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Ismail Zihni¹, Burcu Zihni², Oktay Karakose¹, Huseyin Pu'lat¹, Kazım Ozcelik¹, Huseyin Eken^{3*}, Ali Duran⁴, Adem Uslu⁵**An Evaluation of the Metabolic Profile in Total Thyroidectomy**¹Su'leyman Demirel University, Isparta, Turkey²Isparta State Hospital, Isparta, Turkey³Erzincan University, Erzincan, Turkey⁴Cukurova University, Mersin, Turkey⁵Bozyaka Training Research Hospital, Turkey**Abstract**

Aim: To investigate the relationship between metabolic parameters and thyroid hormone changes which occur in patients treated with thyroid replacement therapy following total thyroidectomy.

Material and Method: The study comprised 30 patients who underwent total thyroidectomy. Evaluations were made preoperatively and after 6 and 12 months postoperatively. Body mass index was calculated by recording height and weight of all patients, waist size was measured, arterial blood pressure was measured with a sphyngomanometer on the right arm after 10 mins of rest. Peripheral blood samples were taken after 12-hour fasting for the evaluation of low density lipoprotein, high density lipoprotein, total cholesterol, triglyceride, fasting glucose, fasting insulin, thyroid stimulating hormone, free T3, free T4, C-reactive protein, and haemoglobin A1c values.

Results: In the postoperative 1-year follow-up, a significant increase was determined in total cholesterol, low-density protein and triglyceride levels, which are related to cardiovascular risk, but no significant change was determined in high density protein levels. In addition, a significant increase was determined in the postoperative trend of both systolic and diastolic arterial blood pressures compared to the preoperative values.

Conclusion: Although euthyroid was achieved with follow-up of thyroid functions in the patients who underwent bilateral total thyroidectomy, it was found that there could be changes in metabolic parameters. Therefore, with close monitoring of the metabolic profile of these patients, it can be recommended that lifestyle changes are made when medical intervention is insufficient.

Key Words: total thyroidectomy; multinodular goitre; metabolic syndrome.

Introduction

Thyroidectomy, meaning the complete or partial removal of a diseased thyroid gland, is still among the most frequently applied surgical interventions in general surgery clinics. The follow-up and treatment of complications which may develop associated with postoperative thyroid hormone changes is as important as attempting to prevent surgery-related complications following thyroidectomy [1-3].

Thyroid hormones expressed by the thyroid gland, are in a general sense, hormones which regulate basal metabolism. Thyroid hormones affect carbohydrate, protein, fat and calcium metabolism and the cardiovascular, gastro-intestinal, hematopoietic, pulmonary and neuromuscular systems. The effects of thyroid disease on the cardiovascular system have been investigated by many researchers. These studies have revealed various negative effects on the cardiovascular system of low or very high values of thyroid hormone levels [4]. In addition, there are various ongoing studies on the effects of low, normal or over-expression of these hormones on lipid metabolism and cholesterol levels. To date there have been few studies, although there is increasing interest in another subject, which is the changes observed in body weight, waist circumference and body mass index (BMI) values when there is thyroid hormone deficiency or excess [5,6].

The definition of the collective risk factors is required for evaluation of the development of metabolic syndrome, Type 2 diabetes and cardiovascular complications. Previous prospective studies, using various definitions of metabolic syndrome, have suggested that the development of the syndrome is associated with a combination of factors. The factors focussed on are in particular insulin, obesity, lifestyle and healthcare habits. Reduced

insulin sensitivity is thought to be at the forefront of the development of metabolic syndrome. Factors playing a role in the pathogenesis include obesity, insulin resistance, atherogenic dyslipidemia, inflammation due to coexisting morbidity, thrombosis and carcinogenesis [7-11].

The aim of this study was to investigate the changes in metabolic parameters and thyroid hormones despite thyroid replacement therapy following bilateral total thyroidectomy.

Material and Method

The study comprised 36 patients who underwent bilateral total thyroidectomy in the General Surgery Clinic of Izmir Bozyaka Training and Research Hospital between October 2011 and May 2012. Informed consent was obtained from all patients. Evaluations of the patients were made preoperatively and at 6 months and 12 months postoperatively. Due to non-attendance of the 6-month follow-up appointment, 6 patients were withdrawn from the study.

