Risk factors for papillary thyroid cancer in obesity and diabetes mellitus

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Overweight and obesity, collectively referred to as «overweight», are defined as abnormal or excessive fat accumulation that causes many chronic diseases and shortens life expectancy [1]. The prevalence of overweight is increasing worldwide. Thus, in 2016, approximately 40 % of adults and 18 % of children (aged 5–19 years) were overweight, amounting to almost 2 billion adults and 340 million children [4]. In 2015, an estimated 4 million deaths were due to overweight [2]. The economic impact of diseases related to overweight is extremely unprofitable as the estimation was around 2.0 trillion USD in 2014 [3]. Except for a few economically independent or high-income countries, others have seen an increase in the prevalence of overweight in recent years among all populations [4]. The fastest growth is observed in low- and middle-income countries, probably due to the introduction of a «Western lifestyle», which consists of a high-calorie diet, nutrient-poor foods, and reduced physical activity [5]. Since obesity is often related to diabetes mellitus (DM) and violation of the microbiota of the intestine, our study aims to summarize the evidence of the impact of these risk factors on the possible development of papillary thyroid cancer.

Adiposity

Being overweight is associated with the risk of developing various cancers [6, 7]. Although the impact of overweight, as a risk of developing on cancer is moderate as compared to other triggers, the development and implementation of a consumer model of behavior in all countries of the world will lead to a significant increase in these figures.

Various mechanisms have been proposed until now to explain how being overweight affects cancer risk. The main ones are changes in the hormonal system (peptide metabolism hormones, sex steroid hormones) and chronic inflammation, which are the most studied hypotheses.

Increased body mass index will increase the number of adipocytes that secrete adipokines that will continue to stimulate mitogenic cell division [12]. A meta-analysis shows that increasing the body mass index by 5 kg/m2 increases the risk of thyroid cancer in men (RR = 1.33; P = 0.02) and women (RR = 1.14; P = 0.001) [13]. Scientists explain this by the effect of adipokines such as leptin, adiponectin, and hepatocyte growth factor on follicular cell proliferation, which provokes the growth of cancer cells. Adiponectin is the most studied adipokine in terms of cancer risk [14, 15]. Serum adiponectin levels are negatively correlated with BMI through several mediators (e.g., insulin, tumor necrosis factor α, estrogen), which inhibit transcription. The influence on the development of the tumor occurs by sensitization of the cells to

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insulin or through anti-inflammatory action. Adiponectin can also have an anti-tumor effect directly by regulating the metabolic, inflammatory, and signaling pathways of the cell cycle [16]. These experimental studies strongly confirm the role of adiponectin in different types of cancer, including breast cancer, kidney, liver, pancreas, thyroid cancer, myeloma, stomach, esophagus, prostate and colorectal cancer [17]. However, observational studies on the relationship between the diagnostic level of adiponectin and the risk of several cancers have reported mixed results [18—22].

Adipose tissue, as an endocrine organ, affects the synthesis and bioavailability of sex hormones. Adipose tissue produces aromatase enzymes that convert androgens to estrogens and convert less active forms of these hormones (androstenedione, estrone) into more active forms (testosterone, estradiol) and increase the concentration of sex hormone-binding globulin in the blood that cause increasing the bioavailability of free estradiol and testosterone. It is believed that the sex steroid hormones appear mediators due to the risk of breast and endometrial cancer and possibly increases the risk of prostate and colon cancer [23]. In post-menopausal obese women, the rate of conversion of androgens to estrogens is increased [24]. In an analysis with a combination of 8 prospective studies, the association of BMI with postmenopausal breast cancer risk was almost entirely explained by an increase in estradiol levels with an increase in BMI [25]. In men, etiologic role that links hormones with advanced prostate cancer is not fully understood [26]. In obese people, there is an increase in serum estradiol levels and a decrease in androgen levels [27]. Because androgens play an important role in the normal growth and differentiation of prostate epithelial cells, one hypothesis is that a reduction in bioavailable testosterone, in particular, may contribute to more advanced prostate cancer [28]. Indeed, at least 2 prospective studies have shown that a lower level of diagnosis of circulating androgens has been associated with a risk of high-quality, poorly differentiated prostate cancer [29, 30].

