

Research Article

Role of Obesity and Diabetes in the formation of Thyroid Nodules - Analysis of Data from Bulgarian Population Screening in 2024

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Abstract

Thyroid nodules (TN), obesity and diabetes affect millions of people individually and in combination, which suggests the existence of pathogenetic link between them. *Aim:* To establish the current prevalence of TN in the country and its connection with some of the risk factors causing the disease - gender, age, obesity and diabetes. *Material and methods:* 936 subjects were divided into three age groups: 20-44 years - 342 (36.5%), 45-59 years - 301 (32.2%) and 60-79 years - 293 (31.3%); Body Mass Index (BMI) was calculated and normal, overweight, and obese groups were formed; TSH (ECLIA-sandwich method), FT4 (competitive ECLIA method) were tested; oGTT was performed to determine plasma glucose at 0 and 120 minutes; Ultrasound examination was applied. *Results:* Thyroid nodules were detected in 40.85% (382/935) of the subjects, with higher prevalence in women compared to men - 46.4% (222/478) vs. 35.0% (160/457), $p < 0.05$. The prevalence of TN increased with age: 60-79 years vs. 20-44 years - more significantly in the overall group (54.3%, 159/293 vs. 29.2%, 100/342, $p < 0.001$) and in women (59.9%, 103/172 vs. 30.2%, 48/259, $p < 0.001$), but less in men (46.3%, 56/121 vs. 28.4%, 52/183, NS). Out of the 382 individuals with TN, only 27.5% (105/382) had normal weight ($BMI < 25 \text{ kg/m}^2$), while 72.5% (277/382) were overweight or obese ($BMI \geq 25 \text{ kg/m}^2$), $p < 0.001$. Among diabetics ($n=155$), 46.5% (72/155) had both type 2 diabetes (T2D) and TN. It was established that 38.1% (59/155) of them had $BMI \geq 25 \text{ kg/m}^2$, whereas only 8.4% (13/155) were with normal weight ($BMI < 25 \text{ kg/m}^2$), $p < 0.02$. In the group of patients with TN ($n=382$), 18.8% (72/382) had a combination of TN and T2D, with 15.4% (59/382) having $BMI \geq 25 \text{ kg/m}^2$ and only 3.4% (13/382) having normal weight ($BMI < 25 \text{ kg/m}^2$), NS. Among the individuals with $BMI \geq 25 \text{ kg/m}^2$ ($n=637$), TN was present in 43.5% (277/637), of whom 21.3% (59/277) had T2D as well. Thus, approximately one in five individuals with $BMI \geq 25 \text{ kg/m}^2$ and TN, also had T2D. *Conclusion:* The current data clearly demonstrate very strong connection between obesity, T2D and TN. When any of these conditions are present, we should be look for the other two in order to ensure early diagnosis and appropriate therapeutic intervention.

Keywords

Thyroid Nodules, Hypothyroidism, Obesity, Diabetes Type 2

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1. Introduction

Thyroid diseases as well as diabetes mellitus are widespread among the population and their prevalence increases with age. Studies indicate a direct link between these two conditions [1]. The normal thyroid gland measures approximately 4 to 4.8 cm in sagittal, 1 to 1.8 cm in transverse, and 0.8 to 1.6 cm front-back direction, which corresponds to volume of 7 to 10 ml measured by ultrasound and 10 to 20 grams average weight. The size of the thyroid, which is larger in men, increases with age and depends on body size. Thyroid enlargement can be diffuse (diffuse goiter). The goiter may involve one or more nodules and is called nodular goiter or nontoxic multinodular goiter. The thyroid tissue may enlarge without affecting its normal function [2].

American Thyroid Association - ATA (2022) reports that thyroid nodules (TN) are very common and can be found in more than half of the US population [3].

Meanwhile, the International Diabetes Federation (IDF) states that in 2021, about 11% of the global population aged 20-79 years (approximately 537 million people) live with diabetes [4].

The research program Global Burden of Disease Study at Washington University (GBD), involving researchers from 160 countries, assesses the global and regional prevalence of socially significant diseases, mortality, and disability caused by major illnesses and the related risk factors. In 2021, GBD published data on the prevalence of obesity and overweight both globally and regionally. It was established that approximately 1.00 billion adult men (95% CI: 0.989-1.01) and 1.11 billion adult women (95% CI: 1.10-1.12) were overweight or obese [5]. These diseases affect millions of people both individually or in various combinations, which suggests pathogenetic connection between them. Only about 5-7% of TN in adult population can be diagnosed with physical examination, while ultrasound examination can detect thyroid nodules in 20% to 76% of the surveyed individuals, which correlates with autopsy findings [6].