All patients were evaluated preoperatively. Body mass index was calculated by recording height and weight of all patients, waist size was measured, arterial blood pressure was measured with a sphyngomanometer on the right arm after 10 mins of rest and a record was made of medications used. Peripheral blood samples were taken after 12-hour fasting for the analysis of low density lipoprotein (LDL), high density lipoprotein (HDL), total cholesterol (TChol), triglyceride (TG), fasting glucose, fasting insulin, thyroid stimulating hormone (TSH), free T3 (FT3), free T4 (FT4), C-reactive protein (CRP), and haemoglobin A1c (HbA1C) values. To evaluate insulin resistance, the homeostatic model assessment (HOMA-IR) test was used. The test was calculated according to the formula:

$$\text{HOMA-IR} = (\text{Fasting insulin (mU/l)} \times \text{fasting plasma glucose (mg/dl)}) / 405$$

All patients started thyroid replacement therapy (L-thyroxin) 2 weeks postoperatively.

All these steps were repeated at the 6 and 12-month follow-up examinations. The data for each patient were recorded on a case report form.

Statistical Analysis

Statistical analysis was made using the SAS system program. Variance analysis was applied for the evaluation of continuous variables between groups. If the variance analysis was homogenous, repeated ANOVA was applied, and if not homogenous, the Friedman test. Subgroup analysis was made between paired groups and if the variance analysis was homogenous, repeated ANOVA was applied, and if not homogenous, the Wilcoxon score test. A value of $p < 0.05$ was accepted as statistically significant in all the analyses.

Results

The basal characteristic properties of the patients were evaluated (Table 1). The patients were 25 females (83.3%) and 5 males (16.6%) with a mean age of 55 ± 13.8 years. The diagnoses were hypertension in 12 (40%) patients, diabetes mellitus in 7 (23%), coronary artery disease in 2 (6.6%) and hyperlipidemia in 3 (10%). No chronic renal disease was found in any patient. Medications used by the patients were B-blockers in 4 (13.3%), ACE inhibitor or angiotensin receptor antagonist in 9 (29.9%), thiazide diuretics in 4 (13.3%), oral anti-diabetics in 6 (20%) and insulin in 1 (3.3%).

The patients were operated on for multinodular goitre (MNG) in 23 cases (76.6%), suspected malignancy of the nodule in 4 (13.3%) and Graves disease in 3 (10%). Preoperative and

Table 1. Baseline characteristics

Age		55 ± 13.8
Gender	Female	25 (%83.3)
	Male	5 (%16.6)
Hypertension		12 (%40)
Diabetes mellitus		7 (%23)
Coronary artery disease		2 (%6.6)
Hyperlipidemia		3 (%10)
Used drugs		
B-blockers		4 (%13.3)
ACEI/ARBs		9 (%29.9)
Thiazide diuretics		4 (%13.3)
Oral antidiabetic		6 (%20)
Insulin		1 (%3.3)

ACEI: angiotensin-converting enzyme inhibitors, ARBs: Angiotensin receptor blockers

postoperative 6 and 12 months data analysis of the patients is shown in Table 2.

The TSH values were determined as pre-operative 1.20±3.45uIU/ml, postoperative 6th month, 1.28±15.3 uIU/ml and postoperative 12th month 1.65±8.4 uIU/ml, with no statistically significant difference between them.

The FT3 values were determined as preoperative 3.06±0.45 pg/ml, postoperative 6th month 2.79±0.53 pg/ml and postoperative 12th month, 2.8±0.29 pg/ml. Although a slight reduction was observed in the postoperative FT3 values, the difference between the preoperative and postoperative values was statistically significant.

The FT4 values were determined as preoperative 0.81±0.14 pg/ml, postoperative 6th month 0.96±0.27 pg/ml and postoperative 12th month, 0.98±0.2 pg/ml. Although a slight increase was observed in the postoperative FT3 values, the difference between the preoperative and postoperative values was statistically significant (Table 2).

The TChol values were determined as preoperative 191.2±31.7mg/dl, postoperative 6th month 204.7±32.8 mg/dl, and postoperative 12th month, 203.9±27 mg/dl. When preoperative and postoperative values were compared, a statistically significant difference was determined, but the difference between the 6th and 12th months postoperatively was not statistically significant.

The TG values were determined as preoperative 119.4±52.4mg/dl, postoperative 6th month 138±61.4 mg/dl, and postoperative 12th month, 54±11.7 mg/dl and no statistically significant difference was determined.

