Kurdistan Regional Government-Iraq

Ministry of Higher Education & Scientific Research

Salahaddin University–Erbil

Directorate of Higher Education & Postgraduate Studies

Chemistry Department

Clinicopathologic significance of adipokines and cytokines in thyroid carcinoma

A Review article in

(Clinical Pathology)

In Partial Fulfillment of the Requirements for the Degree of (Ph.D.)

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(2023-2024)

Clinicopathologic significance of adipokines and cytokines in thyroid carcinoma

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Abstract

A complicated interaction between molecular signalling and the pathogenesis of thyroid carcinoma is shown by the clinicopathologic relevance of adipokines and cytokines in this frequent endocrine malignancy. Thyroid carcinoma's clinical and pathological features are increasingly being determined by adipokines, such as leptin and adiponectin, as well as cytokines, which are important regulators of immune responses. This abstract summarises the present study and sheds light on the correlation between changes in adipokine and cytokine expression patterns and several clinicopathologic characteristics, such as tumour aggressiveness and metastatic potential. As a result of their effects on inflammation, angiogenesis, and cell proliferation, these signalling molecules determine how thyroid cancer develops. Adipokines, cytokines, and thyroid tumour cells all have complex relationships that modulate the tumour microenvironment and impact the course of illness. The abstract also explores the possibility of these compounds' use as biomarkers for diagnostics and prognosis. The abstract delves into the therapeutic possibilities of targeting adipokine and cytokine pathways, proposing new techniques to interrupt tumorigenic signalling and improve treatment effectiveness, going beyond their significance for thyroid cancer knowledge. In the ever-changing field of thyroid cancer research, this synthesis of clinicopathologic findings highlights the complex involvement of adipokines and cytokines in the disease, suggesting a potential pathway for diagnostic and treatment strategies.

Keywords: Adipokines, Cytokines, Clinicopathologic significance, Thyroid carcinoma

1. Introduction

Studying the clinicopathologic involvement of adipokines and cytokines in thyroid carcinoma is crucial to understanding its complicated molecular landscape. Thyroid cancer has several histological subtypes and clinical behaviours, making its aetiology complex. The thyroid, an essential endocrine organ, may be dysregulated and produce tumours, requiring molecular research. Recent studies have indicated that thyroid cancer is linked to cytokines, which regulate immune responses, and adipokines like leptin and adiponectin. This section introduces the complex link between molecular signalling, adipokine and cytokine involvement, and thyroid cancer to offer a full overview.

We need to understand the molecular processes that cause thyroid carcinoma to vary so much. Cancer biology has lately drawn attention to adipokines, which are secreted by adipose tissue, and cytokines, which regulate the immune system. Adiponectin and leptin, two thyroid cancer adipokines with diverse domains of activity, demonstrate their functional differences. Leptin promotes inflammation and proliferation, whereas adiponectin is anti-inflammatory and antiproliferative. Cytokines modulate inflammation in cancer microenvironment and angiogenesis. Two thorough reviews, Kim et al. (2018) and Lee et al. (2020), examine adipokines and cytokines in thyroid cancer to understand their clinicopathologic role.

Analysing adipokine and cytokine expression patterns in relation to disease features is required to determine their clinicopathologic importance in thyroid cancer. These signalling molecules' levels may alter, which may indicate a health problem, according to research. Rocha et al. (2017) and Chen et al. (2021) reveal that adipokines and cytokines correlate with clinicopathologic features in thyroid cancer, demonstrating their diagnostic utility.

Beyond the primary tumour, adipokines and cytokines alter systemic and local immune responses. Signalling molecules and thyroid cancer cells interact complexly to change the tumour microenvironment and disease progression. These interactions include complicated molecular processes that help tumours develop, survive, and spread, according to Xing (2019) and Kim et al. (2019). Research on adipokines and cytokines in thyroid cancer considers systemic variables that affect the disease trajectory in several ways. Trustworthy biomarkers are needed to improve thyroid cancer diagnosis. Finding biomarkers via adipokine and cytokine expression variations is exciting. Rocha et al. (2017) and Chen et al. (2021) demonstrate these chemicals' diagnostic potential,

suggesting clinical usage. Understanding their diagnostic usefulness requires examining thyroid cancer patients' expression patterns and clinicopathologic factors.

The aim of the study

1. Investigate the altered expression profiles of adipokines and cytokines in thyroid carcinoma patients, aiming to discern their association with distinct clinicopathologic features, including tumor aggressiveness and metastatic potential.
2. Assess the diagnostic potential of adipokines and cytokines as biomarkers in thyroid carcinoma by evaluating their expression levels and correlating them with clinicopathologic parameters, providing insights into their utility for accurate and personalized clinical assessments.
3. Explore the therapeutic implications of modulating adipokine and cytokine pathways in thyroid cancer, aiming to identify innovative strategies to disrupt tumorigenic signaling and enhance treatment efficacy for improved patient outcomes.