Although evidence concerning the effect of iodine on the natural development of TN is scarce, the relationship between iodine intake and the appearance of TN has been the subject of numerous studies [7]. TN are more common in countries, where the population has proven iodine deficiency [8]. The prevalence of goiter depends on the level of iodine deficiency in the population. With mild iodine deficiency, the prevalence of goiter is 5% to 20%. In cases of moderate deficiency, the incidence increases and reaches 20-30%, while in severe iodine deficiency, the prevalence exceeds 30%. Thus even with the use of iodine, there is increase in the cases of TN. In fact, despite the introduction of iodized salt and the elimination of iodine deficiency in most countries of the world, the actual prevalence of thyroid nodules remains largely unknown [8]. At present, the data regarding the mechanism by which excessive iodine intake leads to the development of TN are still unconvincing [9]. Due to diverse epidemiological condi-

tions worldwide, there has been a long-standing debate regarding the relationship between the prevalence of TN and iodine deficiency.

External ionizing radiation or radioactive iodine (either accidental or due to medical exposure) can cause abnormalities of the thyroid gland. Individuals exposed to radiation at under 20 years of age have increased incidence of TN in their early years and papillary thyroid cancer as they grow up. Genetic factors and mutations, some of which are specific for benign nodules and others associated with papillary thyroid carcinoma, should be taken into account.

The role, which gender and advanced age play in increasing frequency of TN, has been confirmed in numerous studies indicating that the female-to-male ratio for TN is approximately 3 to 4:1 [10]. Women are about four times more likely to develop goiter compared to men, with no racial differences observed [11]. There is no solid evidence of connection between the X chromosome and goiter [12]. Estrogen receptors are present in thyroid follicular cells in normal and neoplastic tissue, which may influence thyroid-stimulating hormone (TSH) and thereby play a role in the formation of TN. In vitro studies have demonstrated that estrogens induce proliferation of thyroid follicular cells, suggesting that estrogens may be an important risk factor for the development of goiter and the formation of TN [13].

With the rapid improvement of ultrasonographic (US) technology in recent years and the availability of high-frequency transducers, small thyroid lesions (up to 2 mm in size) can now be detected [14]. It is unclear whether the rise in the prevalence of multinodular goiter is due to real absolute rise or whether it is simply because of the increased detectability owing to improved equipment, the introduction of educational programs, and the implementation of regular screenings.

However, good imaging diagnostics and screening are not the only reasons for the rising incidence. Obesity, metabolic syndrome, insulin resistance, and diabetes may also be factors contributing to the increased frequency of thyroid nodules [2, 15-17]. The investigation of the pathophysiological pathways involved in this process includes stimulating the MAPK cascade (Mitogen-activated protein kinase) through insulin signaling, as well as activating the IGF receptor pathway [2]. Insulin resistance is cited as a cause of thyroid enlargement. In a study by Rezzonico et al., nodules were observed in 53% of patients with insulin resistance, regardless of obesity, while the frequency of nodules was only 19% in patients without insulin resistance [18]. In another study by Rezzonico et al., among patients treated with metformin for insulin resistance, it was demonstrated that the volume of the thyroid gland decreases without the administration of thyroid hormone therapy [19].

The AIM of our study is to determine the current prevalence of thyroid nodules in the country and the connection

with some of the risk factors for their development—gender, age, obesity and diabetes.

2. Material and Methods

The study was carried out from 25th March to 16th May 2024 in 16 regions with 51 nests. 1352 individuals from the age of 20 to 79 were invited. They were randomly selected from the regional population registers according to age and

gender. A total of 936 people (69.2%) agreed to participate, signed informed consent, and were included in the study - 479 women (51.1%) and 457 men (48.9%). The mean age of the participants was 50.5 ± 13.6 years (from 20 to 79). The studied subjects were divided by gender and age in three age groups according to the last population census of 2022: 20-44 years - 342 (36.5%), 45-59 years - 301 (32.2%), 60-79 years - 293 (31.3%), [Table 1](#) [20].

Table 1. Distribution by gender and age of 936 subjects and the ratio between the two genders - in total and in the three age groups.

Gender, age, number (%)	20-44 years	45-59 years	60-79 years	Total
Women	159 (33.2%)	148 (30.9%)	172 (35.9%)	479 (100%)
Men	183 (40.0%)	153 (33.5%)	121 (26.5%)	457 (100%)
Total	342 (36.5%)	301 (32.2%)	293 (31.3%)	936 (100.0%)
Ratio between the two genders				
Women	159 (46.5%)	148 (49.2%)	172 (58.7%)	479 (51.2%)
Men	183 (53.5%)	153 (50.8%)	121 (41.3%)	457 (48.8%)
Total	342 (100%)	301 (100%)	293 (100%)	936 (100%)

Precise criteria for the selection of the study participants were set in advance. The participants in the study were divided into groups by their age, gender and place of residence. This distribution was made according to the data from the population census in Bulgaria by the National Statistical Institute (NSI), documented in December 2022. Non-institutionalized individuals from the population were studied as advised in the Recommendations of NHANES (2022) [21]. The data came from cross-sectional population-based multicenter study of the Bulgarian Society of Endocrinology. The regions for the study were preselected and the optimal representative number of subjects from each region was determined after thorough statistical analysis.

