ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ
ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
«Η ΔΙΑΤΡΟΦΗ ΣΤΗΝ ΥΓΕΙΑ ΚΑΙ ΣΤΗ ΝΟΣΟ»

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

Συσχέτιση της παχυσαρκίας και της διαταραγμένης γλυκόζης νηστείας με θυρεοειδικούς όζους

Αθανάσιος Τζιωρτζιώτης

Ενδοκρινολόγος - Διαβητολόγος

ΤΡΙΜΕΛΗΣ ΣΥΜΒΟΥΛΕΥΤΙΚΗ ΕΠΙΤΡΟΠΗ

Μπαργιώτα Αλεξάνδρα, Αναπληρώτρια Καθηγήτρια Παθολογίας - Ενδοκρινολογίας, Τμήμα Ιατρικής Πανεπιστημίου Θεσσαλίας, Επιβλέπουσα Καθηγήτρια

Βλυχού Μαριάννα, Καθηγήτρια Ακτινοδιαγνωστικής, Τμήμα Ιατρικής Πανεπιστημίου Θεσσαλίας, Μέλος Τριμελούς Επιτροπής

Τίγκας Στυλιανός, Αναπληρωτής Καθηγητής Ενδοκρινολογίας, Τμήμα Ιατρικής Πανεπιστημίου Ιωαννίνων, Μέλος Τριμελούς Επιτροπής

Λάρισα, 2022

UNIVERSITY OF THESSALY

SCHOOL OF HEALTH SCIENCES

FACULTY OF MEDICINE

POSTGRADUATE STUDIES PROGRAM

NUTRITION IN HEALTH AND DISEASE

DIPLOMA THESIS

Association of Obesity and Impaired Fasting Glucose with Thyroid Nodules

Larissa, 2022

CONTENTS

ACKNOWLEDGEMENTS

First of all i would like to thank the Professors of Gastroenterology Mr. Kapsoritakis and Mr. Potamianos who gave me the opportunity to participate in this postgraduate program. I would like to warmly thank my supervisor and the members of the supervision committee, Dr. Alexandra Bargiota, Dr. Stulianos Tigas and Dr. Marianna Vlychou for their valuable time, their guidance and support. Especially I would like to express my sincere gratitude to my supervisor Dr Alexandra Bargiota for her willingness to take on my project, her ideas, her precious advice, her patience and her encouragement throughout the whole project. Your support and guidance stimulated me to think in a more broad scientific way, my deepest respect and a heartfelt thank you.

ABSTRACT

The incidence of Thyroid nodules is increasing, as is that of obesity and people with impaired fasting Glucose. Associations between these conditions have been hypothesized, but they remain unclear.

This Study evaluates the strength of relation between Body Mass Index (BMI), Impaired Fasting Glucose (IFG) and the presence and number of thyroid nodules. Furthermore, we investigate the correlation of these metabolic parameters (BMI and IFG) with the existence of suspicious sonographic patterns in Greek Subjects of both sexes.

Our participants have taken a high – resolution ultrasonographic evaluation with a 13MHz linear probe, anthropometric measurements and laboratory tests. Body mass index (BMI) has been obtained by dividing the body weight (kg) to the square of height (m). Overweight and obesity have been defined as BMI $\geq$ 25 kg/m2 and $\geq$ 30kg/m2 respectively. The diagnostic criteria recommended by the American Diabetes Association have been used for the definition of Impaired Fasting Glucose (100-125mg/dl) and each venous sample have been taken after a minimum fasting period of 8 hours and serum glucose have been measured by the Glucose oxidase technique. The classification of sonographic patterns have been defined by the ACR-TIRADS based on features such as microcalcifications, echogenity, composition, shape (taller than wide), margins. Subjects with known Diabetes, pregnant women, Patients with subacute and Graves Thyroiditis have been excluded.

We have sampled 520 subjects from both sexes and various ages from Central Greece. 379 were females (72,88%) and 141 were males (27,12%), while the mean age of the total number of participants equaled 51,54 ± 16,17 years. According to BMI, participants were divided in three groups, underweight 3,46% (18/520), normal weight 21,15% (110/520) and almost 75% (392/520) overweight and obese. In total there were 384 out of 520 patients with IFG (73,85%) and 136 out of 520 without IFG (26,15%). and 44.04% (229/520) of the patients were diagnosed with nodules, not necessarily one in each.

Our Study showed a statistically significant correlation between the presence of nodules and IFG (Impaired Fasting Glucose) and AGE. The chances of having nodules proved to be higher in Patients with IGF comparing to those without and the mean age of patients diagnosed with nodules was statistically significantly higher than the mean age of patients without nodules. Furthermore showed no statistically significant correlation not only between our parameters (Gender, Age, BMI and IFG) and the Count of nodules but also for the ACR TIRADS classification. On the other hand

there are data showing a correlation between the size of nodules and BMI and AGE. Of course further large, high-quallity, randomized controlled trials are required to confirm or exclude our findings.

Keywords: Thyroid nodules, Obesity, Impaired Fasting Glucose, ACR-TIRADS Score

INTRODUCTION

Thyroid

Development, Anatomy and Physiology of the Thyroid Gland

The Thyroid is one of the biggest and most important endocrine glands of human body, as it controls the functioning of many organs and many metabolic processes. The Thyroid (the word is derived from Greek terms thyreos, meaning shield, and eidos, meaning form) is a butterfly- shaped gland (''H'' or ''U''), comprised of two lobes (lobus Right and lobus Left) which are connected with a small, thin segment of thyroid tissue, called the Isthmus. Lobes are devided in poles upper, middle and lower and extend on either side of trachea, while Isthmus cuddles trachea interiorly. 15-30% patients have another lobe, which comes from Isthmus and extends superiorly anterior to thyroid cartilage, called Pyramidal Lobe. Normal thyroid is soft in consistency, weighs approximately 12-20 gr and its dimensions are height 3-4 cm, width 1,5-2 cm and depth 1,5-2 cm [1,2]. In the opposite site of Thyroid, attached to him, there are usually four small glands named Parathyroid glands, secreting a hormone called Parathormone which regulates calcium levels in human body.

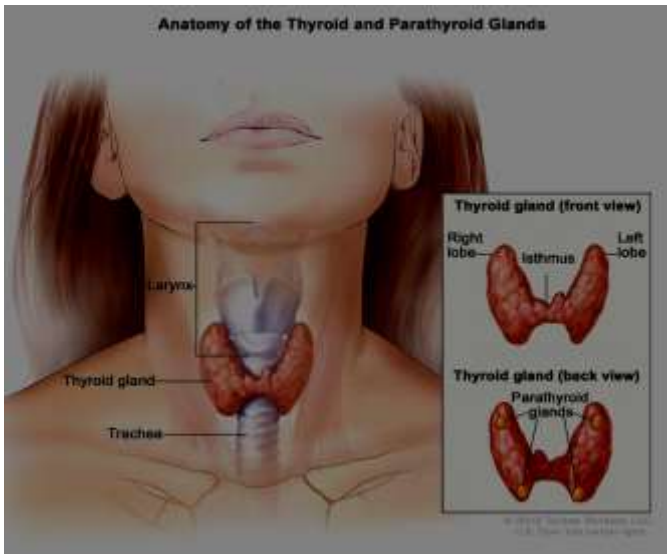

Fig. 1 Anatomy of the Thyroid and Parathyroid Glands [3]

(Source: https://www.cancer.gov/types/thyroid/patient/thyroid-screening-pdq)

Histologically, the Thyroid gland presents a particular and well organized architecture, which main structural units are some closed cavities with sphenoidal shape known as Follicles.This cavity

constitutes the morphofunctional unit of Thyroid gland, peripherally consists of a single layer of epithelial cells called thyroid follicular cells and in the centre there is the follicular lumen. Thyroid follicular cells represent the vast majority of thyroid gland and are responsible for thyroid hormone production because they contain Thyroglobulin. Other types of Thyroid cells are the epithelial cells, the thyroid stem cells and the C-cells. Throughout Thyroid gland interspersed c-cells, which produce Calcitonin, another hormone, which plays a role in calcium lowering, but even more important is that these cells are responsible for medullary thyroid cancer [1,2].

Thyroid gland growth and function are controlled by Thyrotropin (TSH), a glycoprotein produced by the thyrotrope cells of the anterior pituitary gland. The major regulating factors of TSH production are stimulation by hypothalamic TRH and suppression by thyroid hormones, known as negative Feedback. TSH is secreted in discrete pulses, has a circadian secretory pattern and performs its control ability through an interaction with TSH receptors of thyroid follicular cells. Thyroid, under the supervision and assistance of Thyrotropin, uses Jod in order to produce two major hormones, Thyroxine (T4) and Triiodothyronine (T3) [1,3]. Jod is the main component of Thyroid Hormones as T4 contains 4 jod atoms and T3 3 atoms [1]. Triiodothyronine (T3) is the activated form of Thyroxine (T4) and it is 4 times more powerful than T4 [1].

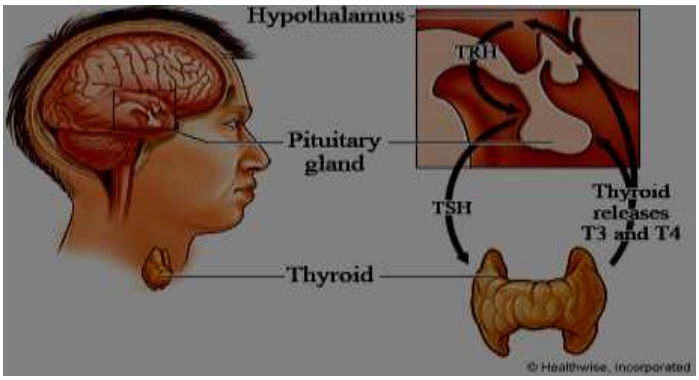

Fig. 2 Thyroid Hormone Production [3]

(Source: https://www.uofmhealth.org/health-library/ug1836)

Circulating thyroid hormones enter cells by passive diffusion and via specific transporters. They act mainly via nuclear receptors, but they also have non genomic action via stimulating mitochondrial enzymatic responses and directly on blood vessels and heart through integrin receptors. The actions are multifarious and affect different levels of human body organization. Some of the major actions of T4 and T3 are to control cell differentiation during development, help to retain a thermogenic homeostasis, control the production, usage and storage of energy in the whole body, the development and maturation of Central Nervous System, the skeletal growth, fertility, and human weight. Furthermore in Leber they are increasing cholesterol synthesis, conversion of cholesterol to

bile acids, Fat oxidation/synthesis and Gluconeogenesis. In Heart they are increasing Heart rate, leading to Hypertrophy. In muscles they are increasing protein catabolism, glucose utilization and Fat oxidation. The proper functioning of the gland ensures the endurance, sexuality, mental vigor and emotional flexibility of the individual. Stimulates resistance to colds and respiratory infections. Prevents depression, lethargy, insomnia, atherosclerosis [4].

Pathophysiologicaly, the main disorders of the thyroid gland are divided into two categories: morphological and functional. The first ones include anatomical deformities such as goiter (swelling of the gland), thyroid nodules (some local swelling of the gland) and neoplasms (benign or malignant). The second category includes hypothyroidism (low thyroid production), hyperthyroidism (overproduction of thyroid hormones) and thyroiditis. [4]. From all these pathologies in the present Thesis, we are interested in Thyroid Nodules, a frequent clinical disorder, since epidemiologic studies showed that the prevalence of palpable thyroid nodules is almost 5% in women and 1% in men living in iodine-sufficient areas around the world [5,6], which clinical importance rests with the need to exclude thyroid cancer.