The HDL values were determined as preoperative 53.6±12.2mg/dl, postoperative 6th month 52.7±12.3 mg/dl, and postoperative 12th month, 133.4±24.9 mg/dl and no statistically significant difference was determined.

The LDL values were determined as preoperative 118±27mg/dl, postoperative 6th month 137.8±32.2 mg/dl, and postoperative 12th month, 133.4±24.9 mg/dl. When preoperative and postoperative values were compared, a statistically significant increase was determined, but the difference between the 6th and 12th months postoperatively was not statistically significant.

The BMI values were determined as

preoperative 29.2±4.8 kg/m², postoperative 6th month 30.05±5.05 kg/m² and postoperative 12th month, 29.9±4.9 kg/m². Although a slight increase was observed in the postoperative BMI values, the difference between the preoperative and postoperative values was statistically significant. In addition, the body weights of the patients were determined as preoperative 75.9±14.09 kg, postoperative 6th month 78.03±14.8 kg and postoperative 12th month 77.5±13.8 kg. When preoperative and postoperative values were compared, a statistically significant increase was determined, but the difference between the 6th and 12th months postoperatively was not statistically significant. The waist circumference values were measured as preoperative 101.2±11.4 cm, postoperative 6th month 103.1±11.2 cm and postoperative 12th month 105.2±12 cm. The difference between preoperative and postoperative values was determined to be statistically significant (Table 2).

The fasting insulin values were determined as pre-operative 9.03±12.8uIU/ml, postoperative 6th month, 7.73±4.09 uIU/ml and postoperative 12th month 7.19±6.04 uIU/ml, with no statistically significant difference between them.

The HbA1c values of the patients were determined as pre-operative 5.92±0.7% postoperative 6th month, 5.96±0.6% and postoperative 12th month 5.97±0.6% with no statistically significant difference between them.

The HOMA-IR values were determined as pre-operative 2.07±4.03, postoperative 6th month, 1.84±1.32 and postoperative 12th month 1.72±2.63, with no statistically significant difference between them.

The CRP values were calculated as preoperative 1.56±3.57mg/dl, postoperative 6th month 0.33±0.2 mg/dl, and postoperative 12th month, 0.31±0.61 mg/dl and a statistically significant difference was determined in the comparison of the preoperative and postoperative values (Table 2).

The systolic arterial blood pressure values were measured

Table 2. Preoperative and 6th and 12th months postoperative data analysis

	Preoperative	Postoperative (6 th months)	Postoperative (12 th months)	p1	p2	p3
TSH* (uIU/ml)	1.20±3.45	1.28±15.3	1.65±8.4	NS	NS	NS
FT3 (pg/ml)	3.06±0.45	2.79±0.53	2.8±0.29	0.02	0.006	NS
FT4 (ng/ml)	0.81±0.14	0.96±0.27	0.98±0.2	0.003	0.0002	NS
TChol (mg/dl)	191.2±31.7	204.7±32.8	203.9±27	0.008	0.02	NS
TG (mg/dl)	119.4±52.4	138±61.4	131.4±77.1	NS	NS	NS
HDL (mg/dl)	53.6±12.2	52.7±12.3	54±11.7	NS	NS	NS
LDL (mg/dl)	118±27	137.8±32.2	133.4±24.9	0.0003	0.002	NS
BMI (kg/ml)	29.2±4.8	30.05±5.05	29.9±4.9	0.0012	0.02	NS
Kilo (kg)	75.9±14.09	78.03±14.8	77.5±13.8	0.001	0.03	NS
Waist circumference (cm)	101.2±11.4	103.1±11.2	105.2±12	<0.001	<0.001	0.0019
Fasting glucose values* (mg/dl)	110.7±31.1	102±19.9	107.9±26.5	NS	NS	NS
Fasting insulin values* (uIU/ml)	9.03±12.8	7.73±4.09	7.19±6.04	NS	NS	NS
HbA1c (%)	5.92±0.7	5.96±0.6	5.97±0.6	NS	NS	NS
HOMA-IR*	2.07±4.03	1.84±1.32	1.72±2.63	NS	NS	NS
CRP* (mg/dl)	1.56±3.57	0.33±0.2	0.31±0.61	0.005	<0.001	0.03
Systolic arterial blood (mmHg)	118.6±11.6	127.6±20	125.8±18.5	0.0014	0.0079	NS
Diastolic arterial blood (mmHg)	76±8.5	84.5±13.6	83.1±13.03	0.0006	0.0016	NS

p1: Preoperative - postoperative (6th months), p2: Preoperative- postoperative (12th months), p3: Postoperative (6th months) - postoperative (12th months)

