ORIGINAL ARTICLE

THE CLINICAL PRESENTATION OF SUBCLINICAL HYPOTHYROIDISM IN PATIENTS WITH TYPE 2 DIABETES MELLITUS ASSOCIATED WITH OBESITY, ITS IMPACT ON CARDIOVASCULAR RISK, AND WAYS OF ITS CORRECTION

DOI: 10.36740/WLek202110221

Taras I. Griadil, Ivan V. Chopey, Ksenia I. Chubirko, Snizhana V. Feysa
STATE HIGHER EDUCATIONAL ESTABLISHMENT «UZHHOROD NATIONAL UNIVERSITY», UZHHOROD, UKRAINE

ABSTRACT

The aim: Calculate CVR in patients with T2DM, obesity and SH and analyze it.

Materials and methods: The selection of patients was carried out based on the Uzhhorod District Clinical Hospital, in the period from November 2016 to July 2021. All examined patients were divided into 3 groups: 1 (n=108) with T2DM and concomitant obesity and SH, 2 (n=91) with T2DM and SH, 3 (n=46) with obesity and SH. The observation and treatment period lasted 1 year. Using American College of Cardiology (ACC) / American Heart Association Guideline on the Assessment of Cardiovascular Risk (AHAGACR) (2013) (ASCVD Risk) and Framingham Risk Score (FRS), CVR was determined in all patients before and at the end of the study.

Results: According to the data obtained, patients in each group had a 10-year risk of CVE, however, worse CVR was observed in patients in group 1. In a more detailed analysis and comparison of the obtained data of patients with 10-year risk of CVE, worse CVR values were observed in patients with concomitant SH than without it ($p<0.05$).

Conclusions: The presence of SH in consumers may be an additional risk factor for unwanted CVE over a 10-year period.

KEY WORDS: type 2 diabetes mellitus, obesity, subclinical hypothyroidism, diagnostics, treatment, dapagliflozin, cardiovascular risk

Wiad Lek. 2021;74(10 p.II):2634-2639

INTRODUCTION

T2DM, obesity, and SH belong to the group of endocrine diseases that contribute to the complex disruption of metabolic processes, the emergence of pathological conditions, and complications in the body.

Obesity, and especially active abdominal adipose tissue, produces pro-inflammatory adipocytokines, which are involved in the stimulation of inflammatory processes, while excessive amounts of leptin, adiponectin, and resistin are closely associated with decreased insulin sensitivity, forming disorders insulin resistance (IR), associated with impaired glucose uptake into peripheral tissues [1]. Thus, in patients with T2DM, a relationship has been established between thyroid-stimulating hormone (TSH) levels, insulin sensitivity, and plasma lipid levels [2].

Several clinical studies have shown that anthropometric parameters (AP) are indicators of the risk of cardiovascular disease (CVD): body mass index (BMI), waist circumference (WC), hip circumference (HC), and subsequent waist-to-hip ratio (WHR) [3].

Hyperinsulinemia leads to an increase in adipose tissue in the liver and contributes to the development of non-alcoholic fat disease (NAFLD) [4]. Hypothyroidism contributes to the development of NAFLD and can provoke functional disorders of the heart: left ventricular diastolic dysfunction and others [5, 6].

Iodine deficiency plays an important role in the development of thyroid disease, which is almost always combined with selenium deficiency, especially this trend is observed in endemic areas, although there are data on the genetic condition of these diseases [7, 8].

Instead, studies show that thyroid hormone replacement therapy, primarily levothyroxine, normalizes lipid metabolism and consequently reduces the manifestations of fatty liver disease and reduces the risk of cardiovascular events (CVE) [9]. The obtained data meta-analysis from several prospective studies showed that individuals with SH and serum TSH levels were greater than 10 mU/L and had age-independent increases in CVE levels [10].

T2DM is considered an absolute risk factor (RF) for atherosclerosis [11]. Disorders of lipid metabolism cause a predisposition to atherosclerosis and contribute to endothelial dysfunction [12]. Lipid-protein glycan complexes contribute to the development of diabetes micro- or macro angiopathy [13, 14].

Data from studies demonstrate that SH is associated with hypercholesterolemia and increased levels of low-density lipoprotein (LDL) [15]. People with elevated levels of TSH and IP have an increased chance of developing dyslipidemia and cardiovascular disease [16].