Adipose tissue produces and secretes a wide range of pro-inflammatory molecules, including tumor necrosis factor α and interleukin-6, which can cause local inflammation of adipose tissue and systemic effects on other organs [16, 29]. Complete chronic inflammation, often found in obese people, predisposes to a particular type of cancer, creating a tissue environment that creates oxidative stress, stimulates DNA damage, increases cell proliferation, and inhibits apoptosis. Several examples of local inflammation related to the risk of cancer include the association of the non-alcoholic fatty liver disease with liver cancer [29, 31] chronic acid reflux, the development of Barrett's esophagus, and esophageal adenocarcinoma [32, 33], and the association of chronic gallstones disease and cholecystitis with gallbladder cancer [34, 35].

Also, fat significantly increases insulin resistance, which significantly increases the chances of carcinogenesis (see below).

Diabetes mellitus

Despite the tremendous development of medicine and the improvement of the quality and life expectancy of people, the incidences of diabetes mellitus (DM) is only increasing. According to WHO's statistics, there were 422 million cases of DM (in adults) in the world in 2014, which is four times more than in 1980 [32]. A significant role in the growth of this indicator is the increase in the incidence of type 2 DM, which is directly related to the rise in factors as overweight and obesity [2].

It is a well-known fact that diabetes is the main trigger in the development of pathological conditions such as macroangiopathy (damage to the coronary vessels of the heart, brain, and vessels of the legs) and microangiopathy (damage to small vessels of the retina, kidneys, legs) [3]. In addition to these complications, DM is also one of the driving factors in the development of cancer, namely, colon cancer, pancreatic cancer, breast cancer, bladder cancer, prostate cancer, and non-Hodgkin's lymphoma [33].

However, does DM have an effect on the development of thyroid cancer since? Because this type of tumor is much more often diagnosed now, we must not forget about the rapid tendency to malignancy and high mortality caused by this pathology [5]. According to epidemiological statistics [6], only ionizing radiation can be directly related to the development of the disease, and benign tumors and abuse or inadequate intake of iodine are a risk factor. However, none of these reasons explains the incline in the thyroid cancer cases. Epidemiological studies [7] show that the occurrence of thyroid cancer pathology in people with DM (10.8 %) are more frequent than in the general population (6.6 %), therefore, in this article, we will try to find a connection

between the nosology by analyzing the research of our foreign colleagues.

To begin with, it is necessary to establish a causal relationship between these pathologies at the pathophysiological level, as DM can cause the development of the neoplastic process of the thyroid gland [34]. DM can affect the mitotic division of follicular cell through several mechanisms. Increased insulin stimulates follicular cells to divide due to structural similarity to insulin-like growth factors [35]. Studies show that when culturing follicular cells, their quantity increases significantly in the presence of insulin and TSH as compared to the presence of only TSH [36]. This is evidence of the phenomenon of insulin mimicry to insulin-like factor 1 which is due to the effect on cell growth receptors. From this, we can conclude that in vivo increased amount of insulin will lead to hyperplasia of the follicular epithelium, which is a prerequisite for carcinogenesis and for a much faster progression of cancer [11].

The anti-diabetic drugs sulfonylurea and injectable insulins increases the concentration of the insulin in the blood [14, 15], which as mentioned above, stimulates receptor for the activation and promotion of cell growth, and proliferation of follicle. Studies show that the risk of cancer increases by 20 % with each year of insulin therapy [16].

Hyperglycemia and hypertriglyceridemia increase oxidative stress [17] by activating nuclear factor «к-В». This factor activates the production of nitric oxide, which is a substance for the formation of reactive oxygen species. These types of small quantities of oxygen are involved in the signaling and proliferative processes of the cell, whereas, in large quantities they are found in cancer cells [18]. However, a significant study in 2011 with a large cohort of subjects shows that women with elevated blood glucose do not affect the development of thyroid cancer, but men, on the contrary — increases the risk of oncology [19]. At the moment, it is impossible to say unequivocally about this thesis, because the interaction of glucose, thyroid hormones, and sex hormones is complex and not fully known.