NS: Not significant, TSH: Thyroid stimulating hormone, FT3: Free T3, FT4: Free T4, TChol: Total cholesterol, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, BMI: Body mass index, HOMA-IR: Homeostatic model assessment, CRP: C-reactive protein

* Median values were used (after Friedman analysis), the average values were used for other values.

as preoperative 118.6 ± 11.6 mmHg, postoperative 6th month 127.6 ± 20 mmHg, and postoperative 12th month, 125.8 ± 18.5 mmHg. When preoperative and postoperative values were compared, a statistically significant increase was determined, but the difference between the 6th and 12th months postoperatively was not statistically significant.

The diastolic arterial blood pressure values were measured as preoperative 76 ± 8.5 mmHg, postoperative 6th month 84.5 ± 13.6 mmHg, and postoperative 12th month, 83.1 ± 13.03 mmHg. When preoperative and postoperative values were compared, a statistically significant increase was determined, but the difference between the 6th and 12th months postoperatively was not statistically significant.

The fasting glucose values were determined as preoperative 110.7 ± 31.1 mg/dl, postoperative 6th month 102 ± 19.9 mg/dl, and postoperative 12th month, 107.9 ± 26.5 mg/dl and no statistically significant difference was determined (Table 2).

Discussion

In the this study the metabolic profiles of patients who underwent bilateral total thyroidectomy were examined preoperatively and in 6 and 12 months postoperatively. The aim of the study was to analyse changes developing in the postoperative period.

No statistically significant difference was determined between the preoperative TSH values and those at 6 and 12 months postoperatively. While a slight decrease in postoperative FT3 values was determined compared to the preoperative values, an increase was determined in the postoperative FT4 values. These changes are thought to be due to thyroid replacement therapy.

Various risk evaluation systems have been developed to be able to calculate the risk of a cardiovascular event developing in a healthy individual (myocardial infarction, stroke, atherosclerotic events which may lead to results such as sudden cardiac death). Some of these currently available systems are Framingham, SCORE, ASSIGN, Q-Risk, PROCAM and WHO [12,13].

In a NHANES III study, 11611 healthy cases were separated into groups of low, moderate and high risk for a cardiovascular event. The Framingham risk evaluation system was developed based on the data of that study. The basis of the Framingham risk evaluation system is the evaluation of TChol, HDL, systolic blood pressure, age, gender, and cigarette use [14].

In 2004, the NHANES III study was re-analysed taking metabolic syndrome criteria into account. In cases determined with metabolic syndrome, the risk of myocardial infarction and/or stroke was determined to be significantly higher [15]. In a TEKHARF study conducted in Turkey, 53% of patients who developed coronary artery disease were determined to have metabolic syndrome [16].

In the dyslipidemia guidelines published by the European Cardiology Society (ESC) in 2011, the SCORE risk evaluation system was recommended for the prediction of cardiovascular events. By evaluating age, gender, TChol, HDL, systolic blood pressure and cigarette smoking, the 10-year development risk of an atherosclerotic event is calculated in this risk evaluation system. According to the risk scores, cases are separated into risk groups of low risk (estimated 10-year risk $<1\%$), moderate risk (estimated 10-year risk $1-4\%$), high risk (estimated 10-year risk $5-9\%$) and very high risk (estimated 10-year risk $\geq 10\%$). In addition, those with a previous diagnosis of coronary artery disease, or with Type 2 diabetes, or with moderate-severe chronic renal disease (glomerular filtration rate <60 ml/min/1.73 m²) are included in the very high risk group. After defining the risk levels, various treatment recommendations, primarily lifestyle changes to prevent cardiovascular events, are presented together with the treatment targets [17].

The results of the current study showed a significant increase over the postoperative year in TChol, LDL and TG levels, which have been correlated to the risk of a cardiovascular event, but no

significant change was determined in HDL levels. It was also determined in the current study, that there was a significantly increasing trend in both systolic and diastolic arterial blood pressure values when preoperative values were compared with postoperative values.