Thyroid Nodules

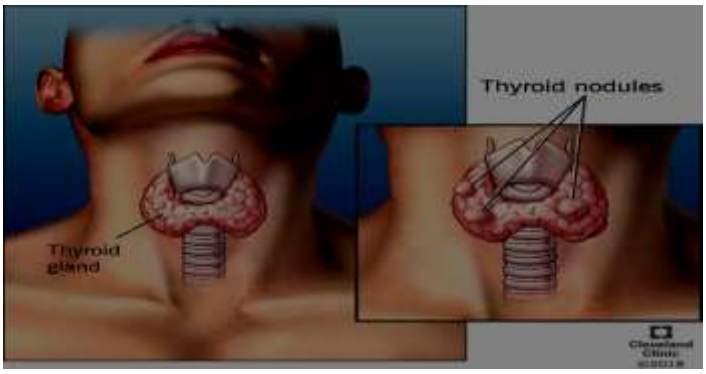

Fig.3 Thyroid nodules Cleveland Clinic 2018 [3]

(Source: https://my.clevelandclinic.org/health/diseases/13121-thyroid-nodule)

Definition of Thyroid Nodules

The term thyroid nodule refers to an abnormal growth of thyroid cells that forms a lump within the thyroid gland. Thyroid Nodular disease constitutes a heterogeneous thyroid disorder, remarkably common in iodine deficient areas which can be distinguished to solitary nodular and multinodular thyroid disease. They can be found not only in a normal gland but also in a diffuse goiter and in the vast majority, they do not cause symptoms because they are not producing Hormones [4].

Epidiomioly of Thyroid Nodules

Thyroid nodules are very common, infact they are the most common endocrine lesion. It is estimated that about half of Americans will have at least one when they will be 60 years old. More or less the same apply in Europe and in Greece, and this was certified in a large population study (Framingham, MA), where clinically apparent thyroid nodules were detected in 6.4 percent of women and 1.5 of men. Moreover in surveys of unselected individulas using ultrasonography, 20-76% of women had at least one thyroid nodule. Despite the fact that the great majority of nodules are benign, thyroid cancer occurs in 4 to 6,5 percent of them.

Fact is that the majority of Thyroid nodules do not produce symptoms, do not interfere with the Thyroid function and they come into clinical notice when found by a clinician during examination, and a radiologic procedure (ultrasound, computed tomography, magnetic resonance imaging and position emission tomography). Symptoms can arise locally in the neck through pressure and in the context of a toxic adenoma, a single autonomously functioning thyroid nodule which can cause a clinical and biochemical hyperthyroidism. Scintiscan is very helpful to distinguish these functioning nodules (known as hot nodules) which have a high uptake [6,7,8].

Etiology of Thyroid Nodules

The exact mechanism of thyroid nodules production is not yet completely explained and understood, but there are many factors which play a significant role to nodule Formation. A Hypothesis which is investigated and seems to be valid is that many endogenous growth factors and exogenous goitrogenic substances (e.g. iodine deficiency), increase Mutagenesis and aberrant growth stimulation. This happens, directly with production of H2O2/ free radicals and indirectly with proliferation and cell divisions leading to Thyroid Hyperplasia. Hyperplasia itself forms cell clones, some of them containing somatic mutations of the TSH-R leading to autonomously functioning nodules while others containing mutations causing a differentiation that leads to cold thyroid nodules or adenomas.

Some of the endogenous growth factors and exogenous goitrogenic substances - factors are:

- Thyroid stimulating hormone and stimulating anti-TSH-R antibodies [1]
- Iodine Deficiency, which leads to increased oxidative stress, causing somatic mutations, leading to benign clonal nodules formation [1]
- Increased IGF-1 and Growth Hormone, very likely promote the growth of goiter and polyclonal benign nodules [9]
- Smoking most likely through thiocyanate [10]
- Nutrition, obesity and metabolic syndrome, through Insulin Resistance. In this case insulin resistance concerns only its metabolic actions and not its mitogonic actions, and the resulting reactive hyperinsulinemia leads to focal thyroid cell proliferation [11,12,13,14]
- Thyroid benign diseases such autoimmune thyroiditis (Hashimoto) [15]
- Ionizing Radiation causes defects in DNA from Thyroid cells [16]
- Genetic Factors and genetic prodisposition (oncogenes and tumor suppresssor genes) [4]

Defects in genes that have a major impact on thyroid physiology and thyroid hormone synthesis could predispose to the evolvent of goiter and nodules mostly when borderline or overt iodine deficiency exist. Contrariwise to sporadic goiters, which are caused by spontaneous recessive genomic variations, most cases of familial goiter reveal an autosomal dominant pattern of inheritance, indicating predominant genetic defects. In medullary thyroid cancer (5-10% of all thyroid cancers), is inherited with autosomal dominant pattern in 20-25%, part of MEN2A AND MEN2B, coming from RET 43 Oncogen -mutation. Moreover, the most frequent mutational event in differentiated thyroid cancer is represented by point mutations of the BRAF gene. Other important genes are RAS, RET/PTC and PAX8/PPAR [4].

Significance of Thyroid Nodules

There are many types of Nodules with various morphological and clinical characteristics such as Cysts, non neoplastic or hyperplastic nodules, toxic or pretoxic adenomas, carcinomas (Papillary, Follicular, Anaplastic, Medullary, Lymphomas, Metastasis). Nodularity of thyroid tissue is very common, but thyroid cancer belongs to rare cancers, 0,6% of all cancers in men and 1,6% in women. The Mortality is also very low, <1% deaths from cancer in USA and <0,5% in Greece. Thyroid cancer is the most frequent cancer of endocrine glands and in the last decades its incidence growed up, and for that responsible is the wide use of ultrasound, but the mortality stayed stabil, perhaps because of

the better treatment [17]. So the clinical significance rests to the need to exclude thyroid cancer, which is present in 4 to 6.5 percent of TN. The prevalence is higher in some specifically groups such as: children, adults <30years old, those with a history of head and neck irradiation and in positiv familiar history for thyroid cancer. Risk factors for the development of thyroid cancer have been identified, including age (<20 or >65) , sex (male gender), increased nodule size (>4cm), history of thyroid irradiation and positive family history, MEN 2 or other genetic syndromes associated with thyroid malignancy [17].

Evaluation of Thyroid Nodules

The initial evaluation includes medical history, physical examination, TSH-Measurement and Ultrasound. The revolution in the Thyroid - Exasmination came after the daily use of Ultrasound. Thyroid Ultrasound offers much more information than physical examination, in terms of the size and anatomy of the gland and adjacent structures in the neck. Also there are several ultrasonographic findings that are suspicious for thyroid cancer which can be used to select nodules for Fine Needle Aspiration (FNA) biopsy. Thyroid scintigraphy is also used to define the functional status of a nodule. Non functional nodules appear cold (uptake of radioisotopes technetium -99m less than surrounding thyroid tissue), and they may demand further evaluation by Fine Needle Aspiration, while Autonomous nodules may appear hot if they are hyperfunctioning and they are rarely cancerous. The existence of suspicious ultrasound characteristics is more predictive of malignancy than nodule size alone [17]. A decision analysis of thyroid nodule biopsy criteria faciliates the approach of selecting nodules with suspicious ultrasonographic characteristics for biopsy over the approach of biopsy for all nodules > 1cm. Several medical societies have tried to form guidelines that are used to categorize thyroid nodules suspicious of malignancy and to select nodules for biopsy, including the American Association of Clinical Endocrinologists, the European Thyroid Association, the American College of Radiology and the Korean Society of Thyroid Radiology. The last two groups name their systems TIRADS. The suspicious elements for a thyroid malignancy are solid, hypoechoic, taller than wide nodules, with irregular margins or /and extra-thyroidal extension with punctate echogenic foci. These guidelines differ in diagnostic performance and yield of FNA. Studies have shown higher sensitivity for cancer detection (ATA criteria), while other studies have shown lower rates of negative FNAs and lower false negative rates with ACR-TIRADS criteria. A meta-analysis of 12 comparative studies found that ACR-TIRADS performed better than the ATA and Korean-TIRADS at identifying malignant nodules [18]. The use of Guidelines is to distinguish which nodules fulfill the criteria for further investigation through FNA. It is a simple and safe procedure, performed under ultrasound guidance in which tissue samples are obtained for cytologic examination using needles in order to establish the nature of the lesion. The Bethesda system classifies thyroid Fine Needle Aspiration

Cytology into six categories. Each category is associated with a malignancy risk and has a recommended clinical management [19].

Nodules that do not meet sonographic criteria for FNA should be monitored. Unfortunately there is not any efficient Therapy against Nodules. Thyroxine suppression seemed to have a role in goitrogenesis (goiter growth and new nodule formation), but only some goiters respond and other do not and continue to grow. T4-suppressive therapy leads to (by definition) in subclinical hyperthyroidism and treated patients are at risk for atrial fibrillation, other cardiac abnormalities , and/or reduced bone density , that's why the treatment or not should be individualized. The optimal therapy for patients with thyroid nodules depends on the lesion characteristics and whether or not it is functioning. Patients with nodules that are suspicious for malignancy or malignant should be referred for surgery [17].

Obesity Definition and Prevalence

Obesity is the pathologically increased disposition of fat in the human body, which also implies weight gain and according to a scientific report published in Lancet, the Global Syndemic (Obesity, Climate Change and Malnutrition) considered to be the greatest threat for Humanity and Planet (the Lancet Jan 27,2019). Obesity epidemic began in the 1980s and since then is constantly and dramatically increasing. In fact according to the latest data from World Health Organisation proved that worldwide obesity has nearly tripled since 1975, affecting both sexes , all age and ethnic groups. . [20,21] and has been further projected that 60% of the world's population, i.e. 3.3 billion people, could be overweight (2.2 billion) or obese (1.1 billion) by 2030 if recent tendency continue. The most widely used method to measure obesity, though not being a direct measure of adiposity, is Body Mass Index (BMI), which is calculated as measured body weight (kg) divided by measured height squared (m2), kg/m2 [22].

Pathogenesis of Obesity

In the ancient times where food was irregular, the ability to reserve energy, more than what was required for instant use, was essential for survival. This was achieved through Fat cells, which exist within the widely distributed adipose tissue, and are capable of storing excess energy in the form of Triglycerides and, when needed, release this energy in the form of free fatty acids for use. This system is well controlled through endocrine and neurological pathways, and allows humans to survive

starvation. However in times of nutritional wealth, lack of activity and exercise and under the pressure of genetic factors, this system raises adipose energy stores leading to adverse health consequences [4].

The development of obesity, basically, is caused by excess energy consumption (dietary intake) comperative to energy expenditure (energy loss through metabolic and physical activity). We are leaving in an obesity promoting environment as our daily routine promotes overeating, especially with highly caloric foods, which are affordable, very easy to find and easy to prepare. Physical activity levels have also dramatically decreased in the previous decades in both adults and adolescents [24]. In reality, obesity arousal is something more complex and multifactorial [22]. From physiological aspect the energy balance is from the Central Nervous System regulated. Signals of nutrient status and energy stores are communicated to the Hypothalamus and brainstem via both humoral and neural pathways. Biological (including genetic and epigenetic), psychological (including chronic stress), behavioral, social, environmental, economic and even political factors interact in varying degrees promoting the development of obesity [23]. Moreover, frequently used medications (psychotropic medications, steroid hormones, contraceptives), sleep restriction, smoking cessation, medical conditions, eating and genetic disorders [25,26,27,28] lead to alterations in adipose tissue structure (hypertrophy and hyperplasia of adipocytes, inflammation) and secretion (e.g. adipokines). Furthermore the composition of intestinal microbiota can activate beneficial metabolic effects via enhancement of mitochondrial activity, prevention of metabolic endotoxaemia and activation of intestinal gluconeogenesis through different routes of gene expression and hormone regulation.