For unknown reasons, DM causes a deficiency of vitamin D, which leads to a decrease in iodothyronine deiodinase 2, which, in turn, reduces the level of triiodothyronine in the intracellular space. Low levels of triiodothyronine in soft tissues help reduce GLUT-4, a glucose transporter that causes insulin resistance. In turn, low levels of T3 cause the production of TSH, which is already in excess due to DM [20].

Thus, as a result, there is an excess of glucose, TSH, insulin, triglycerides, adipokines that activate uncontrolled division of follicular cells, which is a prerequisite for the neoplastic process [21] in theory. However, to confirm this theory, it requires meta-analyzes and cohort studies of actual patients who prove, or disprove the link between DM and thyroid cancer.

According to several studies [6, 8, 22—24], the link between DM and thyroid cancer is weak in women, but for men with DM, the connection is even weaker or not observed at all. The results are controversial and ambiguous, so it is impossible to claim that DM is one of the risk factors for thyroid cancer at this stage.

However, in the process of the study, a connection between DM and the rate of progression of cancer was established [25], namely the growth and invasion of the primary tumor through the influence of insulin on insulin-like growth factor receptors. Therefore, we can say that this effect is not DM itself, but drugs for its treatment, drugs that raise the natural level of insulin or injectable insulin drugs themselves [26].

Proof of this is the number of studies that demonstrate a significantly lower incidence of cancer and remission in cancer patients with type 2 DM treated with metformin [27, 28] and acarbose [25] compared to other comorbid patients treated with insulin replacement therapy and its synthetic analogues.

The **Fig. 1** illustrates pathologic mechanisms underlying the increase in the risk of the development of thyroid cancer.

Also, the research to indicate a positive effect of metformin in the treatment of papillary cancer of the thyroid caused by overweight is very interesting [29]. Metformin reduces the development, invasion, and metastasis of this type of cancer by blocking leptin receptors [30], and to some extent, prevents the occurrence of papillary thyroid cancer induced by obesity [31].

Microbiota

Summarizing all the above risk factors for cancer, we must mention the intestinal microbiota, the violation of which leads to both obesity and DM. The role of commensal microorganisms is often underestimated, but they are indispensable in the development and functioning of the immune system [58]. For example, cells of microbiota feeds on signals required for the normal development of lymphoid her tissue associated

Table

**Overview of results of prospective cohort studies and meta-analyzes of communication
in between diabetes mellitus and thyroid cancer**

№	Year and author of a study	Country	Name of investigations	Form of research	Number of cases/years of research	Risk ratio
1 [6]	2010 C.L. Meinhold et al.	USA	The US Radiologic Technologists Study	special cohort study	69,506 women, 21,207 men from 1983 to 2006	women : HR = 1.37 (95 % CI: 0.49—3.77) forehead Ages: NA
2 [8]	2011 B. Aschebrook-Kilfoy et al.	USA	The NIH-AARP Diet and Health Study	prospective cohort study	200,556 women, 295,992 men Average study time: 10 years	women: HR = 1.54 (95 % CI: 1.08—2.20) men: HR = 1.11 (95 % CI: 0.74—1.66)
3 [22]	2012 C.M. Kitahara et al.	USA	Physical activity, diabetes, and thyroid cancer risk: a pooled analysis of five prospective studies	Combined analysis of five prospective studies, including diet and health research NIHAARP (NIH-AARP), Prostate, Lung Cancer, Colorectal Cancer and Ovarian Cancer Screening Study (PLCO), Breast Cancer Detection and Demonstration Project), Agricultural Health Research (AHS) and US Radiological Technology Research (USRT)	312,149 women, 362,342 men Average study time: 10.5 years	women: HR = 1.19 (95 % CI: 0.84—1.69) men: HR = 0.96 (95 % CI: 0.65—1.42)
4 [23]	2014 Yohwan Yeo et al.	Korea	Diabetes Mellitus and Risk of Thyroid Cancer: A Meta-Analysis	Purpose — analysis	19 cohort studies were analyzed, the results of which were published in 1992—2012	Women (RR = 1.384. 95 % CI 1.13—1.67) Men (RR = 1.11, 95 % CI 0.80—1.53).
5 [24]	2016 Juhua Luo et al.	USA	Diabetes, Diabetes Treatment, and Risk of Thyroid Cancer	prospective cohort study	147 934 women for 16 years of observation	hazard ratio = 1.09; 95 % confidence interval, 0.79—1.52