Reduced sensitivity to insulin, or in other words, insulin resistance has been related in many studies with increased risk of atherosclerosis and carotid intima media thickness, even in healthy individuals [18,19]. The method most widely used in clinical practice to determine insulin resistance is the HOMA-IR formula. In the current study, no statistically significant difference was determined between the HOMA-IR values calculated preoperatively and postoperatively. Furthermore, no significant difference was determined in respect of fasting glucose and HbA1c values in the comparison of preoperative and postoperative values. Although a slight reduction was determined in the fasting glucose levels of the patients postoperatively compared to the preoperative levels, this was not statistically significant.

In a 2010 study by Izzemir et al, no change was determined in weight and BMI in 3 and 6 months follow-up in patients who had undergone total thyroidectomy for benign nodular goitre [20]. Similarly in the current study, no significant change was determined in BMI in the preoperative and postoperative periods. However, a significant increase was seen in the postoperative weight and waist circumference measurements compared to those of the preoperative period.

The CRP values, which had increased preoperatively because of the thyroid gland or environmental factors, showed a statistically significant fall postoperatively.

In several previous studies of hypothyroidic patients, a decrease in carotid intima media thickness and improvement in endothelial functions and the lipid profile have been shown after treatment with L-thyroxin [21-23]. In the current study, although euthyroid was achieved with L-thyroxin treatment, the disorder in the lipid profile continued in the postoperative 1-year follow-up period, systolic and diastolic arterial blood pressures increased and waist circumference values continued to increase. The negative effects of the metabolic profile of temporary hypothyroid (before starting thyroid replacement therapy) which develops in the postoperative acute period could still have an effect in the long-term despite later starting L-thyroxin therapy and this can be interpreted as L-thyroxin therapy remaining insufficient to reverse these negative effects.

Conclusion

The results of this study showed that even if euthyroid is achieved in patients following bilateral total thyroidectomy, the lipid profile, blood pressure and BMI values show negative changes in the postoperative period. Therefore, in postoperative follow-up, these parameters must be closely monitored in addition to the thyroid hormones and lifestyle changes should be implemented and where necessary, medical treatment.

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Зозуляк Н.В.

Потенціювання антиішемічної терапії хворих на стабільну стенокардію III ФК

ДВНЗ «Івано-Франківський національний медичний університет», Україна

e-mail: natalia.doc@mail.ru

Резюме: Ішемічна хвороба серця є надзвичайно поширеною патологією. Саме тому важливим є пошук оптимізації лікування таких хворих з метою зменшення ускладнень, інвалідизації населення, а також фатальних наслідків. Зазвичай терапія цієї патології спрямована на гемодинамічну ланку серцево-судинної системи, але такі препарати не захищають клітину міокарда від ішемічних змін. **Метою дослідження** було підвищити ефективність лікування хворих на стабільну стенокардію (СС) III ФК шляхом застосування на фоні базової терапії метаболіто-тропних препаратів L-аргініну та етилметилгідроксипіридину сукцинату. **Матеріал та методи дослідження.** Було обстежено 125 хворих на СС III ФК. Ефективність терапії оцінювали за динамікою клінічних проявів та рівня толерантності до фізичних навантажень. **Результати та висновки.** У результаті проведеного дослідження найефективнішою в плані потенціювання антиішемічної терапії хворих на СС III ФК виявилась схема комбінованого застосування L-аргініну та етилметилгідроксипіридину сукцинату на тлі базової

терапії. Отримані результати дозволяють рекомендувати L-аргінін та етилметилгідроксипіридину сукцинат як засоби потенціювання базової терапії.

Ключові слова: стабільна стенокардія, велоергометрія, L-аргініну та етилметилгідроксипіридину сукцинат.

Постанова проблеми і аналіз останніх досліджень. Основним завданням у лікуванні хворих на ішемічну хворобу серця є зменшення кількості ішемізованих кардіоміоцитів, покращення кровопостачання ураженого міокарда, а також зменшення навантаження серцевого м'язу. Цю мету можна досягти різними способами: призначення бета-блокаторів (зменшують роботу серця, подовжують діастолу), нітратів (зменшують переднавантаження, покращують кровопостачання міокарду), блокаторів кальцієвих каналів і т. д. Проте, окрім базової терапії, існує важливий клас