2. Literature review

Due to the clinicopathologic importance of adipokines and cytokines in thyroid carcinoma, the complex molecular landscape that governs its creation and progression has been scrutinised in the literature. Because the thyroid, an essential endocrine gland, may dysregulate and become cancerous, the molecular pathways that produce thyroid carcinoma must be studied. Thyroid cancer clinical and pathological aspects depend on several variables. Adipokines—leptin and adiponectin—and cytokines—which influence immune responses—are two of these variables. Kim et al. established our molecular understanding of papillary thyroid cancer in their 2018 review. They stressed the role of molecular changes such adipokines and cytokines in thyroid cancer development (Kim et al., 2018).

Cytokines, which modulate the immune system, and adipokines, which are secreted by adipose tissue, are important in cancer biology, notably thyroid carcinoma. In thyroid cancer, adipokines like adiponectin, which is anti-inflammatory and antiproliferative, and leptin, which is pro-inflammatory and proliferative, stand out. Moreover, cytokines regulate inflammatory responses, which impact the tumour microenvironment and angiogenesis.

Lee et al.'s 2020 study illuminates papillary thyroid carcinoma's molecular profile and suggests that adipokines and cytokines may promote thyroid cancer. In two recent investigations, Rocha et al. (2017) and Chen et al. (2021) emphasised the diagnostic usefulness of adipokines and cytokines in thyroid cancer. Both studies show clinicopathologic marker connections. Research suggests that

adipokines and cytokines may be employed as thyroid cancer biomarkers. This may improve diagnostic accuracy and prognostic categorization (Rocha et al., 2017; Chen et al., 2021). Adipokines and cytokines affect systemic and local immune responses beyond the tumour site. Thyroid cancer cells and signalling molecules interact complexly, changing the tumour microenvironment and disease progression. Kim et al. (2019) and Xing (2019) study adipokines and cytokines' complicated molecular pathways to understand cancer formation, survival, and metastasis. Adipokines and cytokines impact thyroid cancer growth systemically, while most research has focused on local effects.

2.1 Adipokines

Adipokines, signalling chemicals generated by adipose tissue, are crucial to the complex immunological and metabolic regulation network. Adiponectin's multiple roles make it unique among bioactive compounds. Due to its anti-inflammatory properties and effects on insulin sensitivity and energy metabolism, adiponectin protects against metabolic disorders including type 2 diabetes and insulin resistance. Yamachi et al. (2001) found that its levels are inversely associated to obesity, suggesting its usefulness as a metabolic health indicator. Adiponectin also lowers vascular tissue inflammation and endothelial dysfunction, making it anti-atherogenic (Ouchi et al., 1999).

Leptin, another adipokine, regulates weight and energy. In adipose tissue, leptin promotes energy expenditure and lowers hunger (Friedman, 2014). Many studies suggest that overweight persons have higher leptin levels. Their bodies may be resistant to leptin, reducing its effectiveness (Myers et al., 2010). Leptin regulates innate and adaptive immune responses and adipose tissue-immune interactions (Lam et al., 2010).

Another adipokine connected to inflammation and insulin resistance is resistin. This hormone is released by adipocytes and macrophages and is connected to obesity-related insulin resistance and type 2 diabetes (Steppan et al., 2001). Steppan et al. (2001) found that resistin increases inflammatory cytokines. This links adipose tissue dysfunction to systemic inflammation.

2.1.1 Types of Adipokines

Important physiological functions including metabolism, inflammation, and immunity are regulated by adipokines, a broad class of bioactive chemicals released by adipose tissue.

1. Adiponectin:

Research on the anti-inflammatory, insulin-sensitizing, and cardioprotective effects of the adipokine adiponectin has shown promising results. It has a role in the metabolism of fatty acids and the control of glucose. Potentially serving as a biomarker for metabolic health, adiponectin levels are inversely associated to obesity. According to Kadowaki et al. (2006), insulin resistance and metabolic syndrome are linked to decreased adiponectin levels.

2. Leptin:

Regarded as the "satiety hormone," leptin is pivotal in maintaining a steady energy balance. It controls hunger and energy expenditure; adipocytes are the principal producers and it sends signals to the brain, especially the hypothalamus. Obesity causes leptin resistance, which throws off energy balance, even though leptin levels are normally directly proportionate to fat mass (Friedman, 2014).