with the intestine (GALT), capture IgA-producing plasma cells, and activation of T-lymphocytes, which proceeded after birth at mammals [59]. In vertebrates animals, many products of the commensal microbiota and pathogens, which act in part on innate receptors of the TLR and NOD-like receptors, affect barrier immunity through pro- and anti-inflammatory mechanisms. The role of TLR and the IL-1 receptor family in the control of intestinal microbiology is demonstrated in mice with deficiency in MyD88 adapter molecules, in which microbial-regulated genes have altered expression [60]. MyD88 — molecules required for epithelial expression of antimicrobial genes such as Reg3β and Reg3γ, and MYD88 deficiency leads to changes in the composition of bacterial microbiota [60, 61]. It is important to remember that, in addition to bacteria, the microbiota has archaea, fungi, viruses, and bacteriophages, and, that overgrowth is often associated with changes in the quantitative part of various members of the microbiota. In addition, in
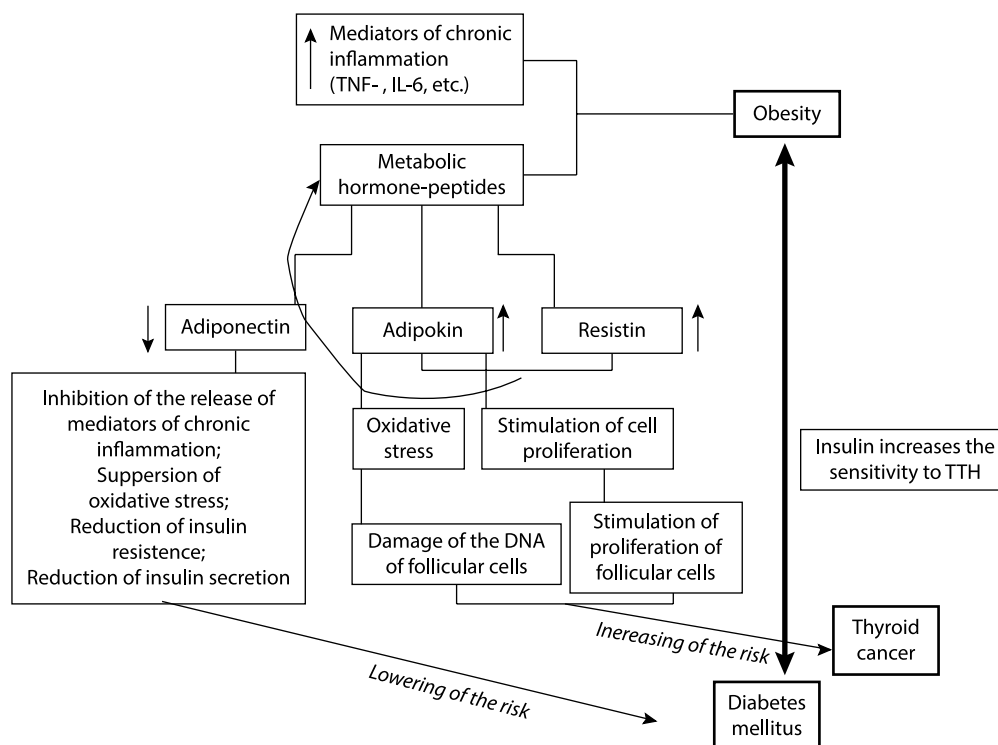
Figure. *Pathologic mechanisms underlying the increase in the risk of the development of thyroid cancer*

animals with MyD88 deficiency grown in conventional facilities, norovirus infection and reactivation of infectious endogenous retroviruses, such as mouse leukemia virus, are common and lead to altered innate and adaptive immune responses [60, 63].

Among the mechanisms to influence the microflora of the immune system, a significant role is occupied by short-chain fatty acids (SCFA), which prodused by bacteria's during fermentation, because it affects an mucosal immunity via signaling through the receptor-associated protein G, i.e. SCFA induce production IL-18 enterocytes [65, 66], and also have a significant effect on T-lymphocytes, affecting their size and function [65—67].