The sample size was calculated with the expectation of at least 6% prevalence of the studied variable among the target population, 95% confidence level and 5% absolute precision. The geographic regions, the nests, the gender and age distribution of the sample were planned to represent the adult population (from 20 to 79 years). All participants signed informed consent approved by the local ethics committee at the University Hospital, and the research was conducted in accordance with the Declaration of Helsinki. The participants filled in a questionnaire containing demographic data, current health status, medical history, family history for cardiovascular, thyroid disorders and diabetes, past history and therapies, menstrual status for the females, and current smoking. Height, weight and BMI (kg/m²) were measured. The established criteria for classification according to BMI were used:

normal (BMI < 25 kg/m²), overweight (BMI ≥ 25 - 29.9 kg/m²), obesity (BMI ≥ 30 kg/m²). Arterial blood pressure was measured in seated position after five minutes rest. Hypertension was defined according to the IDF consensus for T2D, which recommends arterial pressure levels up to 130/80 mmHg and the same recommendation in the Guideline of European Society of Hypertension (ESH) [22, 23].

Diabetes status was defined according to the criteria of the WHO/IDF 2016 report [24]. Standard OGTT (oral glucose tolerance test) of 75 g glucose in 200 ml water was performed with measuring plasma glucose on the day of blood sampling. Venous blood samples were taken from the cubital vein after a 12-hour overnight fasting. Glycemia was measured at 0 and at 120 minutes during the test. Exceptions were made only for individuals who presented evidence of existing diabetes. HbA1c was also examined by certified standardized method NGSP according to the Diabetes Control and Complications Trial (DCCT) [25]. All laboratory tests were performed in a certified central laboratory on the day of blood sampling. Analysis was performed based on the criteria from the WHO/IDF 2016 report for determining the actual status of diabetes in our country [24].

2.1. Methodology

The lack of consensus regarding the reference ranges for thyroid hormone levels used for diagnosis, as well as the sensitivity analysis, has led to some differences in the as-

assessment of the prevalence of thyroid dysfunction. The most commonly cited reference range for TSH concentration in the clinical literature has set the upper limit at 4.0 mIU/L and the lower limit at 0.4 mIU/L [26]. Electrochemiluminescence immunoassay (ECLIA) for the *in vitro* quantitative determination in human serum was used for the determination of TSH, with measuring range of 0.005-100 μ IU/mL > 20 years TSH: 0.27 - 4.20 mIU/L. The conceptual definition of subclinical hypothyroidism (increased TSH and normal free thyroid hormone) and clinical hypothyroidism (high TSH and low free thyroid hormone) is currently in effect [27]. Our criteria for assessing thyroid function are as follows: subjects with TSH values below 0.27 mIU/L were grouped as hyperthyroid and those with values above 4.20 mIU/L - as hypothyroid. Subclinical hypothyroidism was defined as TSH > 4.20 mIU/L with normal FT4 levels (11.9 - 21.6 pmol/L) and overt hypothyroidism - as TSH > 4.20 mIU/L with FT4 < 11.9 pmol/L. Subclinical hyperthyroidism was defined as TSH < 0.27 mIU/L with normal FT4 levels (11.9 - 21.6 pmol/L) and overt hyperthyroidism - as TSH < 0.27 mIU/L with FT4 > 21.6 pmol/L.

2.2. Laboratory Analysis

After a 12-hour overnight fast, cubitalis venipuncture blood samples were taken to determine TSH (Thyroid-Stimulating Hormone), FT4 (Free thyroxine). The laboratory analysis of all blood samples was performed in a central laboratory in the morning on the day of taking the fasting blood sample. Thyroid-Stimulating Hormone (TSH) - reference limits 0.27 - 4.2 mIU/L was quantified using the ECLIA-sandwich method of the Cobas e601 analyzer; Free thyroxine (FT4) with a competitive ECLIA method (reference limits 11.9 - 21.6 pmol/L).

Venous blood was collected in tubes containing Na2EDTA and NaF, which serve as glycolysis inhibitors for stabilizing glucose levels in the samples. The samples were transported to the laboratory after centrifugation. All samples were analyzed in a central laboratory on the day of taking the blood sample. Glucose was quantitatively determined using enzyme reference method with hexokinase (Roche reagent) on Cobas e501 analyzer. The results are presented in mmol/L. Assessment of precision and controls:

- 1) Intra-assay: Level 1 (n=6) CV=1.12%; Level 2 (n=6) CV=0.42%
- 2) Inter-assay: Level 1 (n=30) CV=1.25%; Level 2 (n=30) CV=1.58%
- 3) Two levels of intra-laboratory quality control were conducted on a daily basis. The laboratory participates in two EQA systems - the Bulgarian EQAS and IN-STDAND and holds a certificate for this parameter.

