder according to thier jobs



92% of them from urban area, 8% from rural areas .

The same numbers, gender, age , job and areas distribution was selected for the control.

Levels of thyroid hormones: TSH level was found to be 2.524±0.21 mlU/Ml in the control group. TSH value was higher in patients with hypothyroidism (44,501±4.51 mlU/Ml). Serum fT3 and fT4 levels(fT3: 2.65±0.07 pg/dl, fT4: 0.402±0.02 ng/dl) were statistically significantly lower in patients with hypothyroidism compared to the control group.

Abnormalities in lipid profiles among control group have been shown in 16 of them (32%) while abnormalities in lipid profiles among patients with overt hypothyroidism have been shown in 92% of them (46)

The TC was more than 200mg/dL and LDL-C was demonstrating more than 150 mg/dL in 92% of them (46), TG was more than 210 mg/dL,48% (n ,24).

HDL-C was high in 3, HDL less than 30 mg/dL. In19

normal in 24 (48%) ranges from 40 to 60mg/dL.

Median TC, TG and LDL-C were higher in hypothyroid patients ($p < 0.01$).

Normal lipid profiles were found only in 4 ,(8%) of all hypothyroid patients.

24 (48%) of hypothyroid patients have prolonged QTc intervals

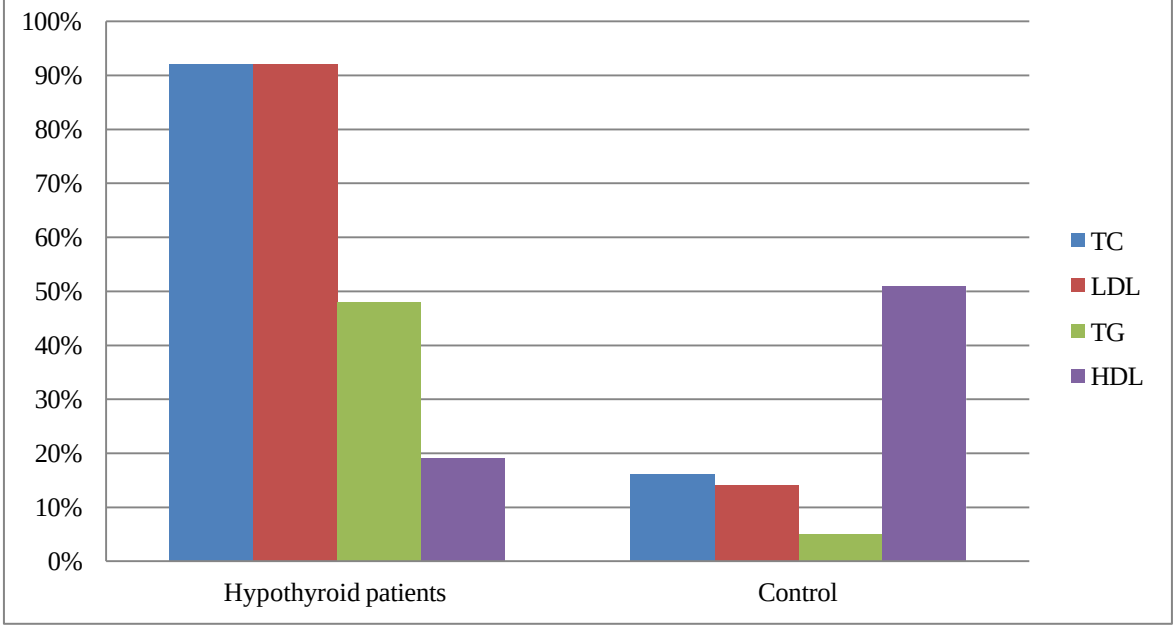
Table 1 :TFT , Lipid profile values of subjects with euthyroidism (control) and hypothyroidism.