According to the recommendations of the European Thyroid Association (ETA) in people under 65 years with

TSH levels of 4.0 – 10.0 mU/L and in the presence of symptoms of hypothyroidism, it is advisable to consider levothyroxine replacement therapy [17]. According to the results of randomized placebo-controlled studies, the efficacy and appropriateness of levothyroxine in different of patients with SH were substantiated [18].

In case of suspicion in a patient CVR in the 10-year perspective for evaluation purposes risk of occurrence cardiovascular events (CVE) in the next 10 years, it is calculated on the following scales: Q risk 2 score calculator and Modified Q risk 2, absolute CVD risk calculator, PROCAM score, Heart Disease Risk Calculator, The Framingham risk score (FRS) for hard chronic heart diseases (CHD), SCORE, ACC/AHAGACR (2013) (ASCVD Risk) [19, 20, 21, 22, 23]. ASCVD Risk is categorized as low-risk (LR) (<5%), borderline risk (BR) (5% to 7.4%), intermediate-risk (IMR) (7.5% to 19.9%), high risk (HR) (≥20%) of 10-year risk of myocardial infarction (MI) and/or stroke [22, 24]. FRS which evaluates the 10-year risk of CVD (CHD, stroke, death) is determined in percentages and classified accordingly LR (<10%), MR (10–20%), and HR (>20%) [21].

THE AIM

Examine patients with T2DM, obesity, and concomitant SH and identify in patients of experimental groups indicator CVR at 10-year CVE risk.

MATERIALS AND METHODS

The selection of patients took place based on the therapeutic department of the Municipal Non-Profit Enterprise "Uzhhorod District Clinical Hospital of Uzhhorod District Council of Transcarpathian region", and at outpatient treatment department of the therapy and the family medicine of the Faculty of Postgraduate and Pre-University Education of the State Higher Educational Establishment «Uzhhorod National University» in the period from November 2016 to July 2021. In the course of the study, 108 people with T2DM and concomitant obesity, who were included in the 1st group (n=108), were examined and 139 medical cards of an inpatient with a diagnosis of T2DM and ambulatory card data included in the 2nd group were retrospectively analyzed. group (n=91), while group 3 included patients diagnosed with obesity (n=46). Before dividing patients into groups, TSH and FT4 levels were determined, and depending on TSH (>4.0 mU/L) and FT4 (normal level), they were further divided into subgroups: 1a, 2a, 3a – patients with SH, and 1b, 2b, 3b – patients without SH. Instead, patients with hyperthyroidism, hypothyroid, subclinical hyperthyroid were excluded from this study. The period of treatment and observation of patients of all groups lasted 1 year and included dietary and exercise recommendations. All patients with T2DM received metformin 850 mg two times a day in combination with dapagliflozin 10 mg one time daily. Patients with SH were given levothyroxine individually at a dose of 25 or 50 μg daily, and if necessary, increasing the dose by 25 μg daily every 14-21 days until a replacement dose was reached, according to ETA recommendations.

All subjects were examined: general clinical examination, AP, measurement WC, HC, calculation of BMI and WHR, data of lipid profile, glycosylated hemoglobin (HbA1c), TSH, Free Thyroxine (FT4) levels, gathering of medical and social anamnesis, and bad habits. Using the American Diabetes Association (ADA) and ACC / AHAGACR and ETA, patients were provided with dietary advice.

CVR was determined at the time of inclusion in the study and after 1 year of treatment. The following calculators were used to calculate the CVR: 1) ACC/AHAGACR (2013) ASCVD Risk is categorized as LR (<5%), BR (5% to 7.4%), IMR (7.5% to 19.9%), high risk (HR) (≥20%) of 10-year risk of MI and/or stroke [22-24], and 2) FRS for hard CHD which evaluates the 10-year risk of CVD (CHD, stroke, chronic heart failure, death) in percentage was calculated by total points was classified as LR (<10%), IMR (10–20%), and HR (>20%) [21, 25]. В обрахунку ACC/AHAGACR (2013) ASCVD Risk used an online calculator (OC) – https://tools.acc.org/ASCVD-Risk-Estimator-Plus/?_ga=2.9302513.517413228.1631233238-717547926.1631233238#!/calculate/estimate/, instead, an OC was used to calculate FRS – https://www.mdcalc.com/framingham-risk-score-hard-coronary-heart-disease.