Venous blood was taken separately in a special tube with the anticoagulant EDTA for the determination of HbA1c by immunoturbidimetric method after hemolysis of a whole blood sample. The method was certified following the National Program for Standardization of Glycated Hemoglobin

(NGSP) and standardized according to the Diabetes Control and Complications Trial (DCCT) [25].

2.3. Ultrasound Examination

Ultrasound examination is a simple reproducible non-invasive method, widely used for the diagnosis of TN, with the ability to differentiate benign and malignant nodules through specific ultrasound imaging characteristics [28]. Ultrasound examination of the neck often identifies TN, which result from abnormal growth in the thyroid tissue. These lesions can be solid, cystic (fluid-filled), or mixed. The TI-RADS (Thyroid Imaging Reporting and Data System) is a classification method that categorizes thyroid nodules into risk zones based on specific features such as size, echogenicity, border, shape, and calcification. Based on this, clinicians can decide whether to do biopsy or make another assessment [29]. To determine the volume and structural characteristic of the thyroid gland, an ultrasound examination was performed with a Digital Color Doppler Diagnostic Scanner, C5 Ex (Shenzhen Landwind Medical Industry, China). According to a standard formula, the volume of the thyroid gland in mL was calculated [30]. According to the protocol of this study, thyroid nodules with size of ≥ 5 mm were registered, and their number was recorded (either solitary or multiple), as well as their ultrasound structural characteristics - solid, cystic or mixed.

2.4. Statistical Analysis

- 1) Descriptive and evaluation methods - Variance analysis of quantitative variables - mean, median, standard deviation, standard error of the mean, 95% confidence interval of the mean and median, minimum, maximum. Frequency analysis of qualitative variables (nominal and rank), which includes absolute frequencies, relative frequencies (in percentages), cumulative relative frequencies (in percentages).
- 2) Hypothesis Testing Methods - Chi-square test or Fisher's exact test - search for a relationship between two qualitative variables. Logistic regression analysis for odds ratios (OR).

The statistical analysis was performed using IBM SPSS Statistics 25. The critical significance level we used was $\alpha = 0.05$. The corresponding null hypothesis is rejected when the P-value is less than α .

3. Results

Of the 935 examined individuals (aged 20-79 years), women numbered 478 (51.1%) and men 457 (48.9%). Among them, 40.85% (382/935) were diagnosed with TN. In the female group, the prevalence was significantly higher than in males - 46.4% (222/478) compared to 35.0% (160/457), $p < 0.05$. When comparing the frequency in women and men in

the group with nodes (n=382), then women are 58.1% (222/382), and men - 41.9% (160/382), Fisher's Exact Test, $p < 0.001$, OR = 1.61, Therefore there is a significantly higher chance of having TN in women compared to men, Table 2.

Table 2. Distribution of individuals with TN - total and for both genders.

	With TN - number (%)	Without TN - number (%)	Total - number (%)
Gender			
Women	222 (46.4%)*	256 (53.6%)	478 (100%)
Men	160 (35.0%)*	297 (65.0%)	457 (100%)
Total	382 (40.85%)	553 (59.15%)	935 (100%)
	* $p < 0.05$		
Ratio between the two genders			
Women	222 (58.1%)**	256 (46.3%)	478 (51.1%)
Men	160 (41.9%)**	297 (53.7%)	457 (48.9%)
Total	382 (100%)	553 (100%)	(100%)

**Fisher's Exact Test - $p < 0.001$; OR = 1.61. Women are significantly more likely to have TN than men.

Table 3 presents distribution of cases with and without TN - in total and by gender in the three age groups. As age increases, the frequency of TN rises - significantly in total and among women, and not significantly among men. This illustrates the role of age in the prevalence of TN.

Table 3. Distribution of cases with TN and without TN in the three age groups - total and for women and men.

Group	With TN - number (%)	Without TN - number (%)	Total - number (%)
20-44 years	100 (29.2%)*	242 (70.8%)	342 (100%)
45-59 years	123 (41.0%)**	177 (59.0%)	300 (100%)
60-79 years	159 (54.3%)*/**	134 (45.7%)	293 (100%)
Total	382 (40.9%)	553 (59.1%)	935 (100%)
p	*p < 0.001; **p < 0.05		
Distribution of WOMEN in group with TN and without TN in the three age groups			
20-44 y	48 (30.2%)*	111 (69.8%)	159 (100%)
45-59 y	71 (48.3%)	76 (51.7%)	147 (100%)
60-79 y	103 (59.9%)*	69 (40.1%)	172 (100%)
Total	222 (46.4%)	256 (53.6%)	478 (100%)
p	*p < 0.001		
Distribution of MEN in group with TN and without TN in three age groups			
20-44 years	52 (28.4%)	131 (71.6%)	183 (100%)
45-59 years	52 (34.0%)	101 (66.0%)	153 (100%)
60-79 years	56 (46.3%)	65 (53.7%)	121 (100%)
Total	160 (35.0%)	297 (65.0%)	457 (100%)