Studies show that Bacteroides fragilis, normal human intestinal microbiota component, can control the differentiation of Treg-cells, that secreting IL-10 through its capsule polysaccharide-A, TLR2 agonist [59]. B. fragilis has also been shown to protect mice from a viral infection — Helicobacter hepaticus and trinitrobenzene sulfonic acid (TNBS) that induce colitis [59, 68].

Among the species with the ability to increase the immune response of the intestinal mucosa is segmented filamentous bacteria (SFB) — a type of bacteria that is present in the ileum of mice. They stimulate postpartum maturation of the immune response with lysis in the intestine of mice [69]. In the absence of SFB in mice, it was shown that they have lower titers of IgA, low mucosal Th1 and Th17 cells quantity and have a poor response to intestinal pathogens such as Citrobacter rodentium and Salmonella spp. This fact allows us assuming that barrier function is supported by an immunological response caused by a microbiota [70—72].

Thus, obesity is one of the factors for the possible development of oncological processes in the body due to hormonal imbalance and the development of chronic inflammation, which stimulate mitogenic cell division. In particular, adipose tissue hormones such as leptin, adiponectin stimulates the proliferation of follicular cells, directly increases the likelihood of developing thyroid cancer.

Although research has shown a weak link between diabetes and thyroid cancer in women and a much weaker link in men, the fact that treatment aimed at increasing own insulin or using its analogues has a direct correlation connection with the development of cancer through the stimulation of receptors that induce proliferation. At the same time, treatment of DM with metformin and/or acarbose, in contrast, induced remission in cancer patients according to studies.

Therefore, obesity, and often associated DM and intestinal microbiota disorders, may increase the risk of cancer, particularly papillary thyroid cancer.

Authors declare that there is no conflict of interest.

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SUMMARY

Risk factors for papillary thyroid cancer in obesity and diabetes mellitus

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Abstract. Obesity and resulting diabetes mellitus are being two of the most prevalent pathological conditions worldwide accounting almost 2 billion adults and 340 million children affected. In the same time, global cancer statistics rises each year showing the growth in the number of cases of papillary thyroid cancer. Relationship between thesediseases has created strong interest among scientists and discovered new directions in prevention and therapy. Moreover, obesity usually leads to the disturbance in gut microbiota. Accordingly, the aim of our research was to summarize the evidence of the impact of these risk factors on the possible development of papillary thyroid cancer.

Current article reflects newest achievements in the understanding of pathological mechanisms underlying the epidemiological trends connecting adiposity, hyperglycemia, diabetes mellitus, antidiabetic therapy and microbiota changes.

Wide range of evidences testify in favor that obesity is one of the factors for the possible development of oncological processes in the body due to hormonal imbalance and the development of chronic inflammation, which stimulate mitogenic cell division. Complete chronicinflammation, often found in obese people, predisposesto a particular type of cancer, creating a tissueenvironment that creates oxidative stress, stimulatesDNA damage, increases cell proliferation, and inhibitsapoptosis.Talking about diabetes mellitus, recent studies suggested that when culturing follicular cells, their quantity increases significantly in the presence of insulin and TSH as compared to thepresence of only TSH. This phenomenon occurs due insulinstructural similarity to insulin-like growth factor 1. Same mechanism is also related to increase in thyroid cancer risk in diabetic patients prescribed with sulfonylurea and injectable insulins.

Other points are still partly unclear and need further investigations and therapeutic implications.

РЕЗЮМЕ

Фактори ризику папілярного раку щитоподібної залози при ожирінні та цукровому діабеті

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Ожиріння і, як наслідок цукровий діабет, є двома захворюваннями з групи найпоширеніших патологічних станів у світі, що вразили вже майже 2 млрд дорослих та 340 млн дітей. Водночас міжнародна канцер-статистика щороку зростає, у тому числі збільшується кількість випадків папілярного раку щитоподібної залози. Взаємозв'язок між цими захворюваннями породжує сильний інтерес серед науковців, а його розуміння відкриває нові напрямки у профілактиці та терапії цих захворювань. Більше того, ожиріння зазвичай призводить до порушення мікробіому кишечника. Відповідно, метою нашого дослідження було узагальнити результати досліджень, присвячених впливу цих чинників на можливий розвиток папілярного раку щитоподібної залози.