Last but not least thyroid function and obesity form an intriguing connection. From a clinical aspect, obesity and mild thyroid dysfunction are common diseases and often coexist. There are several studies supporting the clinical evidence that thyroid dysfunction is connected with changes in body weight and composition, body temperature, and total and resting energy expenditure independently of physical activity. An Indian study presented that between the obese, 33% had overt, and 11% had subclinical hypothyroidism while obesity was more frequent (46% vs. 34%) in overt than in subclinical hypothyroidism [32]. Nowadays, is already proved that both subclinical and overt hypothyroidism are often associated with weight gain, decreased thermogenesis and metabolic rate [33,34] by affecting lipid and glucose metabolism, food intake and fat oxidation [35,36]. Furthermore, data showed that there is an inverse association between free thyroxine (fT4) values and body mass index (BMI), even when fT4 values remain in the normal range [37]. From the laboratory findings we usually have a typical image of high TSH, low fT4, and high fT3 [29], but the exact mechanisms of these alterations are not fully clarified. One theory suggests an increased deiodinase activity leading to a higher conversion rate of T4 to T3, forming a defense mechanism in obese subjects capable of counteracting the accumulation of fat by increasing energy expenditure [30]. Moreover, obese patients seem to have a reduced tissue responsiveness to circulating thyroid hormones, probably because of

reduced expression of both TSH - and thyroid hormones receptors. This unresponsiveness leads to a compensatory increase in secretion of TSH/FT3 in an attempt to overcome it [31]. Hormon Leptin, which is found in increased quantities in obese people, seem to play a very significant role in the homeostasis of energy intake. Leptin mainly informs CNS about the amount of fat, leading to a decrease in appetite and food intake, but her role is something more than that as she stimulates centrally the transcription of pro-thyrotropin-releasing hormone (TRH) and therefore also that of TRH and TSH and increases the activity of deiodinases. Last but not least, inflammatory cytokines produced from adipose tissue, such as tumor necrosis factor alpha, interleukin (IL)-1 and IL-6, inhibit sodium/iodide symporter mRNA expression and iodide uptake activity [29]. For these reasons Clinicians should be especially alert to the probability of thyroid dysfunction in obese patients.

Categories of Increased Risk for Diabetes

Obesity, undoubtedly, is the major risk factor for several non-communicable diseases, in particular type 2 diabetes. This combination is often called Diabesity, highlighting the fact that the vast majority of individuals with diabetes are overweight or obese [38] and the prevalence of obesity - related diabetes is expected to double to 300million by 2025 [39].

In 1997 and 2003, the Expert Committee on Diagnosis and Classification of Diabetes Mellitus [1,2] recognized an intermediate group of individuals whose glucose levels do not meet criteria for diabetes, thus are higher than those considered normal. These people were identified as having impaired fasting glucose (IFG) [fasting plasma glucose (FPG) levels 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L)] or impaired glucose tolerance (IGT) [2-h values in the oral glucose tolerance test (OGTT) of 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L)]. Impaired Fasting Glucose and Impaired glucose tolerance are known as prediabetes, trasitional stages that precede the officialy diagnose of Diabetes Mellitus. Following the evolution of people with prediabetes, 3-10% of them develop diabetes on annual basis. The Studies DECODE and DECODA which include Data from 13 European and 10 Asian substudies have shown that the total prevelance of prediabetes is 21,9% [40]. According the American Diabetes Association, almost 20 million people in USA are in the prediabetes category [42].

Studies showed also a correlation not only between prediabetes and cardiovascular events but also between prediabetes and mortality [43,44]. IFG and IGT are clearly linked to other comorbidities such as obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension. Several studies have investigated mechanisms and potential

etiological factors which can lead to the development of the different prediabetic states. The etiologies of IFG are predominantly related to genetic factors, smoking and male sex. The pathophysiology of IFG seems to be multifactorial and complex including the following key defects: decreased hepatic insulin sensitivity, gradual beta cell dysfunction and/or chronic low beta cell mass, changes in glucagon-like peptide-1 secretion and inappropriately elevated glucagon secretion. In other word, the major pathophysiological mechanism is called insulin resistance. Insulin perform its role through specific receptors , existent on the surface of most cells of the body , mainly on adipoytes, hepatocytes, striated muscle cells but also on thyroid cells in smaller amounts. Insulin resistance is defined as an impaired biologic response to insulin stimulation of target tissues, impairing glucose disposal, resulting in a compensatory increase in beta-cell insulin production and hyperinsulinemia [66,69].

From a pathophysiological point of view, there seems to be a close relation between thyroid function and insulin resistance. Thyroid hormones play an important on glucose metabolism and in the development of insulin resistance, especially in hyperthyroidism prevails the hepatic part while in hypothyroidism the resistance of peripheral tissues. On the other hand, the higher circulating levels of insulin act as a growth factor that stimulates cell proliferation in general and specifically in thyroid cells causing possibly a larger thyroid volume and formation of nodules [67].

The importance of IFG is not only the fact that it is a prediabetic state, but also because it is a major criteria for the diagnosis of metabolic syndrom a new entity where many risk factors for cardiovascular disease coexist in the same person. Metabolic syndrom is not uncommon27% of American adults and 4.1% of American teenagers, 50% of> 60 year olds, 16% of Danes. In Greece there no official evidence, in officially 25% of Men and 15% of Women. The complications that may result from metabolic syndrome are often serious and long-term (chronic). They comprise: hardening of the arteries (atherosclerosis), diabetes, heart attack, kidney disease, stroke, nonalcoholic fatty liver disease, peripheral artery disease, cardiovascular disease. Since the evolution from the prediabetic states to overt type 2 diabetes is defined by a non-reversible vicious cycle that includes severe deleterious effects on glucose metabolism, there are good reasons to use the well-established aetiological and pathophysiological differences in IFG, IGT and IFG/IGT to design individualised preventive strategies [45,46,47,48]. The target of treatment is to reduce the risk of developing further health complications. Structured lifestyle intervention, aimed at increasing physical activity and producing 5–10% loss of body weight, quit of smoking, mental calmness and certain pharmacological agents have been demonstrated to prevent or delay the development of diabetes in people with IGT and further health problems.

Association of Obesity and impaired fasting Glucose with thyroid nodules

Recent years have witnessed a worldwide increase in the prevalence of Thyroid nodules, which concurs with the increasing trend of obesity and the number of people with impaired fasting glucose.

Nowadays, with the routine use of high resolution Ultrasound, thyroid nodules proved to be the most common endocrine lesions. Although the vast majority of TN are benign, their clinical significance is principally related to the need to exclude thyroid cancer [17]. Many factors have been linked to the formation of them, including Thyroid stimulating hormone, iodine deficiency, IGF-1 and GH , gender Smoking, Nutrition and obesity [9,10,11,12,13,14]. On the other hand Obesity epidemic began in the 1980s and since then is constantly and dramatically increasing, forming the major risk factor for several non-communicable diseases, especially Type 2 diabetes and pre-diabetic Conditions such as Impaired Fasting Glucose and impaired Glucose Tolerance.

So these three Entities (Thyroid Nodules, Obesity and Impaired fasting Glucose) are very common in the clinical practice and associations between these conditions have been hypothesized and investigated. The possible pathophysiologic mechanisms which can explain their connection are the oxidative stress and Insulin Resistance/ IGF-1.

Oxidative stress results from a positive balance of increased production of oxygen-derived radicals and decreased excretion and plays an important role in many pahologial conditions. Adipose tissue is also an endocrine organ as it secretes hormones and peptides (f.e cytokines/adipokines) which regulate several mechanisms in human body. Obesity is linked with low-grade chronic systemic inflammation because in physiological and even more in pathological conditions , these adipokines generates the production of reactive oxygen species (ROS), producing oxidative stress (OS) triggering a systemic acute-phase response, systemic oxidative damage and (pro)- inflammatory processes.This inflammation of adipose tissue in Obesity, through the over- expression of FR and ROS and the under – production of anti-oxidant mechanisms, plays a significant role in the pathogenesis of obesity-related complications and other chronic diseases (e.g metabolic syndrome,diabetes mellitus, atherosclerosis, hypertension, hepatic steatosis and cancer) by damaging cellular structures, including membranes, proteins and DNA [61,62]. The same also apply for Thyroid Gland. In Thyroid reactive oxygen species (ROS) are essential for normal thyroid hormone synthesis, but an excessive production of ROS in combination with an uneffective antioxidant defense, can produce excessive damage detectable in lipids, DNA and proteins of thyroid epithelial cells, leading in alternations of thyroid function and disease [63]. This oxidative DNA damage and spontaneous mutations may represent the basis for the

frequent tumor- and nodulegenesis and soome studies have reported that patients with thyroid nodules have elevated oxidative stress status [63].

On the other hand, the main thyroid growth stimualting factors are Thyroid Stimulating Hormon (TSH), Thyroid Stimulating Immunoglobulin's (TSIs in Graves disease), **Insulin and IGF-1.** A few years ago, the endemic colloid goiter derived from the iodine defieciency and an increase in TSH, but nowadays with the Obesity-epidemic, the hyperinsulinemia that accompanies the metabolic/insulin resistance syndrome has been linked with an increase in the incidence of nodular thyroid disease. Insulin is an anabolic peptide hormone which act through receptors located in the membrane of target cells (major ones being liver, skeletal muscle, fat, brain), where it is pleiotropic effects (metabolic and mitogenic). Insulin Resistance, protrudes in metabolic abnormalities such Obesity, Diabetes and metabolic syndrome, derives from reduced sensitivity of the target tissues to insulin, leading to a compensatory increase in insulin secreation (hyperinsulinamia). Patients with IR are at high risk for developing manifestations related to the increased mitogenic actions of insulin [64].

The IGF system consists of four ligands (insulin, proinsulin, IGF-1 an IGF-2) , four receptors (the insulin receptor, IR, the IGF-1 receptor , the insulin receptor-related receptor and the IGF-2 receptor) and six binding proteins (IGFBP-1 to 6). IGF-1 is mainly produced in the liver under stimulation by growth hormone (GH), is usually bound to IGF-binding protein 3 (IGFBP-3) in circulation, has an almost 50% amino acid sequence homology with insulin and has vital effects on metabolism and proliferation through mediation of metabolic actions, regulation of cellular proliferation and gene expression [69]. Its anti-apoptotic effects in some cases can help cell survival, which in other cases it, may promote cell proliferation and lead to tumorigenesis, cancer or increment of adipocytes [64]. Obesity and metabolic syndrome may highly dysregulate IGF1 system, offering to hyperinsulinemia and increased free IGF-1 [64]. The IGF system affect directly thyroid function and morphology. In patients with insulin resistance, on one hand through the mitogenic effects of the compensatory hyperinsulinemia and on the other hand through the activation of IGF-1 axis (IGF-1 receptor and a variety of IGF-binding proteins (IGFBPs) are expressed in thyroid tissue) there is a stimulation of thyroid cell proliferation leading to a larger thyroid volume and formation of hyper plastic nodules, making generally Thyroid another victim of insulin resistance syndrome [66,68].

In the literature, there are conflicting data investigating the correlation between Body Mass Index (BMI), Impaired Fasting Glucose (IFG) and the presence, number and suspicious sonographic patterns of thyroid nodules. So far ,worldwide, evidence from early studies have suggested a positive association between obesity and Thyroid Nodules [51,52,53]. This hypothesis was also investigated in a large cross -sectional survey with 67,781 residents in Shanxi China, showing that Age, BMI and metabolic disorders (Blood pressure, Triglycerides, total-cholesterol, LDL-C, HDL-C, Fasting

Glucose), have increased not only the prevalence but also the number and size of TN [58]. The same seems to apply also in European population , as a cohort of randomly selected adults living in Palermo (Italy), a mild iodine deficiency area, showed an association between obesity, diabetes and thyroid nodules [54]. On the other hand, to make things more complicated , there are two studies outside Asia, that showed a negative relation between BMI and TN [70,71] and another Study in a Multi-center Healthy Population concluded that low weight, low BMI and IFG are associated with high risk thyroid nodules especially among people older than 55 years old [60]. As far as the gender disparity is concerned there are data showing a superiority of female gender especially the older ones in the prevalence of TN, [12,49,50], while male gender and underweight might be protective factors [49,50]. Contrariwise in the literature, there are some controversial issues regarding the factors that influence the number of nodules, the suspicious sonographic patterns and the correlation between severe obesity and nodules. The number of nodules is important because Thyroid cancer is less frequent in multinodular goiter compared to single nodule. Buscemi has shown that the number was correlated with age, female gender and BMI, but not with IFG while Liu Y has shown that metabolic disorders, such as IFG, are related to the increased incident of multi-nodularity and larger Thyroid nodules [54,57,58]. Furthermore, a large cross sectional epidemiological study has shown that the suspicious nodules were associated with greater weight and BMI in both sexes, particularly women over the age of 45years [51,56,59]. Moreover obesity, central obesity and NAFLD seem also to contribute to the development of suspicious nodules (taller than wide) [14]. Many data also exist, showing that waist circumference is superior to BMI for assessing risk of TN [12,55] and Body Fat Percentage is even better for assessing risk of TN and also for them with high – suspicion sonographic pattern [56]. Data from Greek population also exist. A cross-sectional study in a healthy population of Northern Greece showed that obesity and lack of exercise, used as surrogate markers of sedentary lifestyle, affect thyroid nodule size and could predict some ultrasonographic features, like hypoechoicity and internal vascularity [51].