Thyroid dysfunction was diagnosed in 152 individuals (135 with hypothyroidism and 17 with hyperthyroidism) or a total of 16.2% (152/936) of those studied. 39 cases of thyroid dysfunction were found among individuals with thyroid nodules (35 with hypothyroidism and 4 with hyperthyroidism), representing 4.1% (39/936) of all examined. The distribution between genders is as follows: women numbered 29 (16 with hypothyroidism and 3 with hyperthyroidism, with a ratio of 5:1), while men were three times fewer—10 in total (9 with hypothyroidism and 1 with hyperthyroidism, ratio 9:1). Newly diagnosed subclinical hypothyroidism was identified in 24 individuals with thyroid dysfunction (15 women and 9 men). Clinical hypothyroidism was registered in one woman. Only one of all women had newly discovered subclinical hyperthyroidism in the presence of TN. In 66.7% (26/39) of cases, thyroid dysfunction in individuals with TN was newly diagnosed. In more than 92% of these cases, hypothyroidism was sub-

clinical.

The combination of TN and type 2 diabetes (T2D) was found in 7.7% (72/935) of all participants. Among individuals with TN, the prevalence of diabetes was 18.8% (72/382). In the diabetic group, 46.4% (72/155) of the people had TN, which is much higher occurrence. These high percentages of co-occurrence of the two conditions highlight the need for patients with diabetes to be screened for thyroid pathology, and conversely, patients with thyroid pathology to be regularly tested for diabetes.

The distribution of TN among individuals with T2D and BMI ≥ 25 kg/m² should be studied in order to assess the combined influence of diabetes and high weight on the development of TN. In Table 4 below shows the total distribution and the distribution for both genders. The groups with BMI ≥ 25 kg/m² and with BMI 18.5-24.99 kg/m² (normal weight) were compared, both in total and by gender.

Table 4. Nodular goiter, diabetes and obesity or overweight.

Group	Nodular goiter and T2D (total)	Nodular goiter and T2D (women)	Nodular goiter and T2D (men)
Obesity (> 30 kg/m ²)	39 (54.2%)	15 (46.9%)	24 (60.0%)
Overweight (25-29.99 kg/m ²)	20 (27.8%)	8 (25.0%)	12 (30.0%)
BMI ≥ 25 kg/m ²	59 (82.0%)*	23 (71.9%)**	36 (90.0%)*
Normal weight (18.5-24.99 kg/m ²)	13 (18.0%)*	9 (28.1%)**	4 (10.0%)*
Total	72 (100%)	32 (100%)	40 (100%)

*p < 0.001 - in total and men; **p < 0.05 - > 0.02 in women (BMI ≥ 25 kg/m² v.s. BMI < 25 kg/m²)

4. Discussion

The frequency of thyroid lesions in Europe is on the increase. There are several classical factors leading to the development of nodular goiter: areas with iodine deficiency, female gender, and advanced age [31].

Widespread iodization of salt across the entire territory of Bulgaria was introduced in 1994. In 2005, an international expert group assessed that the country had successfully addressed the problem of iodine deficiency [32, 33]. According to WHO / UNICEF / ICCIDD, iodine deficiency does not exist in countries where over 90% of the households use iodized salt. Bulgaria is officially among these countries [34]. Our country has sufficient levels of iodine, which allows correct interpretation of the obtained data and excludes iodine deficiency as risk factor for the development of TN. Data from our previous screening in 2012 show that 24.4% of the participants (32.1% of women and 15.7% of men, p < 0.001) had thyroid nodules (TN) with a diameter of ≥ 5 mm. Increase in the prevalence of TN with advancing of age was observed -

for women: from 8% in the 20-44 age group to 52% in the elderly group (60-79); for men: from 6% in the 20-44 age group to 27% in the elderly (60-79) [35].

In this screening, we report that the prevalence of TN is 40.85% (382/935), with a significantly higher frequency in women compared to men - 46.4% (222/478) compared to 35.0% (160/457), p < 0.05. As observed over the 12-year period, the overall prevalence increased from 24.4% in 2012 to 40.85% in 2024. The same trend is present for both genders - women: from 32.1% in 2012 to 46.4% in 2024; men: from 15.7% in 2012 to 35.0% in 2024. As can be seen from the data of our material, with advancing age the frequency of TN increases significantly and in the young age group (20-44 years) from 29.2% (100/342) reaches 41.0% (123/300) at 45-59 years and 54.3% (159/293) in the third age group (60-79 years) - p < 0.001 (20-44 years vs. third group) and p < 0.05 (45-59 years vs. third group), Table 3. The role of age is the second powerful factor in the genesis of TN. In the TN group (n=382), the young group accounts for 26.2% (100/382), the middle-aged group for 32.2% (123/382), and the elderly for 41.6% (159/382). The difference between the young and elderly

groups is significant - $p < 0.02$.