3. Resistin:

Insulin resistance and inflammation are both impacted by resistin. It has been linked to insulin resistance in obesity and is generated by adipocytes and macrophages. The systemic inflammatory state seen in obesity is exacerbated by resistin, which stimulates the release of pro-inflammatory cytokines (Steppan et al., 2001).

4. Visfatin:

Visfatin modulates insulin action and is involved in glucose metabolism; it is also called nicotinamide phosphoribosyltransferase (NAMPT). Obesity and metabolic diseases are associated with increased visfatin levels. Depending on the concentration and metabolic environment, visfatin might have an impact on insulin sensitivity and resistance (Fukuhara et al., 2005).

5. Chemerin:

In addition to its role in adipogenesis, chemerin acts as a chemoattractant for immune cells. It has been linked to metabolic syndrome and obesity, and it also has a function in inflammation. There may be a connection between inflammation and dysfunctional adipose tissue since chemerin levels are higher in circumstances of excess adiposity (Bozaoglu et al., 2007).

6. Retinol-Binding Protein 4 (RBP4):

Retinol (vitamin A) transport is facilitated by RBP4, an adipokine. Insulin resistance, diabetes type 2, and cardiovascular disease have all been associated with elevated RBP4 levels. Yang et al. (2005) suggested that RBP4 might play a role in metabolic dysfunction via influencing insulin sensitivity in peripheral tissues.

7. Lipocalin-2:

One protein that has been linked to inflammation and insulin resistance is lipocalin-2, which is another name for neutrophil gelatinase-associated lipocalin (NGAL). Adipocytes and macrophages release it, and it might have a role in the development of metabolic diseases associated with obesity. Inflammation of adipose tissue is associated with increased levels of lipocalin-2 (Guo et al., 2010).

8. Omentin:

An adipokine with insulin-sensitizing capabilities, Omentin also has anti-inflammatory effects. Vesicular adipose tissue is where it is most often found. Obesity and insulin resistance are inversely associated to omentin levels, and those with metabolic diseases have been shown to have lower omentin levels (Yang et al., 2006).

2.1.2 Advantages and Disadvantages of Adipokines in Health

2.1.2.1 Advantages of Adipokines

1. Metabolic Regulation:

Metabolic functions are significantly impacted by adipokines like adiponectin. One example is adiponectin, which is essential for increasing insulin sensitivity, boosting glucose utilisation, and easing the oxidation of fatty acids. Preventing insulin resistance and type 2 diabetes requires this metabolic control (Kadowaki et al., 2006).

2. Anti-inflammatory Effects:

As part of their role in immune system regulation, several adipokines have anti-inflammatory characteristics. Some examples of these proteins that have functions in reducing inflammatory responses include adiponectin and omentin. The adipokines have a positive impact on vascular health and cardioprotection by lowering inflammation and preventing endothelial dysfunction (Yang et al., 2006).

3. Cardioprotective Effects:

Adiponectin, in addition to its metabolic benefits, has been linked to cardioprotective effects. It helps maintain vascular integrity, inhibiting the development of atherosclerosis. This protective function is vital for cardiovascular health, reducing the risk of heart-related complications (Yamauchi et al., 2001).

4. Appetite Regulation:

The "satiety hormone," or leptin, is an important regulator of hunger. Leptin, which is produced by fat cells, tells the brain, specifically the hypothalamus, to reduce hunger and boost energy

expenditure. Maintaining a healthy weight and avoiding calorie overload depend on this appetite control (Friedman, 2014).

5. Insulin Sensitivity:

Insulin sensitivity in peripheral tissues is aided by adipokines, especially adiponectin. These adipokines are essential for glucose homeostasis and lowering the likelihood of insulin resistance and metabolic diseases because they improve the body's reaction to insulin (Kadowaki et al., 2006).

2.1.2.2 Disadvantages of Adipokines

1. Leptin Resistance:

People who are overweight may become resistant to the effects of leptin. The body's ability to control hunger decreases even while leptin levels are high. As a result of this resistance, energy balance becomes upset, leading to overeating and more weight gain (Myers et al., 2010).

2. Inflammatory Consequences:

Inflammation may be caused by certain adipokines and alleviated by others. For instance, resistin connects malfunction in adipose tissue to systemic inflammation by promoting the production of pro-inflammatory cytokines. Guo et al. (2010) found that metabolic problems, cardiovascular illnesses, and other inflammatory ailments are all linked to chronic inflammation.

3. Insulin Resistance:

The role of adipokines such as resistin and retinol-binding protein 4 (RBP4) in insulin resistance has been suggested. According to Steppan et al. (2001), when these adipokines are high, insulin sensitivity is reduced, which in turn increases the risk of developing type 2 diabetes and cardiovascular illnesses.