This community – based prospective study aims to identify differences in the presence of nodules based on gender, age, BMI and IFG, as well as differences from these characteristics in the nodules total count, size and ACR - TIRADS classification It was hypothesized that an ultrasound screening strategy for thyroid morphology at people with early stages of abnormal glucose metabolism (IFG) or metabolic Syndrom may provide early diagnosis, prevention, better treatment and better approach of nodular thyroid disease.

Material -Methods - Statistics

Sample of current research was conducted by 520 participants, from Central Greece, not randomly collected from the community, but patients who have visited an endocrinology clinic and all of them were included in the Study. Subjects with known Diabetes, pregnant women, Patients with subacute and Graves Thyroiditis or other known endocrinopathies were de novo excluded.

.This community - based study aims to identify differences in the

1. presence of nodules based on gender, age, BMI and IFG, as well as differences from these characteristics in
2. the nodules total count
3. size and
4. ACR - TIRADS classification

Participants took a high – resolution ultrasonographic evaluation with a 13MHz linear probe (Logic F8, GE Medical Systems USA) [1] by professional endocrinologist who had received the proper training, anthropometric measurements and laboratory tests. Ultrasound provides a safe and fast method of thyroid examination, actually is the first-line imaging modality for the detection and assessment of thyroid nodules, guiding further investigation/management decisions.

Height and weight were measured using standard protocols by the same doctor. We have used Body mass index (BMI) in order to measure and define Obesity, obtained by dividing the body weight (kg) to the square of height (m), though not being a direct measure of adiposity, it is simple and the most widely used method. Overweight and obesity have been defined as BMI $\geq$ 25 kg/m2 and $\geq$ 30kg/m2 respectively.

The diagnostic criteria proposed by the American Diabetes Association have been used for the definition of Impaired Fasting Glucose (elevated blood sugar levels from 100mg/dl to 125mg/dl). Each venous sample have been taken after a minimum fasting period of 8 hours and serum glucose have been measured by the Glucose oxidase technique.

The classification of sonographic patterns were defined by the ACR-TIRADS, a system proposed by the American College of Radiology, used to categorize thyroid nodules suspicious of malignancy based on features such as microcalcifications, echogenity, composition, shape (taller than wide), margins.

Means and standard deviations were used to describe scale measurements of the study, such as age and nodule size. Frequencies and percentages were used for categorical variables like BMI

category and ACR - TIRADS classification. Pearson chi square tests were used to assess relationships among categorical variables. Independent samples t – tests, or the equivalent non parametric Mann Whitney were used to assess differences in scale measurements by binary variables, and the Kruskal Wallis test for BMI and total count of nodules. Logistic regression analysis was applied to identify independent prognostic factors on the presence of nodules. Generalized linear mixed models were applied to assess the effect of gender, age, BMI category, and IFG on the nodule size and the ACR-TIRADS classification. The Bonferroni criterion was used to assess differences from multiple comparisons in these models. All analyses were carried out with the use of SPSS v.26.0 and the significance was set at 0,05 in all cases.

Results

Of the 520 individuals recruited , all of them were included in the survey, resulting in a response rate of 100%. The mean age of the total number of participants equaled 51,54 ± 16,17 years. Most of the participants were females 379 (72,88%), while on Table 1, appears the distribution of the participants depending on their BMI. There was a small number of underweight patients 3,46% (18/520), and many normal weight 21,15% (110/520) and the remaining almost 75% (392/520) regarded patients that were overweight 34,04% (177/520) obese 24,04% (125/520) and severely obese 17,31%(90/520).

Table 1. Gender and BMI characteristics of the patients

		N	%
Gender	Female	379	72,88
	Male	141	27,12
BMI category	Underweight	18	3,46
	Normal	110	21,15
	Overweight	177	34,04
	Obese	125	24,04
	Severely obese(> 35)	90	17,31

		BMI			
		Mean	Standard Deviation	Minimum	Maximum
BMI category	Underweight	18,81	,90	17,17	19,92
	Normal	23,04	1,30	20,06	24,99
	Overweight	27,49	1,46	25,01	29,98
	Obese	32,18	1,37	30,02	34,96
	Severely obese(> 35)	39,33	3,84	35,08	51,18

The patients' Fasting Glucose levels were recorded and were characterized as Impaired when exceeding 100 mg/dL up to 125mg/dl. In total there were 384 out of 520 patients with IFG (73,85%) and 136 out of 520 without (26,15%).

44.04% (229/520) of the patients were diagnosed with nodules, not necessarily one in each. 20,19 % (105/520) had an uninodular and 23,85% (124/520) a multinodular thyroid disease (Table 2) .The distribution of the number of nodules in the patients appears on table 2 and ranges from 1 to 10.

		N	%
IFG	No	136	26,15
	Yes	384	73,85
Nodules	No	291	55,96
	Yes	229	44,04
# Nodules	0	291	55,96
	1	105	20,19
	2	54	10,38
	3	19	3,65
	4	20	3,85
	5	14	2,69
	6	6	1,15
	7	4	0,77
	8	3	0,58
	9	1	0,19
	10	3	0,58

Table 2. Characteristics of the Nodules and Fasting Glucose

Presence of Nodules

Table 3 examines the differences in the percentage of nodule presence according to gender, BMI category and IFG. The Pearson Chi square test showed no statistically significant differences in males and females (X_1^2 = 2,587; p=0,108) indicating that they are both equally likely to be diagnosed with nodules. Regarding BMI category, the inference was similar, indicating no differences in the chances of nodule presence (X_4^2 = 7,036; p=0,134). The relationship was also examined after merging obese and severely obese in a single category, with no substantial differences in the statistical estimations (X_3^2 = 5,506; p=0,138). **Differences in the odds of having nodules were though**

observed depending on IFG, (X_1^2 = 4,793; p=0,029), with higher chances of nodules appearing in IFG patients comparing to non IFG patients, (OR = 1,567; 95% C.I.: 1,047 – 2,345).

		Nodules				
		No		Yes		
		N	%	N	%	P
Gender	Female	204	53,8	175	46,2	0,108
	Male	87	61,7	54	38,3	
BMI category	Underweight	14	77,8	4	22,2	0,134
	Normal	67	60,9	43	39,1	
	Overweight	94	53,1	83	46,9	
	Obese	63	50,4	62	49,6	
	Severely obese(> 35)	53	58,9	37	41,1	
IFG	No	87	64,0	49	36,0	**0,029**
	Yes	204	53,1	180	46,9	

Table 3. Gender, BMI and IFG depending on presence of nodules

The difference is attributed by the comparative barchart of Figure 1

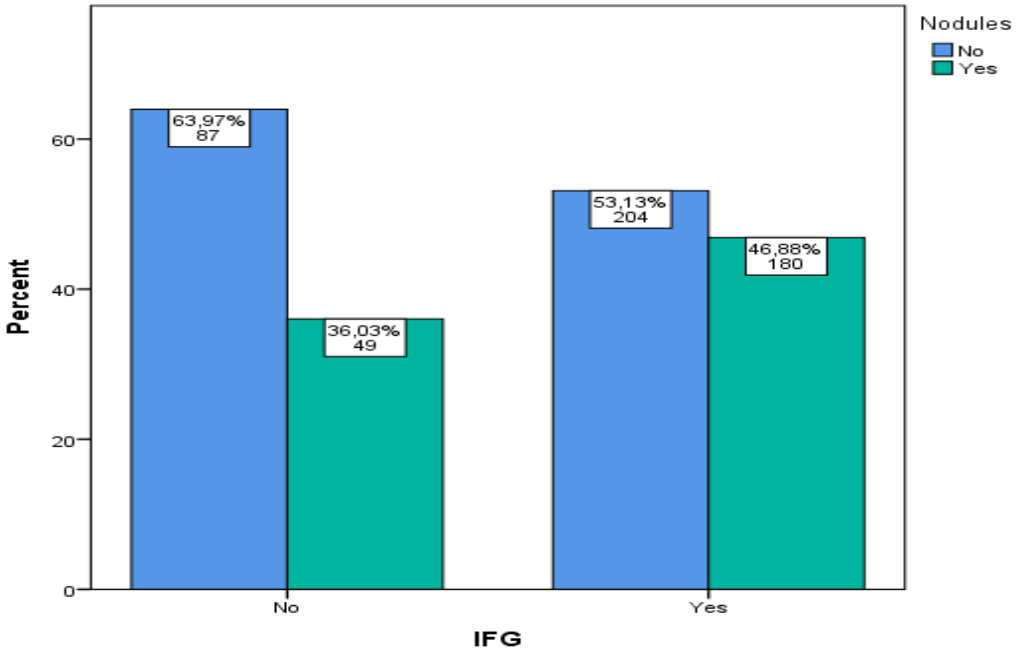

Figure 1. Comparative barchart of the presence of nodules depending on IFG.

Regarding age, an independent samples t-test that was applied after implementation of the Shapiro Wilk test and the related QQ plot to assess normality, and **showed that the mean age of patients diagnosed with nodules (55,68) is statistically significantly higher than the mean age of patients with no nodules (48,29), t= -5,305; p<0,001.**

NODULES	No		Yes		
	Mean ± SD		Mean ± SD		P
Age	48, 29	± 16,25	55,68	±15,13	**<0,001**

Table 4. Age of the participants depending on presence of nodules

The difference is attributed by the comparative boxplot appearing on the following Figure 2

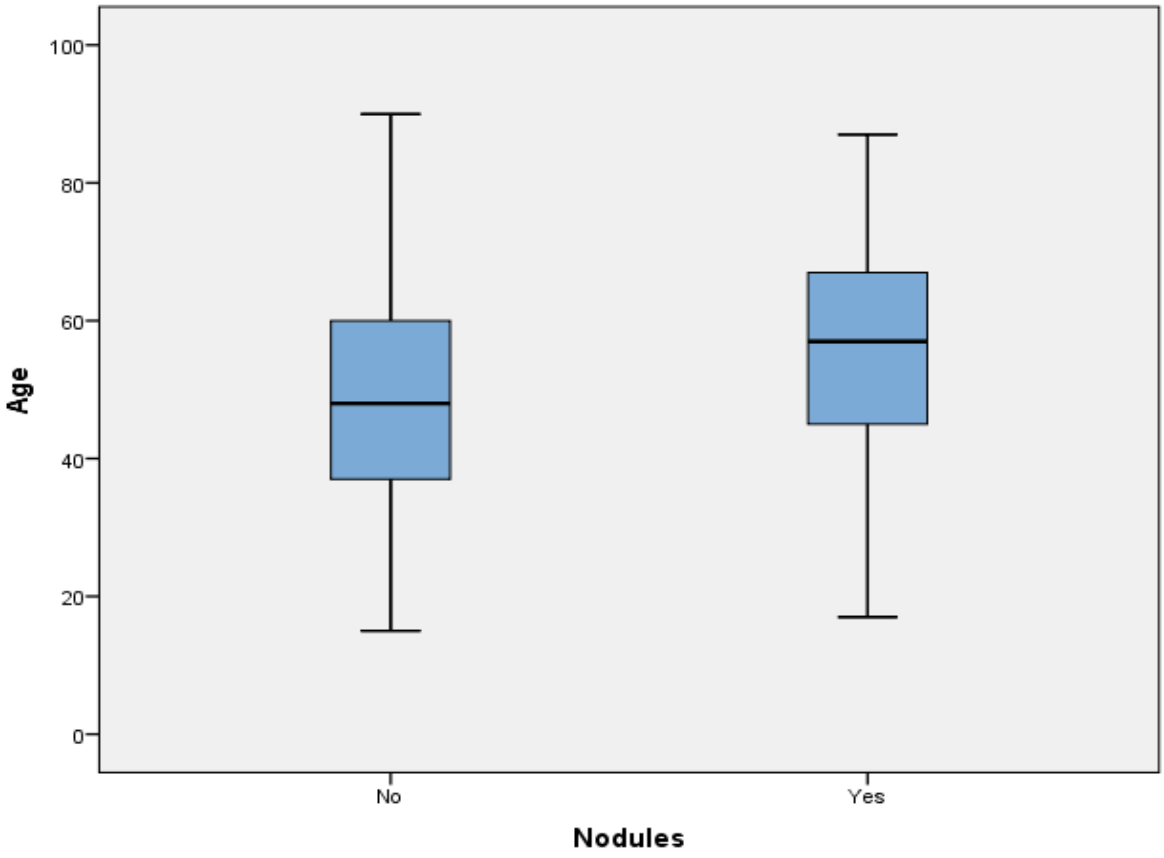

Figure 2. Comparative boxplot of the age of the participants depending on the presence of nodules

The logistic regression analysis that was applied to assess the affect of all the factors simultaneously, indicated **that only age remained statistically significant (p<0,001) and not IFG (p=0,54)**. Specifically for every year of older age a patient is getting by 2,6% (95%C.I.: 1,4% - 3,9%) more likely to be diagnosed with a nodule, therefore a patient that is 60 years old is 26% (95%C.I.: 14% - 39%) more likely to be diagnosed with a nodule compared to a patient that is 50 years old. BMI category and gender remained not statistically significant (p=0,639 and p= 0,180 respectively).