Дана стаття відображає новітні досягнення у розумінні патологічних механізмів, що лежать в основі епідеміологічних тенденцій, які пов'язують ожиріння, гіперглікемію, цукровий діабет, протидіабетичну терапію та зміни мікробіому.

Широкий спектр фактів свідчить на користь того, що ожиріння є одним із чинників можливого розвитку онкологічних процесів в організмі через гормональний дисбаланс та розвиток хронічного запалення, що стимулює мітогенний поділ клітин. Тривале хронічне запалення, яке часто зустрічається у людей із ожирінням, призводить до підвищеного ризику розвитку певних типів раку, створюючи тканинне середовище з підвищеним оксидантним стресом, що, у свою чергу, стимулює пошкодження ДНК, пришвидшує проліферацію клітин і гальмує апоптоз. Щодо цукрового діабету, то останні дослідження продемонстрували, що при культивуванні фолікулярних клітин їх кількість значно зростає в присутності інсуліну та ТТГ порівняно з наявністю лише ТТГ. Це явище відбувається через структурну схожість

інсуліну до інсуліноподібного фактора 1. Цей же механізм також пов'язаний із збільшенням ризику раку щитоподібної залози у хворих на цукровий діабет, яким призначають сульфонілсечовину та ін'єкційні інсуліни.

Інші аспекти досі лишаються частково незрозумілими і потребують подальших досліджень для зміни терапевтичних підходів до профілактики і лікування.

Ключові слова: щитоподібна залоза, папілярний рак щитоподібної залози, ожиріння, цукровий діабет, фактори ризику.

РЕЗЮМЕ
Факторы риска папиллярного рака щитовидной железы при ожирении и сахарном диабете

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Ожирение и, как следствие сахарный диабет, являются двумя заболеваниями из группы самых распространенных патологических состояний в мире, поразили уже почти 2 млрд взрослых и 340 млн детей. В то же время международная канцер-статистика ежегодно растет, в том числе увеличивается количество случаев папиллярного рака щитовидной железы. Взаимосвязь между этими заболеваниями порождает сильный интерес среди ученых, но его понимание открывает новые направления в профилактике и терапии этих заболеваний. Более того, ожирение обычно приводит к нарушению микробиом кишечника. Соответственно, целью нашего исследования было обобщить результаты исследований, посвященных влиянию этих факторов на возможное развитие папиллярного рака щитовидной железы.

Данная статья отражает новейшие достижения в понимании патологических механизмов, лежащих в основе эпидемиологических тенденций, которые связывают ожирение, гипергликемию, сахарный диабет, противодиабетическую терапию и изменения микробиома.

Широкий спектр доказательств свидетельствует в пользу того, что ожирение является одним из факторов возможного развития онкологических процессов в организме из-за гормонального дисбаланса и развития хронического воспаления, стимулирует митогенное деление клеток. Длительное хроническое воспаление, которое часто встречается у людей с ожирением, приводит к повышенному риску развития определенных типов рака, создавая тканевую среду с повышенным оксидантным стрессом, что, в свою очередь, стимулирует повреждения ДНК, ускоряет пролиферацию клеток и тормозит апоптоз. Относительно сахарного диабета, последние исследования показали, что при культивировании фолликулярных клеток их количество значительно возрастает в присутствии инсулина и ТТГ по сравнению с наличием только ТТГ. Это явление происходит из-за структурного сходства инсулина с инсулиноподобным фактором 1. Этот же механизм также связан с повышением риска рака щитовидной железы у больных с сахарным диабетом, которым назначают сульфонилмочевину и инъекционные инсулины.

Другие аспекты до сих пор остаются частично непонятными и требуют дальнейших исследований для изменения терапевтических подходов к профилактике и лечению.

Ключевые слова: щитовидная железа, рак щитовидной железы, ожирение, сахарный диабет, факторы риска.