Additionally, to find the potential risk for patients with T2DM, obesity, subclinical hypothyroidism, a bibliographic search was performed on the keywords "treatment of type 2 diabetes mellitus", "type 2 diabetes mellitus", "subclinical hypothyroidism", "treatment of subclinical hypothyroidism", "obesity", "dapagliflozin", "metformin", "levothyroxine", "risk factors", "cardiovascular risk" in the following databases PubMed, MEDLINE, Web of Science, Cochrane Library, Google Scholar.

The diagnosis criteria for T2DM were established based on the ADA. The diagnosis of obesity was established by measuring BMI≥30 kg/m^2, and the value of BMI was assessed by the degree of obesity. It was evaluated depending on laboratory indicators and recommendations ETA thyroid function as euthyroid, hyperthyroid (known diagnosis of hyperthyroidism or TSH<0.3 mU/L and FT4>24 pmol/L), hypothyroid (known diagnosis of hypothyroidism or TSH>4.0 mU/L and FT4<10 pmol/L), SH (TSH>4.0 mU/L and normal FT4), and subclinical hyperthyroid (TSH<0.3 mU/L and normal FT4) [17].

The statistical processing of the research results was performed using the program software International Business Machines Corporation Statistical Package for the Social Sciences Statistics. The statistical analysis of the materials, the summary, and also the summary of the conclusions were made by the method of the variation statistics, taking into account the average values (mod, median, arithmetic mean) and the average error (M±m), with the estimation of the reliability of the values by the Student's t-criterion, as well as with the determination of the correlation coefficient using the Pearson's paired method to identify the relationships between the obtained indicators. For the minimum threshold of probability, the values $p<0.05$ were taken.

Table I. Anthropometrical parameters in group 1, 2 and 3.

Parameter	Group								
	Group 1 (n=108)	Subgroup 1a (n=28)	Subgroup 1b (n=80)	Group 2 (n=91)	Subgroup 2a (n=17)	Subgroup 2b (n=74)	Group 3 (n=46)	Subgroup 3a (n=11)	Subgroup 3b (n=35)
BMI ^{B} (kg/m^2)	32,9 ± 1,8	33,76± 2,51	32,55± 0,9	28,55± 0,12	28,83 ±2,19	28,26± 0,71	32,08± 0,19	32,69± 2,57	31,48± 0,14
BMI ^{AT} (kg/m^2)	31,43± 0,22	31,73± 2,07	31,58± 0,14	26,92± 0,15*	27,96± 2,34 $^{\mu}$	25,87± 0,63	30,57± 0,29#	31,03± 2,15$^{¥}$	30,1± 0,25
WC ^{B} (cm)	112,9± 1,4	114,6± 2,1	111,2± 1,5	88,6± 1,9	92,1± 2,4	88,3± 1,1	109,3± 1,6	111,0± 3,2	107,5± 1,6
WC ^{AT} (cm)	106,9± 1,3	107,5± 2,7	106,3± 1,1	86,35± 1,18*	87,4± 2,41$^{\mu}$	85,3± 1,4	102,7± 1,9#	103,5± 2,9$^{¥}$	101,9± 1,3
HC ^{B} (cm)	104,9± 1,1	105,7± 2,3	104,1± 1,9	91,9± 1,4	92,7± 2,1	91,1± 1,2	106,1± 0,7	106,8± 1,5	105,3± 1,2
HC ^{AT} (cm)	101,8± 1,04	102,5± 2,1	101,1± 1,6	91,0± 1,6*	91,3± 2,7$^{\mu}$	90,7± 1,8	102,7± 0,9$^{\#}$	103,9± 1,3$^{¥}$	101,5± 1,2
WHR ^{B}	1,08± 0,1	1,08± 1,1	1,07± 0,4	0,96± 0,2	0,99± 0,8	0,97± 0,1	1,03± 0,1	1,04± 0,2	1,02± 0,1
WHR ^{AT}	1,05± 0,2	1,05± 1,3	1,05± 0,1	0,95± 0,2*	0,96± 1,1$^{\mu}$	0,94± 0,2	1,00± 0,2 #	1,00± 0,4$^{¥}$	1,00± 0,1

Note: B - patient data at the beginning of the study; AT - patient data after 12 months of treatment and follow-up; BMI - Body Mass Index; WC - Waist circumference; HC - the hip circumference; WHR - waist-to-hip ratio; * - statistically significant difference when comparing the indicators between the respective groups 1 and 2 ($p<0.05$); μ - statistically significant difference when comparing the indicators between the respective groups 1a and 2a ($p<0.05$); # - a statistically significant difference when comparing the indicators between the respective groups 1 and 3 ($p<0.05$); ¥ - statistically significant difference when comparing the indicators between the respective groups 2a and 3a ($p<0.05$).