		Betas	P	OR	95% C.I.for OR	
					Lower	Upper
	Age	**,026**	**,000**	**1,026**	**1,014**	**1,039**
	Gender(1)	-,282	,180	,754	,499	1,140
	IFG(1)	,137	,540	1,147	,740	1,776
	BMI category		,639			
	Constant	-2,217	,000	,109		

Table 5. Logistic regression analysis on the presence of nodules. Betas are unstandardized

Nodules count

Table 6 examines the differences in the number of nodules that were recorded according to gender, BMI category and IFG in the 229 patients were nodules were present. The Mann Whitney U test showed no statistically significant differences in males and females (U = 4543; p=0,650) indicating that similar number of nodules is expected in males and females that have at least one. Regarding BMI category, the inference was similar, indicating no differences in the count of nodules recorded based on the Kruskal Wallis test (W = 1,695; p=0,792). The relationship was also examined after merging obese and severely obese in a single category, with no substantial differences in the statistical estimations (W = 1,695; p=0,638). Differences in the total count of nodules were also non statistically significant based on the Mann Whitney U test depending on IFG, (U = 4543; p=0,857). It is worth noting that for all three comparisons the estimated p- values were rather high.

		# Nodules				
		Mean ± SD	Median	Range	N of patients	P(non parametric)
Gender	Female	2,42 ± 1,91	2,00	9	175	0,650
	Male	2,30 ± 1,97	2,00	9	54	
BMI category	Underweight	1,75 ±,96	1,50	2	4	0,792
	Normal	2,19 ± 1,55	2,00	6	43	
	Overweight	2,31 ± 2,08	2,00	9	83	
	Obese	2,60 ± 2,07	2,00	9	62	
	Severely obese (> 35)	2,51 ± 1,79	2,00	6	37	
IFG	No	2,45 ± 2,10	2,00	8	49	0,857
	Yes	2,37 ±1,87	2,00	9	180	

Table 6. Differences in the number of nodules depending on gender, BMI category and IFG

Regarding age (mean = 55,68 ±15,13), the Spearman's Rho was examined to assess whether age is expected to be related to higher or lower number of nodules in patients that had at least one nodule. The choice of the test was based on the skewness observed in the nodules count and showed no statistically significant correlation, Rho= 0,053; p=0,421. Regression analysis was not applied as no statistically significant factors were identified.

		# Nodules		
		Correlation Coefficient	P	N
Spearman's rho	Age	,053	,421	229

Table 7. Correlation of Age and number of nodules

Nodules size

Table 8 shows the mean size of the nodules depending on gender, BMI category and presence of IFG. These averages were based on the total number of nodules observed regardless of the number of nodules observed in each individual and were estimated on the mean size observed for each patient. Examining differences in these baseline characteristics of the patients would provide results that would not be weighted for the fact that the characteristics of the patients with more nodules would gain a larger weight in the statistical analysis and would lead to biased estimations.

		Nodule size			
		Mean ± SD	Median	Range	N of patients
Gender	Female	,87 ± ,55	,73	4	175
	Male	,89 ± ,51	,76	3	54
BMI category	Underweight	,64 ± ,12	,67	0	4
	Normal	,66 ± ,45	,50	2	43
	Overweight	,89 ± ,48	,74	3	83
	Obese	,92 ± ,61	,75	4	62
	Severely obese(> 35)	1,03 ± ,62	,88	3	37
IFG	No	,76 ± ,49	,63	2	49
	Yes	,91 ± ,55	,75	4	180

Table 8. Nodule size depending on Gender, BMI and IFG.

In order to adjust the results for this fact, Generalized Linear Mixed Models were applied to assess the effect of gender, BMI category, IFG and age. The Generalized mixed model that was applied entailed a normal probability distribution with a log link function and the corrected AIC equaled 915,362 and the BIC equaled 957,687. **Table 9 indicates a statistically significant effect of age and BMI on nodules size, with p values <0,001 in both cases, while the effect of gender and IFG was not statistically significant with p-values equal to 0,887 and 0,636 respectively.**

Independent variable	F	df1	df2	p
Model	7,513	7	531	,000
IFG	,225	1	531	,636
Gender	,020	1	531	,887
Age	23,416	1	531	,000
BMI category	5,011	4	531	,001

Table 9. Results of the Generalized linear mixed models regarding the effect of gender, BMI category, Age and IFG

Tables 10 and 11 show the expected nodule size by gender and IFG respectively.

Estimates				
IFG	Mean	Std. Error	95% Confidence Interval	
			Lower	Upper
No	,830	,067	,699	,962
Yes	,857	,049	,761	,952

Table 10. Estimations of nodule size depending on IFG

Estimates				
Gender	Mean	Std. Error	95% Confidence Interval	
			Lower	Upper
Female	,847	,048	,753	,942
Male	,840	,067	,709	,970

Table 11. Estimations of nodule size depending on gender

Table 12 shows the estimates of size based on the model and indicates that nodule size is expected to be higher in severely obese patients comparing to all other categories, but this is to be verified by the statistical tests that follow on Table 13. A graphical representation of the findings is provided by Figure 3, where it appears that there is a higher dispersion in the category of underweight patients that is definitely due to the small number of patients (4).

Size Estimates				
BMI category	Mean	Std. Error	95% Confidence Interval	
			Lower	Upper
Underweight	,787	,202	,391	1,183
Normal	,692	,059	,577	,808
Overweight	,841	,042	,758	,924
Obese	,863	,047	,771	,955
Severely obese(> 35)	1,035	,061	,914	1,155
Continuous predictors are fixed at the following values: age=56,24				

Table 12. Estimations of the nodule size in the different BMI categories

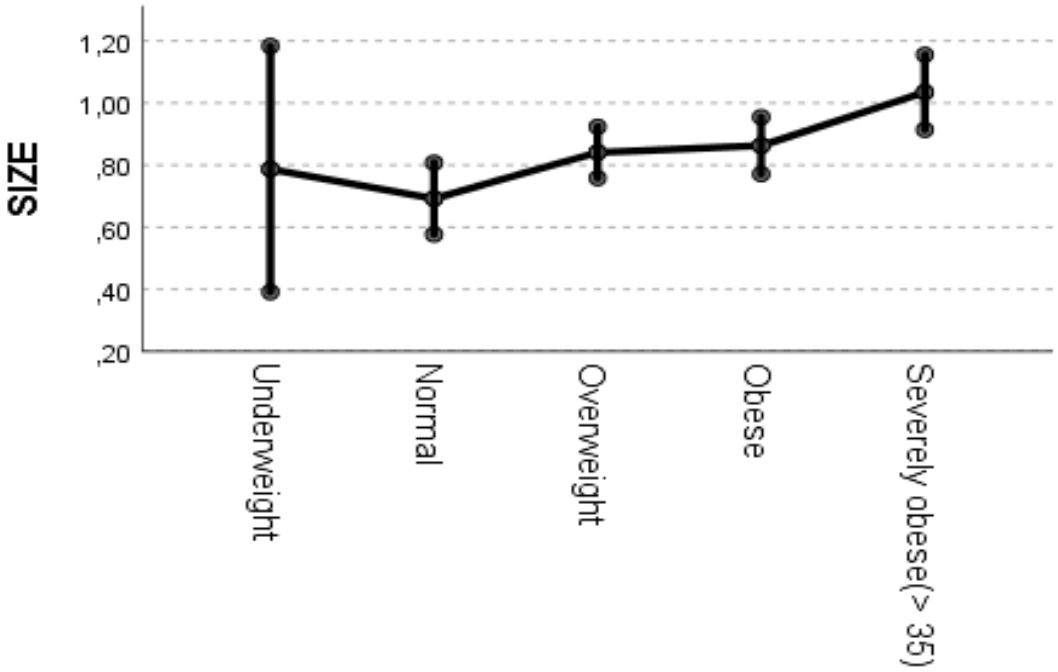

Figure 3. Means plots of the size estimations in the different BMI categories

Pairwise comparisons after the Bonferroni correction were implemented to assess which BMI categories differ between them regarding nodules size. Table 13 shows the contrast estimates and their standard error along with the performed t tests and the adjusted significance with the respective 95% confidence interval of the estimates. **The results show that the nodule size is expected to be significantly bigger in severely obese patients comparing to overweight patients (p=0,037) and also comparing to normal weight patients (p<0,001).** The difference comparing to obese patients is close to significance but does not reach it, as the mean size is slightly bigger than that of the overweight category (p=0,102) and so is the difference between the groups of normal and overweight patients (p=0,168). The comparison of nodule size between normal and obese is also close to significance, and equal to 0,102, as well, while all differences to the group of underweight patients are non-significant, mainly because of the small number of patients in it.

BMI Pairwise Comparisons	t	df	p	95% Confidence Interval	
				Lower	Upper
Underweight - Normal	,464	531	1,000	-,345	,534
Underweight - Overweight	-,265	531	1,000	-,472	,364
Underweight - Obese	-,374	531	1,000	-,503	,352
Underweight - Severely obese(> 35)	-1,209	531	1,000	-,777	,282
Normal - Overweight	-2,204	531	,168	-,327	,030
Normal - Obese	-2,500	531	,102	-,358	,017
Normal - Severely obese(> 35)	**-4,436**	**531**	**,000**	**-,560**	**-,125**
Overweight - Obese	-,386	531	1,000	-,142	,098
Overweight - Severely obese(> 35)	**-2,879**	**531**	**,037**	**-,381**	**-,006**
Obese - Severely obese(> 35)	-2,494	531	,102	-,361	,017

Table 13. Differences in the nodule size in the different BMI categories

The correlation that was detected between nodule size and age was statistically significant and positive as well (p=0,001), indicating **that bigger nodule sizes are expected for**

older patients. The relationship is attributed by the following scatterplot that appears on Figure 4.