	Euthyroidism	Hypothyroidism
Thyroid function (median, IQR) TSH FT4	1.65 (1.13 – 2.34)13.60 (12.10 – 15.35)	22.84 (13.54 – 47.69) **9.90 (7.15 – 12.2) **

	Euthyroidism (control)	Hypothyroidism.
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)**

In the study, mean urea: 30.5±14.8mg/dl, creatinine: 0.7±0.1mg/dl, uric acid: 4.1±1.1mg/dl in the control group. Serum urea level was found to be 35.6±7.1mg/dl in patients with overt hypothyroidism, which was statistically significantly higher than the control group (p=0.002). The creatinine value in patients with overt hypothyroidism was found to be 0.8±0.1mg/dl, and it was

Figure5: Lipid profile of subjects with euthyroidism (control) and hypothyroidism



significantly higher than the control group (p=0.001). The uric acid level was also found to be 5.5±1.3mg in patients with overt hypothyroidism and was significantly higher than the control group (p = 0.334)

Table 2: Urea, creatinine and uric acid comparisons between Control and Hypothyroid patients

Variables	Control	Hypothyroid patients	p
Urea	30.5±14.8	35.6±7.1	0.002
Creatinine	0.7±0.1	0.8±0.1	0.001
Uric acid	4.1±1.1	5.5±1.3	<0.001

Disscussion

The study included fifty patients diagnosed with hypothyroidism and compared them to fifty euthyroid individuals (controls). Among the hypothyroid patients, the majority (74%) were female, while the remaining 26% were male. Female sex hormones, such as estrogen and progesterone, can influence thyroid function, and hormonal fluctuations during different stages of a woman's life can affect thyroid hormone levels. Additionally, the most common cause of hypothyroidism, Hashimoto's thyroiditis, is more prevalent in females as autoimmune diseases have a higher incidence in women. Genetic factors and certain genes may also contribute to the higher incidence of thyroid disorders in women. In terms of age distribution, the most commonly affected group among the hypothyroid patients was teenagers between the ages of 11 and 20, accounting for 72% of the total hypothyroid group. This finding was unexpected, as the risk of developing thyroid disorders generally increases with age. Most of the hypothyroid patients were students (80%) from urban areas. A large proportion (72%) reported experiencing hypothyroid symptoms for approximately 2 months. The study found that 48% of hypothyroid patients had prolonged QTc intervals on electrocardiograms (ECGs) [17,18] , compared to only 4% of the control group. This finding, known as "hypothyroid QT

prolongation," can be attributed to altered ion channel function and reduced sympathetic tone. In hypothyroidism, decreased thyroid hormone levels can impair the function or expression of ion channels responsible for cardiac repolarization, leading to delayed repolarization and a prolonged QT interval on the ECG. Hypothyroidism can also disrupt the balance of intracellular calcium levels, further affecting cardiac conduction. The thyroid-stimulating hormone (TSH) level in the control group was 2.524±0.21 mlU/Ml. In patients with hypothyroidism, the TSH level was significantly higher (44,501±4.51 mlU/Ml). Serum levels of free triiodothyronine (fT3) and free thyroxine (fT4) were also significantly lower in hypothyroid patients compared to the control group (fT3: 2.65±0.07 pg/dl, fT4: 0.402±0.02 ng/dl). Abnormalities in lipid profiles were observed in 16% of the control group, while 92% of hypothyroid patients showed abnormalities [2,15,17]. Specifically, total cholesterol (TC) levels were higher than 200mg/dL, and LDL cholesterol (LDL-C) levels were higher than 150 mg/dL in 92% of hypothyroid patients. Additionally, 48% of hypothyroid patients had elevated triglyceride (TG) levels, with more than 210 mg/dL. In individuals with hypothyroidism, the levels of high-density lipoprotein cholesterol (HDL-C) can vary and may be normal, high, or low. According to the Colorado Thyroid Disease Prevalence Study, the severity of hypothyroidism is directly related to increases in total cholesterol (TC) and low-density lipoprotein cholesterol