Table II. TSH and FT4 levels in patients of 1a, 2a, 3a subgroups

Subgroup	Parameter			
	TSH (mU/L) ^{B}	TSH mU/L) ^{AT}	FT4 (ng/dL) ^{B}	FT4 (ng/dL) ^{AT}
Subgroup 1a (n=28)	5,6±1,9	4,9±1,3	0,8±1,2	1,4±1,7
Subgroup 2a (n=17)	5,2±1,1	4,6±1,5$^{\mu}$	1,1±1,9	1,3±1,2
Subgroup 3a (n=11)	4,7±0,1	4,4±1,2$^{¥}$	1,6±0,2	0,9±1,1

Note: B - patient data at the beginning of the study; AT - patient data after 12 months of treatment and follow-up; normal values of TSH – 0.5–4.0 mU/L; normal values of FT4 – 0.7 to 1.9 ng/dL; μ - statistically significant difference when comparing the indicators between the respective groups 1a and 2a ($p<0.05$); ¥ - statistically significant difference when comparing the indicators between the respective groups 2a and 3a ($p<0.05$).

The whole set of the surveys were by the Articles 3,44 of the Fundamentals of the Legislation of Ukraine on Healthcare, the Articles 7, 8 of the Law of Ukraine "On Medicines", the Law of Ukraine "On Protection of Personal Data", taking into account the requirements of the European Parliament and Council Directives 2001/20/ EU of April 4, 2001, 2001/83/ EU of November 6, 2001, the Decisions of the European Parliament and of the Council 1901/2006 of December 12, 2006, and 1902/2006 of December 20, 2006, ICH GCP, International Ethical Principles for Biomedical human-related research and physician code of conduct, and order in the Ministry of Health of Ukraine No. 690 of September 23, 2009.

RESULTS

All patients included in this study were ≥40 years old. The mean age of the patients in the 1st group was 53.5±1.1 years, compared with 54.2±1.3 years of the patients in the 2nd group, whereas in group 3 the age of patients was 55.3±1.1 years. The ratio of men and women in group 1 was 44 men and 64 women against 33 men and 58 women in group 2 and 21 men and 25 women in group 3. The mean duration of T2DM in group 1 was 13.4±2.8 years, as opposed to 13.1±1.4 years in group 2 (Table I).

Currently, the status of a smoker was in group 1 – 34 patients, group 2 – 21 patients, and group 3 – 25 patients. Instead, in the past, there were additionally smokers in group 1 – 14 patients,

Table III. FPG and HbA1C levels

Parameter	Group								
	Group 1 (n=108)	Subgroup 1a (n=28)	Subgroup 1b (n=80)	Group 2 (n=91)	Subgroup 2a (n=17)	Subgroup 2b (n=74)	Group 3 (n=46)	Subgroup 3a (n=11)	Subgroup 3b (n=35)
FPG ^{B}	9,45±0,1	9,7±0,3	9,2±0,4	8,9±0,2	9,1±0,1	8,7±0,3	5,9±0,1	6,1±0,4	5,7±0,2
HbA1C (%) ^{B}	8,5±0,2	8,7±0,3	8,3±0,1	8,1±0,2	8,3±0,1	7,9±0,2	6,1±0,2	6,2±0,4	6,0±0,1
FPG ^{AT}	7,25±0,1	7,4±0,4	7,1±0,2	6,65±0,2*	6,8±0,5$^{\mu}$	6,5±0,3	5,6±0,1$^{\#}$	5,8±0,3$^{¥}$	5,4±0,1
HbA1C (%) ^{AT}	7,55±0,2	7,69±0,3	7,41±0,1	6,35±0,04*	6,4±0,02$^{\mu}$	6,3±0,02	5,4±0,1$^{\#}$	5,1±0,6$^{¥}$	5,7±0,2

Note: B - patient data at the beginning of the study; AT - patient data after 12 months of treatment and follow-up; FPG – Fasting plasma glucose; HbA1C – glycated hemoglobin; normal values of FPG – 3.3-5.5 mmol/l; normal values of HbA1C – 4-6.4%; * - statistically significant difference when comparing the indicators between the respective groups 1 and 2 ($p<0.05$); μ - statistically significant difference when comparing the indicators between the respective groups 1a and 2a ($p<0.05$); # - a statistically significant difference when comparing the indicators between the respective groups 1 and 3 ($p<0.05$); ¥ - statistically significant difference when comparing the indicators between the respective groups 2a and 3a ($p<0.05$).