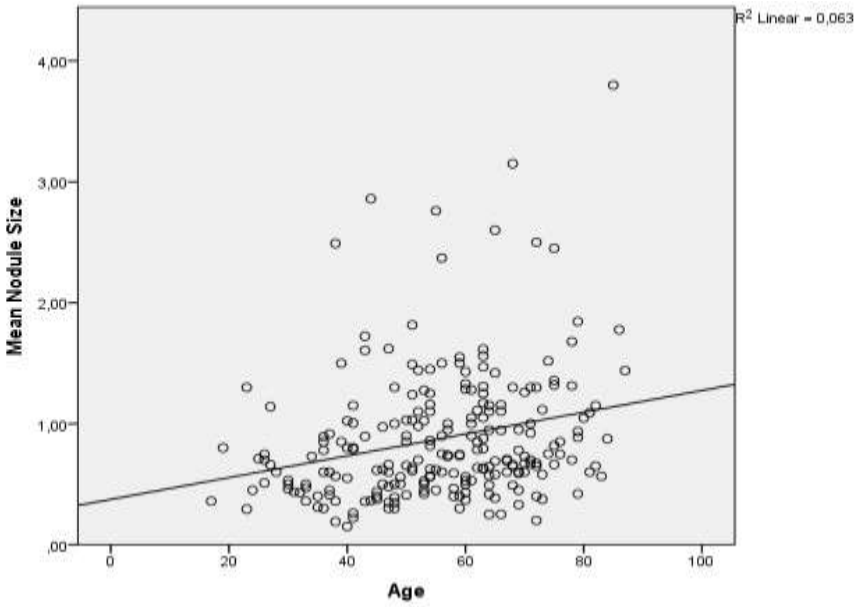

Figure 4. Scatterplot of age and Nodule size

It is important to mention that the significance of the interaction term between the two statistically significant findings, BMI category and age, could not be examined as sample size was not large enough in each category to lead to a model that converges and produces estimates. A graphical representation though, that analyses Figure 4 incorporating the 5 subcategories of BMI provides indications that the relationship is mostly observed in overweight, obese and severely obese patients (Figure 5).

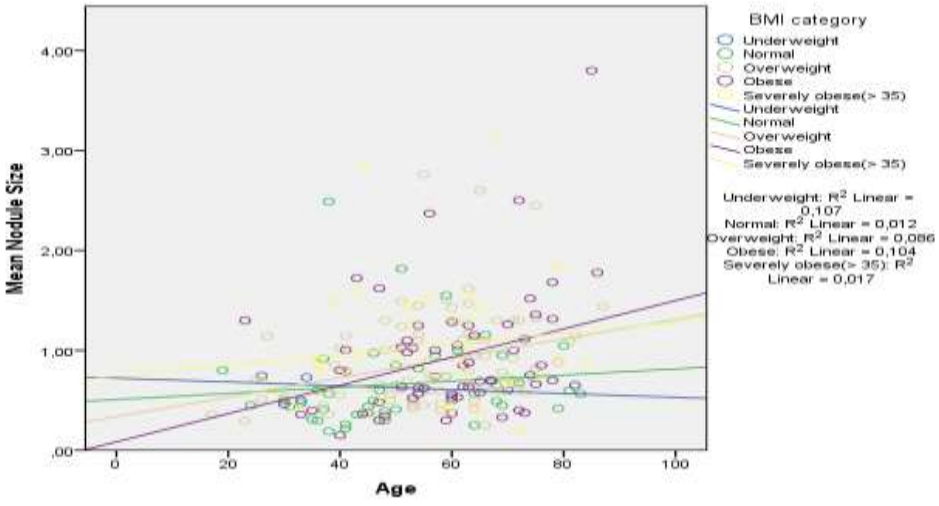

Figure 5. Scatterplot of age and Nodule size by BMI category

Notice: The analysis regarding nodule size was also carried out with a different categorization of the BMI, i.e in 4 categories, rather than 5, merging the two highest BMI groups. The results were similar but the prominent difference of the severely obese group was partially covered, thus distorting the true differences, as in fact the group of obese patients was more similar to the overweight group of patients in terms of nodule size.

Nodules and ACR-TIRADS Classification

The effect of the four variables (BMI category, gender, IFG and age) on "ACR -TIRADS score" was also examined with the use of Generalized mixed models. Even though the initial categorization of ACR-TIRADS was based on a five point scale as shown on Figure 5, the Generalized mixed model that was applied entailed a binomial distribution with a logit link function as the distribution of the responses was merged in two categories (1-3 vs 4-5) to strength inference and interpretation of the results.

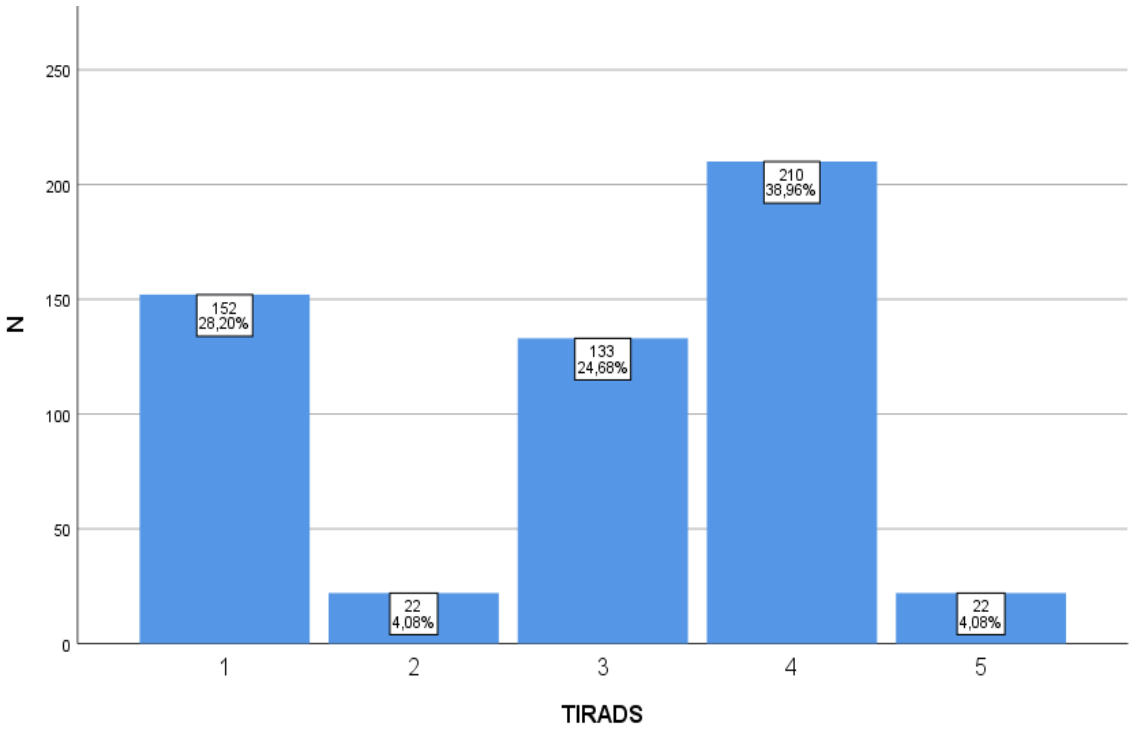

Figure 6. Distribution of ACR-TIRADS score in the total of nodules observed

Table 14 shows the counts and percentages of the ACR -TIRADS score depending on gender, BMI category and presence of IFG. It must be noted that the numbers are frequencies and percentages of the total number of nodules observed and not of the total number of patients which was definitely smaller. The corrected AIC equaled 2341,999 and the BIC equaled 2384,323.

		ACR -TIRADS			
		<=3		4 or 5	
		N	%	N	%
Gender	Female	229	55,2	186	44,8
	Male	78	62,9	46	37,1
BMI category	Underweight	5	71,4	2	28,6
	Normal	63	67,7	30	32,3
	Overweight	108	56,3	84	43,8
	Obese	85	53,8	73	46,2
	Severely obese(> 35)	46	51,7	43	48,3
IFG	No	72	60,0	48	40,0
	Yes	235	56,1	184	43,9

Table 14. ACR-TIRADS percentages and frequencies by gender, BMI category and IFG

Table 15 indicates no statistically significant effects for any of the examined parameters with p values equal to 0,516 for IFG, 0,201 for age and 0,152 for BMI category, while the significance for gender is slightly above 0,05 and equal to 0,062. This borderline non significance indicates a slightly higher percentage of women having ACR-TIRADS score 4 or 5 compared to men, but the difference cannot be clearly stated.

Independent variable	F	df1	df2	p
Model	1,465	7	531	,177
IFG	,423	1	531	,516
Gender	3,508	1	531	,062
Age	1,640	1	531	,201
BMI category	1,687	4	531	,152

Table 15. Results of the Generalized linear mixed models regarding the effect of gender, BMI category, Age and IFG

Table 16 below, shows all possible comparisons that were examined for differences in the ACR -TIRADS score regarding the BMI category of the patients. The adjusted significance is in all cases clearly higher than 0,05 indicating no statistically significant differences.

BMI - Pairwise Comparisons	t	df	p	95% Confidence Interval	
				Lower	Upper
Underweight - Normal	-,500	531	1,000	-,394	,246
Underweight - Overweight	-1,340	531	1,000	-,580	,187
Underweight - Obese	-1,434	531	1,000	-,606	,183
Underweight - Severely obese(> 35)	-1,461	531	1,000	-,627	,187
Normal - Overweight	-2,069	531	,348	-,286	,042
Normal - Obese	-2,263	531	,241	-,308	,034
Normal - Severely obese(> 35)	-2,073	531	,348	-,342	,050
Overweight - Obese	-,277	531	1,000	-,127	,097
Overweight - Severely obese(> 35)	-,367	531	1,000	-,160	,112
Obese - Severely obese(> 35)	-,132	531	1,000	-,142	,125

Table 15. Differences in the nodule ACR-TIRADS classification in the different BMI categories

The interaction effects, as in the case of the nodule size, could not be examined as sample size was not large enough in each category. Still no significant effects were expected in view of the main effect outcomes of Table 15.

Notice: The model, as in the case of the Nodule size, was reexamined, substituting the 5 BMI categories by 4 where severely obese patients were merged with the group of obese patients. The inference was similar and no statistically significant factors were identified for their impact on nodule ACR - TIRADS classification.

Discussion

We performed this community – based Study in order to investigate on one hand the prevalence of thyroid nodules , their number and their characteristics in Greek Subjects of both sexes and on the other hand the possible correlation between Body Mass Index (BMI), Impaired Fasting Glucose (IFG) and the presence, number and suspicious sonographic patterns of thyroid nodules. With our data, we were unable to confirm a significant association between BMI and the presence of nodules , even when we have compined obese and severe obese patients in a single category . There was also no gender disparity indicating that both males and females are equally likely to be diagnosed with nodules. In contrast we found differences in the odds of having nodules depending on IFG, with higher chances of nodules appearing in IFG patients comparing to non IFG patients. The possible explanation is through insulin resistance and hyperinsulinemia (over production of insulin and insulin -like growth factors), which encourage thyroid cells proliferation as well as inhibit apoptosis. Furtheromore the mean age of patients diagnosed with nodules was statistically significantly higher than the mean age of patients with no nodules . However when a logistic regression analysis was applied, in order to assess the affect of all the factors simultaneously, indicated that only age remained statistically significant and not IFG.

Worldwide, evidence from early studies have suggested a positive association between obesity and Thyroid Nodules [51,52,53]. Data from Greek population also exist. A cross-sectional study in a healthy population of Northern Greece showed that obesity and lack of exercise, used as surrogate markers of sedentary lifestyle, affect thyroid nodule size and could predict some ultrasonographic features, like hypoechoicity and internal vascularity [51]. A cohort of randomly selected individuals living in Palermo (Italy), a mild iodine deficiency area, seems to indicate that an association exists between obesity, diabetes and thyroid nodules [54]. This hypothesis was also investigated in a large cross -sectional survey with 67,781 residents in Shanxi China , showing that Age, BMI and metabolic disorders (Blood pressure, Triglycerides, total-cholesterol, LDL-C, HDL-C, Fasting Glucose, have increased not only the prevalence but also the number and size of TN [58]. On the other hand, to make things more complicated , there are two studies outside Asia, showing the same results with our population ,that means, a negative relation between BMI and TN [70,71]. It is important to mention, that perhaps our sample size was modest and insufficient. Anyway , many data exist, showing that waist circumference is superior to BMI for assessing risk of TN [11,12], by reflecting the abdominal adipose distribution, and Body Fat Percentage is even better for assessing risk of TN and also for them with high – suspicion sonographic pattern [56]. This deficiency in accuracy in the predictability or as an indicator of BMI for TNs risk may be due to the fact that it is a nonspecific measurement method for adiposity aggregating measures of muscle mass, peripheral and abdominal adipose tissue

and bone mass. Therefore , the role of Adiposity in the development of TN and cancers demands further investigation.