(LDL-C) levels. The impact of thyroid hormones on metabolism plays a significant role in the lipid abnormalities observed in hypothyroidism. Thyroid hormones are involved in regulating key enzymes in the synthesis and metabolism of cholesterol. For example, thyroid hormones stimulate the activity of an important enzyme called 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is involved in cholesterol synthesis. In hypothyroidism, impaired thyroid hormone production leads to reduced cholesterol synthesis. T3, also upregulate the expression of low-density lipoprotein receptors (LDL receptors) on liver cells, which increases the uptake of LDL-C from the bloodstream. Consequently, even though cholesterol synthesis in the liver may be impaired, the disproportionate effect of thyroid hormones on LDL receptor function results in elevated levels of TC and LDL-C in the blood. Thyroid hormones also activate enzymes called lipoprotein lipase (LPL) and hepatic lipase (HL). LPL breaks down triglycerides into very low-density lipoproteins (VLDL), while HL breaks down HDL-C and intermediate-density lipoproteins. The activation of these enzymes by thyroid hormones further contributes to the lipid abnormalities observed in hypothyroidism. [20]. Smoking with hypothyroidism can lead to abnormalities that impair the action of thyroid hormones and increase the risk of cardiovascular disease. The effects of hypothyroidism on cardiovascular hemodynamics and the development of atherosclerosis are thought to contribute to this

increased risk [21,22] Dyslipidemia, a common feature of hypothyroidism, is believed to play a role in the development of insulin resistance and oxidative stress, further increasing cardiovascular risk [1,2,14]. In patients with hypothyroidism, there is a rise in diastolic blood pressure [2,20], a decrease in heart rate and cardiac output, and an increase in insulin resistance and oxidative stress. These factors contribute to the higher risk of cardiovascular disease associated with hypothyroidism. Dyslipidemia, specifically, has been implicated in the development of insulin resistance and oxidative stress [3,14]. Fortunately, replacement therapy with thyroxine, the main treatment for hypothyroidism, has shown improvements in lipid abnormalities. Studies have demonstrated that serum urea, creatinine, and uric acid levels are significantly higher in individuals with overt hypothyroidism compared to controls. Furthermore, there is a positive correlation between thyroid-stimulating hormone (TSH) levels and creatinine and uric acid values, while thyroid hormone (T4) levels have a negative correlation with uric acid in overt hypothyroidism. In a particular study, the researchers examined the levels of urea, creatinine, and uric acid in patients with overt hypothyroidism compared to a control group. The control group had a mean urea level of 31.5±14.8mg/dl, creatinine level of 0.7±0.2mg/dl, and uric acid level of 4.2±1.1mg/dl.In patients with overt hypothyroidism, the study found that the serum urea level was significantly higher at 35.6±7.1mg/dl compared to the control

group (p=0.002). The creatinine level in patients with overt hypothyroidism was also significantly higher at 0.8±0.1mg/dl compared to the control group (p=0.001). Furthermore, the uric acid level in patients with overt hypothyroidism was 5.5±1.3mg/dl, although the difference from the control group was not statistically significant (p=0.344).The relationship between kidney function and thyroid hormones has been recognized for some time [2,6,12]. Thyroid hormones are essential for kidney development and the maintenance of water and electrolyte balance. The kidney also plays a role in the metabolism and elimination of thyroid hormones [12]. Hypo- and hyperthyroidism can affect electrolyte and fluid metabolism as well as cardiovascular functions [11,12]. Kidney dysfunction can lead to changes in the synthesis, secretion, and elimination of thyroid hormones.In hypothyroid patients, increased serum creatinine levels, decreased glomerular filtration rate (GFR) and renal blood flow, impaired free water excretion, and hyponatremia are commonly observed renal dysfunctions.

Conclusion

Dyslipidemia, or abnormalities in lipid levels, is a common feature of hypothyroidism, a condition of underactive thyroid gland. The impact of dyslipidemia on cardiovascular disease risk in hypothyroidism is a topic of ongoing research. This study have suggested that the increased risk of cardiovascular disease in hypothyroidism may be due in part to the dyslipidemia that occurs in this condition. The underlying mechanism of dyslipidemia in hypothyroidism involves reduced activity of lipolytic enzymes, altered lipoprotein metabolism, and impaired cholesterol clearance, leading to increased levels of TC, LDL cholesterol, TG, serum urea, creatinine and uric acid levels as compared to controls .

Recommendations

It is prudent that hypothyroid patients at risk to get cardiovascular complications so they should monitor their lipid profiles aloung with renal function. Medications, such as statins or fibrates can help lower LDL cholesterol and triglyceride levels. Properly managing hypothyroidism can improve lipid profiles. The primary treatment for hypothyroidism is thyroid hormone replacement therapy, usually in the form of levothyroxine. Follow a balanced diet that is low in saturated, trans fats, cholesterol. losing weight and engage in regular physical activity can positively impact lipid levels.