Table IV. Assessment of CVR on the ACC/AHAG on the Assessment of CVR (2013) (ASCVD Risk)

Group	Parameter	
	ASCVD Risk (%) ^{B}	ASCVD Risk (%) ^{AT}
Group 1 (n=108)	12,9±0,2	9,7±0,3
Subgroup 1a (n=28)	13,6±1,5	10,4±1,2
Subgroup 1b (n=80)	12,2±0,3	9,7±0,8
Group 2 (n=91)	11,8±0,1	9,2±0,2*
Subgroup 2a (n=17)	12,1±1,6	9,6±1,6$^{\mu}$
Subgroup 2b (n=74)	11,4±0,2	8,8±0,4
Group 3 (n=46)	6,8±0,2	6,4±0,1#
Subgroup 3a (n=11)	7,1±1,8	6,5±1,3$^{¥}$
Subgroup 3b (n=35)	6,5±0,3	6,2±0,2

Note: B - patient data at the beginning of the study; AT - patient data after 12 months of treatment and follow-up; * - statistically significant difference when comparing the indicators between the respective groups 1 and 2 ($p<0.05$); μ - statistically significant difference when comparing the indicators between the respective groups 1a and 2a ($p<0.05$); # - a statistically significant difference when comparing the indicators between the respective groups 1 and 3 ($p<0.05$); ¥ - statistically significant difference when comparing the indicators between the respective groups 2a and 3a ($p<0.05$).

Table V. Assessment of CVR on the Framingham Risk Score (FRS)

Group	Parameter	
	FRS (%) B	FRS (%) AT
Group 1 (n=108)	25,2±0,4	23,1±0,6
Subgroup 1a (n=28)	26,6±1,9	24,7±1,5
Subgroup 1b (n=80)	23,8±0,5	21,5±0,8
Group 2 (n=91)	18,7±0,2	16,7±0,4*
Subgroup 2a (n=17)	19,8±1,6	17,4±0,9μ
Subgroup 2b (n=74)	17,6±0,1	15,9±0,7
Group 3 (n=46)	15,0±0,8	12,2±0,2#
Subgroup 3a (n=11)	15,3±1,7	12,9±1,1¥
Subgroup 3b (n=35)	14,8±0,2	11,4±0,3

Note: B - patient data at the beginning of the study; AT - patient data after 12 months of treatment and follow-up; FRS - Framingham Risk Score; * - statistically significant difference when comparing the indicators between the respective groups 1 and 2 ($p<0.05$); μ - statistically significant difference when comparing the indicators between the respective groups 1a and 2a ($p<0.05$); # - a statistically significant difference when comparing the indicators between the respective groups 1 and 3 ($p<0.05$); ¥ - statistically significant difference when comparing the indicators between the respective groups 2a and 3a ($p<0.05$).

in group 2 – 9 patients, and group 3 – 7 patients. Arterial hypertension diagnosis and received treatment for it: in group 1 – 49 patients, in group 2 – 37 patients, and group 3 – 24 patients. MI was suffered in the past: in group 1 – 13 patients, in group 2 – 9 patients, and group 3 – 5 patients. Instead, during 1 year of observation, MI was additionally transferred: in group 1 – 5 patients, in group 2 – 2 patients, and group 3 – 4 patients. Stroke was suffered in the past: in group 1 – 11 patients, in group 2 – 4 patients, and group 3 – 3 patients. Instead, during 1 year of follow-up, an additional stroke: in group 1 – 3 patients, in group 2 – 4 patients, and in group 3 – 2 patients. Aspirin therapy was taken: in group 1 – 45 patients, in group 2 – 17 patients, and group 3 – 14 patients. Statins were taken: in group 1 – 27 patients, in group 2 – 14 patients, and in group 3 – 9 patients.