However, the ratios between genders differ in each case, indicating that age influences the prevalence of TN in a different way for the two genders. Among women, the prevalence of TN in the elderly group is a lot higher compared to the young age group - 59.9% (102/222) vs. 30.2% (48/222), $p < 0.001$. In contrast, among men, aging does not affect TN prevalence to such a high degree, [Table 3](#).

Within each age group, the ratio of TN prevalence between genders varies, and the likelihood of having TN differs for women compared to men across the three age groups. In the young age group (20-44 years), there is no significant difference between genders. However, in the middle age group (45-59 years) and the elderly age group (60-79 years), women have much higher chance of having TN. Specifically, in the 45-59 age group, women are 1.82 times more likely to have TN than men - 48.3% (71/147) vs. 34.0% (52/153), Fisher's Exact Test, $p = 0.014$; OR = 1.815 ([Table 3](#)). In the 60-79 age group, women are 1.73 times more likely to have TN compared to men - 59.9% (103/172) vs. 46.3% (56/121), Fisher's Exact Test, $p = 0.024$; OR = 1.733 ([Table 3](#)).

Thus, the strength and interaction of these two powerful risk factors for the formation of TN nodules (gender and age) were analyzed more precisely. These factors compete for dominance; while in the younger group, age is the primary factor, in middle-aged and elderly groups, gender is the leading factor.

Thyroid diseases, as well as diabetes mellitus, are common chronic endocrine conditions that often coexist. A higher prevalence of thyroid disorders is observed among patients with type 1 diabetes (T1D) and type 2 diabetes (T2D) compared to the general population. Conversely, a higher prevalence of diabetes is noted among patients with thyroid diseases [\[36\]](#).

Along with the main risk factors for nodular goiter (female gender and advancing age) additional risk factors include subclinical hypothyroidism, diabetes, and obesity or overweight. In the current material, 31.6% (294/931) of the examined individuals had normal weight ($BMI < 25 \text{ kg/m}^2$), while 68.4% (637/931) had $BMI \geq 25 \text{ kg/m}^2$ ($p < 0.001$, $BMI \geq 25 \text{ kg/m}^2$ vs. normal weight). From them, 327 individuals (35.1%) were overweight ($BMI > 25 \div 29.9 \text{ kg/m}^2$), and 310 (33.3%) - obese ($BMI > 30 \text{ kg/m}^2$).

Among individuals with obesity ($n=310$), TN existed in 15% (140/931) of all examined, while among the 327 overweight individuals, TN was present in 14.7% (137/931). Thus, out of all 931 participants, those with $BMI \geq 25.00 \text{ kg/m}^2$ had a nodular goiter prevalence of 29.75% (277/931), whereas among those with normal weight it was only 11.45% (105/931), $p < 0.001$ ($BMI \geq 25 \text{ kg/m}^2$ vs. normal weight).

In the group of overweight and obese individuals ($n=637$), the prevalence of TN was 43.5% (277/637), with similar rates among those who were overweight - 41.9% (137/327) and obese - 45.16% (140/310). In the group with normal weight ($n=294$), the prevalence of TN was 35.7% (105/294), which is

not statistically significant.

Out of a total of 382 individuals with TN, only 27.5% (105/382) had normal weight ($BMI < 25 \text{ kg/m}^2$). The remaining 277 individuals with TN, or 72.5% (277/382), were overweight or obese ($BMI \geq 25 \text{ kg/m}^2$), $p < 0.001$. All these facts clearly indicate that high body weight contributes to the pathogenesis of TN.

When we analyzed thyroid dysfunction among individuals with TN ($n=382$), we found out that only 1.05% (4/382) were hyperthyroid, while 9.16% (35/382) were hypothyroid - that is, a total of 10.2% (39/382) of the individuals with TN had thyroid dysfunction. The remaining 89.8% (343/382) were euthyroid. Our data showed that thyroid dysfunction was newly diagnosed in 66.7% (26/39) of the cases among individuals with TN. About 92% (36/39) of these cases were with subclinical hypothyroidism.

Subclinical hypothyroidism is the most common thyroid dysfunction, which is often discovered incidentally and may not be diagnosed for a long time. TSH is a potent, natural growth factor for thyroid cells, playing a crucial role in the development of formations in the thyroid gland. TSH activates adenylate cyclase by binding to TSH receptors on thyrocytes, increasing levels of cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA). Thus, TSH regulates the growth and proliferation of thyroid cells [\[37\]](#). To summarize, subclinical hypothyroidism is considered a potential risk factor for the development of TN, which our data confirmed.