As far as the size of the nodules is concerned, our data showed a statistically significant effect of age and BMI on nodules size, while the effect of gender and IFG was not statistically significant . A subgroup analysis presented a significantly bigger nodule size in severely obese patients comparing to overweight patients and also comparing to normal weight patients , perhaps due to an excessive insulin resistance, the compensatory hyperinsulinemia and the intense oxidative stress.The correlation that was detected between nodule size and age was statistically significant and positive as well , indicating that bigger nodule sizes are expected for older patients of both sexes.

Contrariwise in the literature, there are some issues regarding the factors that influence the number of nodules, the suspicious sonographic patterns and the correlation between severe obesity and nodules. The number of nodules is important because Thyroid cancer is less frequent in multinodular goiter compared to single nodule. Buscemi has shown that the number was correlated with age, female gender and BMI, but not with IFG. On the other hand, Liu Y has shown that metabolic disorders, such as IFG, are related to the increased incident of multi-nodularity and larger Thyroid nodules. [54,57,58]. Here in our sample , 44% (229/520) had minimum one nodule, 20,19 % (105/520) had an uninodular and 23,85% (124/520) a multinodular thyroid disease (Table 2). The Mann Whitney U test which was used, showed no statistically significant gender disparity indicating that similar number of nodules is expected in males and females that have at least one. Regarding BMI category, the inference was similar, indicating no differences in the count of nodules recorded based on the Kruskal Wallis test even when we examined obese and severely obese pastients in a single category. Last but not least we have observed no statistically significant correlation between the count of nodules and IFG and age.

According to literature, conflicting data exist as far as the relation between obesity, gender and high suspicion sonographic pattern is concerned. A large cross sectional epidemiological study has shown that the suspicious nodules were associated with greater weight and BMI in both sexes, particularly women over the age of 45years [51,56,59]. On the other hand, a Study in a Multi-center Healthy Population concluded that low weight, low BMI and IFG are associated with high risk thyroid nodules especially among people older than 55 years old [60]. For the risiko stratification of the Nodules, we chose the ACR-TIRADS score , published in 2017. Comparative studies show the ACR system has a sensitivity ranging 75-97% and specificity ranging 53-67%, which is either the highest sensitivity and lowest specificity amongst compared systems, or, to the contrary, the highest specificity. A meta-analysis of 12 comparative studies found that ACR-TIRADS performed better than the ATA and Korean-TIRADS at identifying malignant nodules [18]. Here in our sample there was no

statistically significant correlation between our examined parameters (IFG, age, BMI, gender) and ACR -TIRADS score, while the significance for gender is slightly above 0,05 and equal to 0,062. This borderline non significance indicates a slightly higher percentage of women having TIRADS 4 or 5 compared to men, but the difference cannot be clearly stated. There can be a lot of discussion about the best identification score and in the future can be found a better one and further investigation needed to come to a clear Result.

In contrast to our results, perhaps because of the sample size, there are Data showing a gender disparity as far as the prevalence of TN is concerned, showing a superiority of female gender, especially the older ones [12,49,50], while male gender might be a protective factor [49,50]. The possible explanation has to do with sex differences in fat distribution in body as well as with the effect of estrogens.

Nevertheless, the results of the present work should be interpreted with caution in light of several limitations. First of all the number of subjects in our study was modest and this was a single-center study, therefore the results may not be generalizable. Secondly, although the main risk factors for thyroid nodules and cancer (BMI, age and gender) were adjusted in the model, other possible confounders were not assessed, including smoking, alcohol consumption and dietary behaviors. The percentage of those with normal weight 21,15% (110/520) and of male participants 27,1% (141/520) were small and perhaps not sufficient to have clear results. Moreover we did not test thyroid function and therefore could not take it as cofounder when analyzing the data. Furthermore, we did not include some other antropometric measurements which can more accurately measure central adiposity, such as waist circumference, the waist to-hip-ratio and Body Fat Percentage. Nevertheless, this study extends work on associations between the presence, count, size and ACR TIRADS score of the nodules and gender, age, BMI and IFG by using binary logistic regression analysis, expanding our understanding of the thyroid nodular disease, therefore the present results remain valuable. In the future, a multicenter study with a larger sample size, a more detailed collection of biochemical indicators, a comprehensive questionnaire, and a long follow-up period may provide more valuable data.

Conclusion

Our community -based Study of a population in Central Greece, showed no significant correlation not only between our parameters (Gender, Age, BMI and IFG) and the Count of nodules but also for the ACR TIRADS classification. On the other hand it showed a statistically significant correlation between the presence of nodules and IFG and AGE. Furthermore there are also data showing a correlation between the size of nodules and BMI and AGE. Maintaining a normal weight and normal fasting Glucose values may help prevent not only the presence of nodules but also their Size. Of course further large, high-quallity, randomized controlled trials are required to reach a clearer result in order to confirm the relation between Body Mass Index, Impaired Fasting Glucose and Thyroid nodules. An ultrasound screening strategy for thyroid morphology at people with early stages of abnormal glucose metabolism (IFG) or metabolic Syndrom could provide early diagnosis, prevention and better treatment of nodular thyroid disease.

REFERENCES

1. Guyton and Hall, Human Physiology and Mechanisms of Disease (Human Physiology & /Mechanisms of Disease (6th Edition), 712-722.
2. Cooper DS, Ladenson PW, Oxon MA. The Thyroid Gland. In Gardner DG, Shoback D. Greenspan's Basic and Clinical Endocrinology, 9th Edition, New York, Lange Medical Books, McGraw Hill 2011:163-226.
3. Mischigan Medicine, https//www.uofmhealth.org/health-library/ug1836
4. Larry Jameson and Leslie J.De Groot, ENDOCRINOLOGY Adult and Pediatric (7th Edition) 1322-1347
5. Vander JB, Gaston EA, Dawber TR 1968 The significance of nontoxic thyroid nodules. Final report of a 15- year study of the incidence of thyroid malignancy. Ann Intern Med 69:537–540. 2.
6. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, Evans JG, Young E, Bird T, Smith PA 1977 The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol (Oxf) 7:481–493.
7. Ezzat, S, Sarti, DA, Cain, DR, Braunstein, GD. Thyroid incidentalomas. Prevalence by palpation and ultrasonography. Arch Intern Med 1994; 154:1838.
8. Vander JB, Gaston EA, Dawber TR. The significance of nontoxic thyroid nodules: final report of a 15-year study of the incidence of thyroid malignancy. Ann Intern Med 1968; 69:537–540
9. Volzke, H, Friedrich, N, Schipf, S, et al. Association between serum insulin-like growth factor-I levels and thyroid disorders in a population-based study. J ClinEndocrinolMetab 2007; 92:4039.
10. Knudsen, N, Bulow, I, Laurberg, P, et al. Association of tobacco smoking with goiter in a lowiodine-intake area. Arch Intern Med 2002; 162:439.
11. Liu J ; Wang C ; Tang X ; Fu S ; Jing G ; Ma L ; Sun W ; Li Y ; Wu D ; Niu Y ; Niu Q ;GuoH ; Song P. "Correlation analysis of metabolic syndrome and its components with thyroid nodules." Diabetes, Metabolic Syndrome and Obesity : Targets and Therapy Vol.12 (01 August 2019): pp.1617-1623.
12. Song, Bin ;Zuo, Zhihua ; Tan, Juan ; Guo, Jianjin ; Teng, Weiping ; Lu, Yibing ; Liu, Chao. "Association of thyroid nodules with adiposity: a community-based cross-sectional study in China." BMC endocrine disorders Vol.18(1) (27 January 2018): pp.3.

13. Yang, Hui-Xia ;Zhong, Yu ; Lv, Wei-Hua ; Zhang, Feng ; Yu, Hong. "Association of adiposity with thyroid nodules: a cross-sectional study of a healthy population in Beijing, China." BMC endocrine disorders Vol.19(1) (16 October 2019): pp.102.
14. Chen, Yi ; Zhu, Chunfang ; Chen, Yingchao ; Wang, Ningjian ; Li, Qin ; Han, Bing ; Zhao, Li ; Chen, Chi ; Zhai, Hualing ; Lu, Yingli Casella, Claudio. "The Association of Thyroid Nodules with Metabolic Status: A Cross-Sectional SPECT-China Study." International Journal of Endocrinology Vol.2018 (2018): 8 pages.
15. Nathalie Silva de Morais, Jessica Stuart, Haixia Guan Zhihong Wang, Edmund S Cibas, Mary C Frates, Carol B Benson, Nancy L Cho, Mathrew A Nehs, Caroline A Alexander, Ellen Marqusee, Mathew I Kim, Jochen H Lorch, Justine A Barletta, Trevor E Angell, Erik Akexander ‘’The Impact of Hashimoto Thyroiditis on Thyroid Nodule Cytology and Risk of Thyroid Cancer,’’J Endocr Soc 2019 Apr 1; 3(4): 791–800.
16. Schneider, AB, Shore-Freedman, E, Ryo, UY, et al. Radiation-induced tumors of the headand neck following childhood irradiation. Medicine 1985; 64:1.
17. Bryan R. Haugen,Erik K. Alexander, Keith C. Bible,Gerard M. Doherty,Susan J. Mandel,Yuri E. Nikiforov,Furio Pacini,Gregory W. Randolph,Anna M. Sawka,Martin Schlumberger,Kathryn G. Schuff,11Steven I. Sherman,Julie Ann Sosa,David L. Steward,R. Michael Tuttle,and Leonard Wartofsky ‘’The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer’’ 2015,Thyroid, 2016 Jan1 , 26(1): 1–133.
18. Mistry, Rakesh ;Hillyar, Christopher ; Nibber, Anjan ; Sooriyamoorthy, Thushanth ; Kumar, Nirmal. "Ultrasound Classification of Thyroid Nodules: A Systematic Review." Cureus Vol.12(3) (11 March 2020): pp.e7239.
19. Safa Alshaiki MBBS, Zainab Harb MBBCh BAO, Eman Aljufairi MD and S Ali Almahari MD ‘’Classification of thyroid fine-needle aspiration cytology into Bethesda categories: An institutional experience and review of the literature’’ Cytojournal 2018; 15:4
20. Flegal KM, Caroll MD, Ogden CL et al. Prevalence and trends in obesity among US adults, 1999-2000. JAMA 2002; 288:1723-1727.
21. Flegal KM, Caroll MD, Kuczmarski RJ et al. Overweight and obesity in the United States: prevalence and trends, 1960-1994. Int J ObesRelatMetab Disord.1998; 22: 39-47.
22. Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, Toplak H, Obesity Management Task Force of the European Association for the Study of Obesity: European guidelines for obesity management in adults. Obes Facts 2015;8:402-424.