At the beginning of the study (BS), according to the obtained data on BMI: in group 1 – 63 patients were with grade I obesity, 31 patients had grade II obesity, 14 patients had grade III obesity; in group II – 56 patients were overweight, while 35 patients were normal weight; in group 3 – 28 patients were with I degree of obesity, 13 patients had II degree of obesity and 5 patients with obesity of III degree (Table I).

According to the data obtained as a result of the measuring AP of the patients of the 1-st and the 2-nd group and 1st and the 3rd group at the BS, no statistically significant difference was found between them ($p>0.05$). The BMI at the BS in group 1 was 32,9±1,8 kg/m^2, respectively 28,55±0,12 kg/m^2 in group 2 and 32,08±0,19 kg/m^2 in group 3. The WC index in group 1 at the BS was 112,9±1,4 cm, respectively 88,6±1,9 cm in group 2, and 109,3±1,6 cm in group 3. WHR after treatment (AT) in the group 1 was 1,05±0,2 and 0,95±0,2, respectively in the group 2 and 1,00±0,2 cm in the group 3 (Table I).

It is noteworthy that 12 months after the course of comprehensive treatment and observation, between AP of patients of the 1st and 2nd group there was a statistically significant difference, the same dynamics were also observed when comparing the 1st and 3rd groups (p<0.05) (Table I).

At the beginning of treatment, TSH in patients of subgroup 1a was 5,6±1,9 mU/L, subgroup 2a – 5,2±1,1 mU/L, and subgroup 3a 4,7±0,1 mU/L, respectively. At the end of treatment (EOT) TSH level in patients of the 1a subgroup 4,9±1,3 mU/L, the 2a subgroup – 4,6±1,5 mU/L, and the 3a subgroup 4,4±1,2 mU/L, respectively. There was a statistically significant difference between TSH levels at EOT in patients of subgroups 1a and 2a and subgroups 2a and 3a (p<0.05). FT4 – was been in normal ranges in all subgroups before and AT (Table II).

If at the BS in group 1 HbA1C was 8,5±0,2%, then after 12 months of complex treatment and observation 7,55±0,2%, against the response of 8,1±0,2% and 6,35±0,04%, respectively, in the 2-nd group. In contrast, in patients of group 3 before and after 12 months of complex treatment and observation, indicators within the norm of HbA1C were observed – 6,1±0,2% and 5,4±0,1%, respectively. According to the obtained laboratory data of FPG and HbA1C, in patients of the 1st and 2nd groups and the 1st and 3rd groups at the BS, no statistically significant difference was found between them (p>0.05). Analyzing the biochemical (BP) of the blood, namely the metabolism of hydrocarbons, there is a tendency to reduce the level of fasting plasma glucose (FPG) and HbA1C in groups 1 and 2. There was a statistically significant difference between FPG and HbA1C in patients of groups 1 and 2 and groups 1 and 3 after 12 months of study (p<0.05) (Table III).

In all study groups, at the BS, there was an increased level of triglycerides, a decrease in high-density lipoprotein, and an increase in low-density lipoprotein. The level of triglycerides slightly decreased AT, compared with a baseline before treatment, but was still extremely high, a statistically significant difference between patients 1 and 2 groups and between patients 1 and 3 groups was not observed (p>0.05). In groups 1 and 2 at the BS, there was an increase in the concentration of apolipoprotein B over 120 mg/dl, while in groups 3 this figure was within normal limits. Targets of the lipid profile in the experimental groups after the course of treatment were not achieved.

The other BP obtained at different stages of the study did not reveal the statistically significant changes in the indicators of the groups 1 and 2 and 1 and 3 (p>0.05).

At the beginning of treatment, ASCVD Risk in patients of group 1 was 12,9±0,2%, group 2 – 11,8±0,1%, and group 3 – 6,8±0,2%, respectively. At the EOT, ASCVD Risk in patients of group 1 was 9,7±0,3%, group 2 – 9,2±0,2%, and group 3, respectively 6,4±0,1%. There was a statistically significant difference between ASCVD Risk, between patients in groups 1 and 2 and groups 1 and 3 after 12 months of study (p<0.05). Patients with concomitant SH subgroups 1a, 2a, 3a before treatment (BT) and AT were statistically significantly worse than in subgroups without concomitant SH (p <0.05) (Table IV).