Studies also show that patients with poorly controlled blood sugar levels in T2D have high risk of subclinical hypothyroidism, which increases with higher levels of glycated hemoglobin [\[38\]](#). Most patients with diabetes have high plasma levels of TSH, which can stimulate the formation of TN. There are studies indicating that in patients with T2D, the nocturnal peak of TSH is low or absent, and the TSH response to Thyrotropin-Releasing Hormone (TRH) is impaired, which causes hypothyroidism [\[39\]](#).

Diabetes, which is a chronic metabolic disease characterized by high blood sugar levels, is the most common endocrine disorder. The rapid development of the global economy has led to changes in lifestyle and earlier aging of the population, resulting in growing prevalence of diabetes each year. Approximately 537 million adults worldwide have diabetes, with type 2 diabetes accounting for nearly 90% [\[40, 41\]](#).

In the present material, among patients with TN, the prevalence of diabetes is 18.8% (72/382). This means that nearly one in five patients with TN also has diabetes. In the group of diabetics, TN is present in 46.4% (72/155), indicating a very high frequency of co-occurrence of the two diseases. According to our data 32 women and 40 men, 72 of all examined individuals carried both diseases - T2D and TN. It was established that 82% (59/72) of the individuals with $BMI \geq 25 \text{ kg/m}^2$ had T2D and TN, whereas in cases with normal weight, the frequency was only 18% (13/72), $p < 0.001$. Among

women with BMI ≥ 25 kg/m² the prevalence is 71.9% (23/32) compared to 28.1% (9/32) in women with normal weight, $p < 0.05 \div > 0.02$. There was a large difference among men - the combination was present in 90.0% (36/40) of men with BMI ≥ 25 kg/m² versus only 10.0% (4/40) among men with normal weight, $p < 0.001$. There was no significant difference between genders with BMI ≥ 25 kg/m² in the frequency of cases with both T2D and TN, as shown in Table 4.

It is evident that high BMI is a more important factor contributing to the increased prevalence of TN than gender. This raises the question of the relationship between the following factors - diabetes, obesity, and the development of TN. What are the specific factors in diabetes and obesity that clearly contribute to the formation of TN?

The studies by Masenga SK. et al. (2023) and Yaribeygi H. et al. (2023) are dedicated to the role of oxidative stress which is typical for diabetes. Hyperglycemia in diabetics can induce the accumulation of ROS (reactive oxygen species), leading to the activation of the polyol pathway, the generation of advanced glycation end products (AGEs), and the activation of protein kinase C (PKC), thereby increasing the level of oxidative stress [42]. On one hand, island β -cells are directly or indirectly affected by oxidative stress, which impairs their function; on the other hand, increased levels of ROS in diabetics and the oxidative stress can affect both cell growth and proliferation of thyrocytes [43]. The accumulation of ROS and free fatty acids increases the expression of uncoupling proteins (UCPs), located in the mitochondrial membrane, including thyroid cells, resulting in rise in their proliferation. Thus, this mechanism also stimulates the formation of TN [44, 45].

Other researchers are studying the role of inflammatory cytokines and chemokines, which increase under conditions of prolonged hyperglycemia in diabetic patients (VEGF, IL, TNF, NF- κ B), and are closely linked to tumorigenesis [46, 47].

There are other factors in diabetes that contribute to the development and growth of TN. In patients with T2D, peripheral insulin resistance is commonly present, which leads to compensatory hyperinsulinemia. This condition can alter the blood flow pattern in the thyroid nodules, thereby changing the distribution, density, and structure of the blood vessels in the thyroid gland, which can influence the growth and development of TN [48, 49]. Hyperinsulinemia associated with insulin resistance has a proliferative effect on thyroid tissue, leading to its enlargement and tendency to form TN [50].

Leptin (produced in adipose tissue) also plays a very important role in stimulating the formation of TN. Leptin is a bioactive molecule that binds to receptors and acts on the hypothalamus to inhibit appetite. It regulates insulin secretion, promotes cellular proliferation, and stimulates angiogenesis. Leptin levels are significantly higher in individuals with T2D compared to healthy individuals, and the leptin receptor is expressed in thyroid tumor cells [51]. Previous studies indi-

cate that insulin resistance, hyperglycemia and leptin influence the level of serum thyroid-stimulating hormone (TSH). In turn, TSH increases leptin secretion from adipose tissue [52].

It can be summarized that abnormal secretion of TSH, oxidative stress damage, insulin resistance, hyperinsulinemia, higher levels of IGF-1, abnormal leptin secretion, increased production of inflammatory factors and chemokines are fundamental for the formation of TN. Another mechanism may be considered - physical pressure from excessive obesity and accumulation of fatty tissue in the neck area, which could affect thyroid function and potentially favor the formation of nodules.