23. Aronne LJ, Nelinson DS, Lillo JL (2009) Obesity as a disease state: a new paradigm for diagnosis and treatment. Clin Cornerstone 9(4):9−25. discussion 26–9
24. Centers for Disease Control and Prevention (2007) Prevalence of regular physical activity among adults—United States. 2001 and 2005. MMWR 56:1209–1212
25. Aronne LJ, Segal KR (2003) Weight gain in the treatment of mood disorders. J Clin Psychiatry 64(Suppl 8):22–29. Review
26. Gangwisch JE, Malaspina D, Boden-Albala B, Heymsfield SB (2005) Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. Sleep 28(10):1289–1296
27. Spiegel K, Tasali E, Penev P, Van Cauter E (2004) Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Ann Intern Med 141(11):846–850
28. Filozof C, Fernández Pinilla MC, Fernández-Cruz A (2004) Smoking cessation and weight gain. Obes Rev 5(2):95–103
29. Debmalya Sanyaland and Moutusi Raychaudhuri, Hypothyroidism and obesity: An intriguing link,Indian J Endocrinol Metab,2016 Jul-Aug:20(4):554-557
30. Longhi S, Radetti G.Thyroid function and Obesity. J Clin Res Pediatr Endocrinol. 2013;5 Suppl 1:40-4
31. Nannipieri M, Cecchetti F, Anselmino M, Camastra S, Niccolini P, Lamacchia M, et al. Expression of thyrotropin and thyroid hormone receptors in adipose tissue of patients with morbid obesity and/or type 2 diabetes: Effects of weight loss. *Int J Obes (Lond)* 2009;33:1001–6.
32. Verma A, Jayaraman M, Kumar HK, Modi KD. Hypothyroidism and obesity? Cause or effect. *Saudi Med J*.2008;29:1135–8.
33. Hoogwerf BJ,Nuttall FQ 1984 Long-term weight regulation in treated hyperthyroid and hypothyroid subjects. *Am J Med* 76:963– 970
34. Asvold BO,Bjøro T,Vatten LJ 2009 Association of serum TSH with high body mass differs between smokers and never-smokers. *J Clin Endocrinol Metab* 94: 5023–5027
35. Silva JE. Thermogenic mechanism and their hormonal regulation.*Physiol Rev*.2006;86:435–464.
36. Rosenbaum M, Hirsch J, Murphy E, Leibel RL. Effects of changes in body weight on carbohydrate metabolism, catecholamine excretion and thyroid function.*Am J Clin Nutr*.2000;71:1421–1432.
37. Knudsen N, Laurberg P, Rasmussen LB, Bulow I, Perrild H, Ovesen L, Jorgensen T. Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population.*J Clin Endocrinol Metab*.2005;90:4019–4024.

38. Leitner DR, FruhbeckG, Yumuk V, Schindler K, Micic D, Woodward E, Toplak H. Obesity and type 2 diabetes : two diseases with a need for combined treatment strategies – EASOcan lead the way.Obesity Facts 2017 10 483-492
39. Dyson PA: The therapeutics of lifestyle management on obesity. Diabetes Obes Metab 2010;12:941-946.
40. Qiau Q, Hu G, Tuomilehto J, et al, for the DECODE Study Group.Age and sex specific prevalence of diabetes and impaired glucose regulation in 13 European cohorts.37th Annual meeting of the European Diabetes Epidemiology Group, Oxford, 2002.Abstract 37.
41. DECODA Study Group.Age and sex specific prevalence of diabetes and impaired glucose regulation in 10 Asian cohorts. Diabetes Research and Clinical Practice 2002; 56 (1):540.
42. Benjamin SM, Valdez R, Geiss et al. Estimated number of adults with prediabetes in the US. Diabetes Care 2003; 26:645-649
43. Coutinho M, Gerstein HC, Wang Y, et al.The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95783 individuals followed for 12.4 years. Diabetes Care 1999; 22:233-240.
44. The DECODE Study Group. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria.Lancet 1999; 354:617-621.
45. Faerch K, Vaag A, Holst JJ, Glümer C, Pedersen O, Borch-Johnsen, Impaired fasting glycamia vs impaired glucose tolerance : similar impairment of pancreatic alpha and beta cell function but differential roles of incretin hormones and insulin action, K.Diabetologia. 2008 May;51(5):853-61. doi: 10.1007/s00125-008-0951-x. Epub 2008 Mar 4.PMID:18317726
46. Faerch K, Vaag A, Holst JJ, Glümer C, Pedersen O, Borch-Johnsen, Natural history of insulin sensitivity and insulin secretion in the progression from normal glucose tolerance to impaired fasting glycemia and impaired glucose tolerance : the Inter99 study x K.Diabetes Care. 2009 Mar;32(3):439-44. doi: 10.2337/dc08-1195. Epub 2008 Dec 3.PMID:19056613Free PMC article.
47. Bacha F, Lee S, Gungor N, Arslanian, From pre-diabetes to type 2 diabetes in obese youth pathophysiological characteristics along the spectrum of glucose dysregulation SA.Diabetes Care. 2010 Oct;33(10):2225-31. doi: 10.2337/dc10-0004. Epub 2010 Jun 30.PMID:20592052Free PMC article.
48. Unwin N, Shaw J, Zimmet P, Alberti, Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention KG.Diabet Med. 2002 Sep;19(9):708-23. doi: 10.1046/j.1464-5491.2002.00835.x.

49. Lai X1, Ouyang P1, Zhu H2, An S3, Xia L1, Yao Y4, Zhang H5, Li Z5, Deng K6. "Detection rate of thyroid nodules in routine health check-up and its influencing factors: a 10-year survey of 309 576 cases." Journal of Southern Medical University 40(2) (Feb. 2020): pp.268-273.
50. Ding, Xiaoying ; Xu, Ying ; Wang, Yufan ; Li, Xiaohua ; Lu, Chunhua ; Su, Jing ; Chen, Yuting ; Ma, Yuhang ; Yin, Yanhua ; Wu, Yong ; Jin, Yaqiong ; Yu, Lihua ; Jiang, Junyi; Zhao, Naisi ; Yan, Qingwu ; Greenberg, Andrew S ; Sun, Haiyan ; Gu, Mingyu ; Zh. "Gender Disparity in the Relationship between Prevalence of Thyroid Nodules and Metabolic Syndrome Components: The SHDC-CDPC Community-Based Study." Mediators of Inflammation Vol.2017 (2017): 11 pages.
51. Panagiotou, Grigorios ;Komninou, Despina ; Anagnostis, Panagiotis ; Linardos, George; Karoglou, Eleni ; Somali, Maria ; Duntas, Leonidas ; Kita, Marina ; Tziomalos, Konstantinos; Pazaitou-Panayiotou, Kalliopi. "Association between lifestyle and anthropometric parameters and thyroid nodule features." Endocrine Vol.56(3) (June 2017): pp.560-567.
52. Yang, Hui-Xia ;Zhong, Yu ; Lv, Wei-Hua ; Zhang, Feng ; Yu, Hong. "Association of adiposity with thyroid nodules: a cross-sectional study of a healthy population in Beijing, China." BMC endocrine disorders Vol.19(1) (16 October 2019): pp.102.
53. Xu, Weimin ; Chen, Zexin ; Li, Na ; Liu, Hui ; Huo, Liangliang ; Huang, Yangmei ; Jin, Xingyi ; Deng, Jin ; Zhu, Sujuan ; Zhang, Shanchun ; Yu, Yunxian. "Relationship of anthropometric measurements to thyroid nodules in a Chinese population." British Medical Journal Publishing Group Vol.5(12) (21 December 2015).
54. Buscemi, Silvio ;Massenti, Fatima ; Vasto, Sonya ; Galvano, Fabio ; Buscemi, Carola ; Corleo, Davide ; Barile, Anna ; Rosafio, Giuseppe ; Rini, Nadia ; Giordano, Carla. "Association of obesity and diabetes with thyroid nodules." Endocrine Vol.60(2) (2018): pp.339-347.
55. Liu J ; Wang C ; Tang X ; Fu S ; Jing G ; Ma L ; Sun W ; Li Y ; Wu D ; Niu Y ; Niu Q ; GuoH ; Song P. "Correlation analysis of metabolic syndrome and its components with thyroid nodules." Diabetes, Metabolic Syndrome and Obesity : Targets and Therapy Vol.12 (01 August 2019): pp.1617-1623.
56. Lai, Xingjian ; Zhang, Bo ; Wang, Yong ; Jiang, Yuxin ; Li, Jianchu ; Gao, Luying ; Wang,Ying. "Adiposity and the risk of thyroid nodules with a high-suspicion sonographic pattern: a large cross-sectional epidemiological study." Journal of thoracic disease Vol.11(12) (December 2019): pp.5014-5022.
57. Brito, Juan P ;Yarur, Andres J ; Prokop, Larry J ; Mciver, Bryan ; Murad, Mohammad Hassan ;Montori, Victor M. "Prevalence of Thyroid Cancer in Multinodular Goiter Versus Single Nodule: A Systematic Review and Meta-Analysis." Thyroid Vol.23(4) (01 April 2013): pp.449-455.

58. Liu, Yao ; Lin, Ziwei ; Sheng, Chunjun ; Zhu, Yikun ; Huang, Yun ; Zhong, Ni ; Jia, Zhao ; Qu, Shen. "The prevalence of thyroid nodules in northwest China and its correlation with metabolic parameters and uric acid." Oncotarget Vol.8(25) (20 June 2017): pp.41555-41562
59. Mijović, Tamara ; How, Jacques ; Pakdaman, Michael ; Rochon, Louise ; Gologan, Olguta; Hier, Michael P ; Black, Martin J ; Young, Jonathan ; Tamilia, Michael ; Payne, Richard J."Body mass index in the evaluation of thyroid cancer risk." Thyroid : official journal of theAmerican Thyroid Association Vol.19(5) (May 2009): pp.467-72.
60. Wang, Ying ; Lai, Xing Jian ; Yang, Xiao ; Deng, Xiao Wei ; Jiang, Shu Qiang ; Yang, Xiao Wei ; Tang, Shi Qi ; Wang, Jun ; Ma, Chun Mei ; Li, Ling ; Zhang, Bo. "Association of Body Mass Index and Risk Stratification of Thyroid Nodules in a Multi-center Healthy Population." Zhongguoyixuekexue yuan xuebao. ActaAcademiaeMedicinaeSinicae Vol.41(1) (28 February 2019): pp.93-98.
61. Lucia Marseglia, Sara Manti, Gabriella D'Angelo, Antonio Nicotera, Eleonora Parisi, Gabriella Di Rosa, Eloisa Gitto and T. Arrigo, Oxidative Stress in Obesity: A Critical Component in Human Diseases,
62. Vmenon, M Ram, J Dorn, D. Armstrong, P.Muti, J.L.Freudenheim, R,Browne, Hschunemann, M Trevisan, Oxidative stress and glucose levels in a population-based sample
63. Ameziane El Hassani, Camille Buffet, Sophie leboulleux, Corinne Dupuy ' Oxidative stress in thyroid carcinomas: bilogical and clinical significance ' Endocr Relat Cancer.2019 Mar 1;26(3):R131-143,doi:10.1530/ERC-18-0476
64. Nazanin Ashhari Hanjani and Mohammadreza Vafa, The role of IGF-1 in obesity, cardiovascular disease, and cancer , Medical Journal of the Islamic Republic of Iran (MJIRI)2019, Vol 33, number 1.
65. Nele Friedrich, Betina Thuesen, Torben Jorgensen, Anders Juul, Christin Spielhagen, henri Wallaschofski, Allan Linneberg'The Association Between IGF-I and Insulin Resistance. A general population study in Danish adults' Diabetes Care.2012 Apr;35(4):768-773.
66. Engin Basturk, Metin Kement, Dilek Yavuzer , Salahattin Vural, Cem Gezenm Hulya Iliksu Gozu, Ayse Karadayi and Mustafa Oncel, The Role of Insulin-Like Growth Factor 1 in the Development of Benign and Malignant Thyroid Nodules , Balkan Med J.2012Jun;29(2):133-138.
67. Marcin Gierach, Joanna Gierach, Roman Junik, Insulin resistance and thyroid disorders, Endokrynol Pol.2014;65(1):70-76.
68. Hamiyet Yilmaz Yasar, Ozden Ertrugrul, Bulent Ertugrul, Derum Ertuglul, Mustafa Sahin, Insulin resistance in nodular thyroid disease, Endocr Res.2011;36(4):167-174

69. A. Tsatsoulis, The role of insulin resistance/hyperinsulinism in the evolution of thyroid nodular disease in humasns , J Clin Med 2018 Mar;7(3):37
70. Cappelli C, Pirola I, Mittempergher F, De Martino E, Casella C, Agosti B, Nascimbeni R, Formenti A, Rosei EA, Castellano M. Morbid obesity in women is associated to a lower prevalence of thyroid nodules. Obes Surg. 2012;22(3):460–4.
71. Sousa PA, Vaisman M, Carneiro JR, Guimarães L, Freitas H, Pinheiro MF, Liechocki S, Monteiro CM, Teixeira PF. Prevalence of goiter and thyroid nodular disease in patients with class III obesity. Arq Bras Endocrinol Metabol. 2013;57(2):120–5.