At the beginning of treatment, FRS in patients of group 1 was 25,2±0,4%, group 2 – 18,7±0,2%, and group 3 15,0±0,8%, respectively. At the end of FRS treatment in patients of the 1st group 23,1±0,6%, the 2nd group – 16,7±0,4%, and the 3rd group 12,2±0,2%, respectively. Patients with concomitant SH subgroups BT and AT were statistically significantly worse than in subgroups without concomitant SH (p<0.05) (Table V).

DISCUSSION

Even though many medical instruments help to individually assess the CVR in a 10-year period, covering several clinical and laboratory data of the patient, they remain quite rough instruments. More individual scales for CVR assessment are currently being developed. Future CVR scales on the way to personalized medicine may take into account individual genetic characteristics, which will significantly increase their sensitivity. However, there is no unequivocal position among scientists that the presence of SH in patients may increase CVR [5-8], so further research data may establish more accurate effects on CVR. Rarely in routine practice without targeted laboratory search, patients are diagnosed with SH and prediabetes, or a combination of these, which may be a prerequisite for T2DM, obesity, and therefore may increase CVR and CVE in the future. Meanwhile, prediabetes may not always progress to T2DM or provoke obesity. So far no definitive point has been made in their pathogenesis.

CONCLUSIONS

As a result of our study on the search and identification of RF to calculate the 10-year risk of CVR, after a course of treatment, there was a tendency to reduce this indicator in all groups. It should be noted that in subgroups 1a, 2a, 3a, ie in patients with SH there was a significantly worse CVR than in patients without SH. Despite 12 months of treatment and follow-up, new episodes of CVE were recorded in patients, which unfortunately could not be prevented. As a result, patients were provided with additional and further treatment recommendations and advice on continuing lifestyle modifications and monitoring BP with their follow-up. Given the data obtained, it can be argued that the presence of obesity in patients with SH, especially in patients with T2DM, significantly increases the risk of CVR and CVE, respectively. It is also important that in the long run CVR can be corrected due to complex and individual treatment.

REFERENCES

1. Wondmkun Y.T. Obesity, insulin resistance, and type 2 diabetes: associations and therapeutic implications. Diabetes, metabolic syndrome and obesity: targets and therapy. Diabetes Metab Syndr Obes. 2020; 13,:3611–3616.
2. Kuś A., Marouli E., Del Greco M.F. et al. Variation in normal range thyroid function affects serum cholesterol levels, blood pressure, and type 2 diabetes risk: a mendelian randomization study. Thyroid. 2021; 31(5): 721-731.