In our material, the combination of T2D, obesity and TN is not rare, and undoubtedly, these additional factors, which have significantly increased in recent years, contribute to the higher prevalence of TN. In the screening conducted in 2012, the prevalence of T2D was 9.6%, whereas in 2024, it increased to 15.7% ($p < 0.001$) [53]. Men predominate among the individuals with diabetes in our population. While among women the prevalence of T2D had increased only moderately, it had almost doubled among men (women: 2012 - 7.8% and 2024 - 10.4%, $p < 0.016$; men: 2012 - 11.5% and 2024 - 21.2%, $p < 0.001$). With advancing of age, the prevalence of T2D rose across all decades, with significant increases observed in the 30-39, 40-49, and 60-69 age groups (from 1.7% to 4.5%, $p < 0.047$; from 4.9% to 9.9%, $p < 0.020$; from 17.5% to 29.9%, $p < 0.001$, respectively). The increase in the number of diabetics in our country followed the global trends, according to data from the Diabetes Atlas of the International Diabetes Federation (2021) [4].

Obesity is often connected with T2D. Screening in 2024 revealed that 88.3% (136/154) of the diabetics had obesity and overweight (BMI ≥ 25 kg/m²), while only 11.7% (18/154) had normal weight, $p < 0.001$. An additional logistic analysis, which was conducted in order to assess the odds ratio of overweight and obesity influencing the development of diabetes as a dependent variable, showed significant impact by both. Overweight increased the chance of developing diabetes - OR = 1.821 (95% CI: 1.008-3.288), $p < 0.047$; obesity had even greater effect - OR = 3.410 (95% CI: 1.935-6.010), $p < 0.001$. This illustrates how the progressively increasing diabetes, a risk factor for TN, together with obesity, contribute to the increase in the prevalence of TN in the same population over this 12-year period [54].

5. Conclusion

Analyzing from three perspectives the group diabetics (n=155), the group with TN (n=382), and individuals with BMI ≥ 25 kg/m² (n=277), we observed the following: 1) In the group of diabetics (n=155), 46.5% (72/155) had both T2D and TN - 38.1% (59/155) also had BMI ≥ 25 kg/m² and only 8.4% (13/155) were with normal weight, $p < 0.02$. 2) In the group of patients with TN (n=382), 18.8% (72/382) had both TN and

T2D, with 15.4% (59/382) having BMI ≥ 25 kg/m² and only 3.4% (13/382) with normal weight, NS. 3) Among individuals with BMI ≥ 25 kg/m² (n=637), 43.5% (277/637) had TN, and from them, 21.3% (59/277) also had T2D. Of these, 14.1% (39/277) were also obese, and 7.2% (20/277) were overweight. Thus, one in five individuals with BMI ≥ 25 kg/m² and TN also had T2D. These data clearly demonstrate strong connection between obesity, T2D, and TN. The presence of any of these conditions requires screening for the other two in order to avoid missing early diagnosis and to enable appropriate therapeutic intervention TN are highly prevalent across all populations worldwide. This requires attention and targeted actions by primary care physicians, specialists, health authorities, as well as increased public awareness [55].

Abbreviations

TN	Thyroid Nodules
BMI	Body Mass Index
oGTT	Oral Glucose Tolerance Test
TSH	Thyroid Stimulating Hormone
FT4	Free Thyroxine
ECLIA	Electrochemiluminescence Immunoassay
T2D	Type 2 Diabetes
ATA	American Thyroid Association
GBD	Global Burden of Disease Study
US	Ultrasound
MAPK	Mitogen-activated Protein Kinase
IGF-1	Insulin-Like Growth Factor-1
NSI	National Statistical Institute
NHANES	National Health and Nutrition Examination Survey
IDF	International Diabetes Foundation
ESH	European Society of Hypertension
WHO	World Health Organization
HbA1c	Glycated haemoglobin
NGSP	National Glycohemoglobin Standardization Program
DCCT	Diabetes Control and Complications Trial
Na2EDTA	Disodium Salt of Ethylenediaminetetraacetic Acid
NaF	Sodium Fluoride
NGSP	National Glycohemoglobin Standardization Program
TIRADS	Thyroid Imaging Reporting and Data System
UNICEF	United Nation Children's Fund
ICCIDD	International Council for Control of Iodine Deficiency Disorders
T1D	Type 1 Diabetes
TRH	Thyrotropin-Releasing Hormone
ROS	Reactive Oxygen Species
AGE	Age Advanced Glycation End Product
PKC	Protein Kinase C
UCP	Uncoupling Proteins
VEGE	Vascular Endothelial Growth Factor

IL	Interleukin
TNF	Tumor Necrosis Factor
NF-kB	Nuclear Factor Kappa-B
OR	Odd Ratio

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Conflicts of Interest

The authors declare no conflicts of interest.

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