3. Choi J.R., Ahn S.V., Kim J.Y. et al. Comparison of various anthropometric indices for the identification of a predictor of incident hypertension: the ARIRANG study. Journal of human hypertension. 2018; 32(4): 294-300.
4. Fatahi S., Sohouli M.H., Rayi A. et all. The association between food insulin index and odds of non-alcoholic fatty liver disease (NAFLD) in adults: a case-control study. Gastroenterol Hepatol Bed Bench. 2021; 14(3): 221–228.
5. Huang B., Yang S., Ye S. Association between thyroid function and nonalcoholic fatty liver disease in euthyroid type 2 diabetes patients. Journal of Diabetes Research. 2020. doi: 10.1155/2020/6538208.
6. Hoshi R.A., Santos I.S., Dantas E.M. et al. Diabetes and subclinical hypothyroidism on heart rate variability. European Journal of Clinical Investigation. 2020; 50(12): e13349. doi: 10.1111/eci.13349.
7. Jin Y., Coad J., Zhou S.J. et al. Prevalence of thyroid dysfunction in postpartum women with suboptimal iodine and selenium and adequate iron status. Clinical Endocrinology. 2021. doi: 10.1111/cen.14502.
8. Kostopoulou E., Miliordos K., Spiliotis B. Genetics of primary congenital hypothyroidism—a review. Hormones. 2021; 20: 225-236.
9. Zlatkina V., Nemtzova V., Ilchenko I. Metabolic effects of levothyroxine as a part of multicomponent therapy in patients with a combination of arterial hypertension, type 2 diabetes mellitus and subclinical hypothyroidism. In Endocrine Abstracts. Bioscientifica. 2021; 73. doi: 10.1530/endoabs.73.AEP653.
10. Ning Y., Cheng Y.J., Liu L.J. 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. doi: 10.1186/s12916-017-0777-9.
11. Poznyak A., Grechko A.V., Poggio A. et al. The diabetes mellitus–atherosclerosis connection: The role of lipid and glucose metabolism and chronic inflammation. International journal of molecular sciences 2020; 21(5): 1835.
12. Xu S., Ilyas I., Little P.J. et al. Endothelial dysfunction in atherosclerotic cardiovascular diseases and beyond: from mechanism to pharmacotherapies. Pharmacological Reviews. 2021; 73(3): 924-967.
13. Demirdogen R.E. Relationship among blood boron level, diabetes mellitus, lipid metabolism, bone metabolism and obesity: Can boron be an efficient indicator for metabolic diseases. Health Sci. J. 2020; 14: 1-11.
14. Cole J.B., Florez J.C. Genetics of diabetes mellitus and diabetes complications. Nature Reviews Nephrology. 2020; 16(7): 377-390.
15. Saber S., Hossain M.D., Alam M.T. et al. Association of Subclinical Hypothyroidism with Dyslipidemia in A Tertiary Care Hospital. Journal of Current Medical Practice. 2021; 18(30): 4.
16. Kolesnikova O.V., Potapenko A.V., Chupina V.I. Influence of Resistance on Cardiometabolic Risk in Non-Alcoholic Fatty Liver Disease Patients Combined with Subclinical Hypothyroidism. Metabolism-Clinical and Experimental. 2021; 116. doi: 10.1016/j.metabol.2020.154587.
17. Bednarczuk T., Brix T.H., Schima W. et al. 2021 European Thyroid Association Guidelines for the Management of Iodine-Based Contrast Media-Induced Thyroid Dysfunction. European Thyroid Journal. 2021; 10(4): 269-284.
18. Zijlstra L.E., Jukema J.W., Westendorp R.G. et al. Levothyroxine Treatment and Cardiovascular Outcomes in Older People with Subclinical Hypothyroidism: Pooled Individual Results of Two Randomised Controlled Trials. Frontiers in endocrinology. 2021; 12: 526. doi: 10.3389/fendo.2021.674841.
19. Aggarwal P., Sinha S.K., Khanra D. et al. Comparison of original and modified Q risk 2 risk score with Framingham risk score-An Indian perspective. Indian Heart Journal. 2021. doi: 10.1016/j.ihj.2021.01.016.
20. Romanens M., Szucs T., Sudano I. et al. Agreement of PROCAM and SCORE to assess cardiovascular risk in two different low risk European populations. Preventive medicine reports. 2019; 13: 113–117.
21. Santos A.S., Rodrigues A.P.S., Rosa L.P. et al. Cardiometabolic risk factors and Framingham Risk Score in severely obese patients: Baseline data from DieTBra trial. Nutrition, Metabolism and Cardiovascular Diseases. 2020; 30(3): 474-482.
22. Goff D.C., Lloyd-Jones D.M., Bennett G. et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2014; 25(2): 49-73.
23. Khanna N.N., Jamthikar A.D., Gupta D. et al. Performance evaluation of 10-year ultrasound image-based stroke/cardiovascular (CV) risk calculator by comparing against ten conventional CV risk calculators: a diabetic study. Computers in biology and medicine. 2019; 105: 125-143.
24. American College of Cardiology/American Heart Association Guideline on the Assessment of Cardiovascular Risk (2013) (ASCVD Risk). http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/
25. Sohn C., Kim J., Bae W. The framingham risk score, diet, and inflammatory markers in Korean men with metabolic syndrome. Nutrition research and practice. 2012; 6(3): 246-253.

The work was carried out in accordance with the plan of the research program of the Department of Therapy and Family Medicine of the Faculty of Postgraduate Education and Pre-University Training of Uzhhorod National University "Optimization of prevention and treatment of obesity and diabetes mellitus and Helicobacter», where the authors are co-authors.

ORCID and contributionship:
Taras I. Griadil: 0000-0002-1048-0656 [A-F]
Ivan V. Chopey: 0000-0003-4626-0855 [A-F]
Ksenia I. Chubirko: 0000-0002-4379-0538 [A-F]
Snizhana V. Feysa: 0000-0002-5064-8222 [A-F]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Taras I. Griadil
Uzhhorod National University
148 Sobranetska str., 88017 Uzhhorod, Ukraine
tel: +380990080218
e-mail: taras.griadil@uzhnu.edu.ua

Received: 19.06.2021
Accepted: 16.09.2021

A – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article