4. Potential for Metabolic Dysfunction:

Metabolic malfunction may occur when adipokine levels are out of whack (Figure 1), which is especially common in obesity. Metabolic syndrome is a group of symptoms including insulin resistance, high blood pressure, and abdominal obesity; altered adipokine levels may play a role in its development (Bozaoglu et al., 2007).

5. Association with Obesity-Related Disorders:

A number of adipokines have been linked to diseases that manifest as obesity. One example is resistin, which has been linked to inflammation and insulin resistance, two factors that have a role in the development of type 2 diabetes.

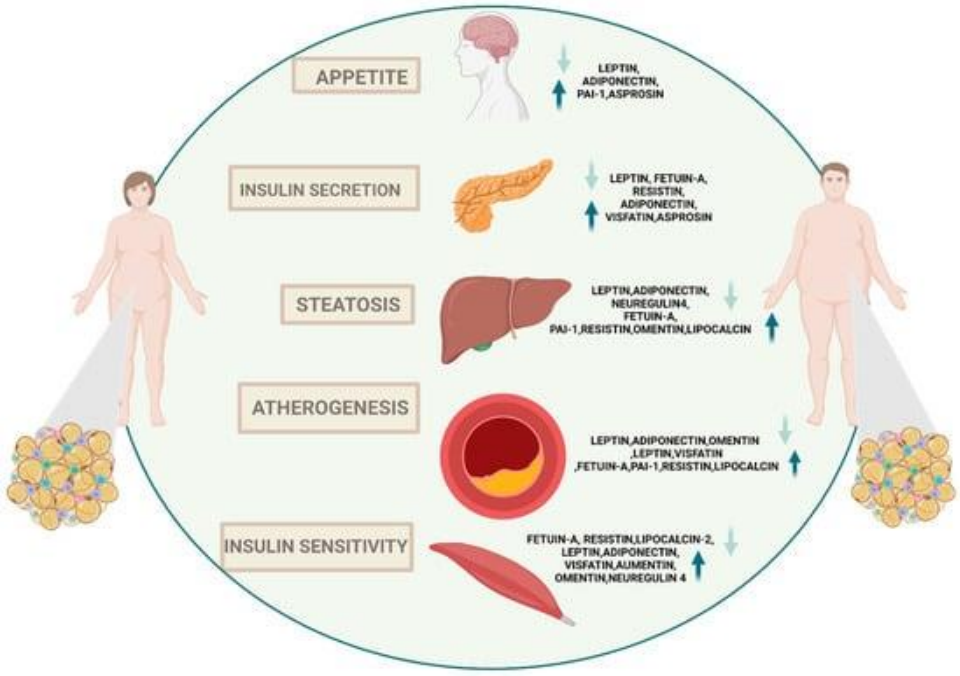

Figure 1: Metabolic disease is revealed by the altered behavior of adipokines (Clemente-Suárez et al., 2023)

2.2 Cytokines

Immune responses, inflammation, and other physiological processes are greatly influenced by cytokines, which are signalling proteins essential for cellular communication. Interleukins, tumour necrosis factors, interferons, and many more are members of this large and varied protein family. To control the maturation, specialisation, and activity of immune cells, cytokines serve as molecular messengers. For example, interleukins allow leukocytes to communicate with one another, which helps the immune system coordinate its response to infections or aberrant cells (Dinarello, 2007). The inflammatory response, the body's first line of defence against pathogens and damaged tissues, relies heavily on cytokines. The cytokine tumour necrosis factor-alpha (TNF-α) plays a significant role in inflammation and regulates how cells react to stress and infection. Multiple inflammatory illnesses, such as inflammatory bowel diseases and rheumatoid arthritis, are linked to TNF-α dysregulation (Tracey et al., 2008).

In addition to their impact on immune function, cytokines play a crucial part in hematopoiesis, the process of making new blood cells. Maintaining a healthy immune system is the job of hemotopoietic cytokines like erythropoietin and granulocyte colony-stimulating factor (G-CSF) (Lieschke et al., 1994). The intricate cascade of signals that facilitates tissue regeneration and repair

also includes cytokines. An example of a factor that is significantly important in tissue homeostasis and wound healing is transforming growth factor-beta (TGF-β).

According to Wynn (2008), fibrotic diseases and defective tissue repair are linked to dysregulation of TGF-β signalling. In the setting of cancer, cytokines play a role in the complex interaction between tumour cells and the immune system. The antiviral and anticancer actions of interferons are due to their ability to improve immune surveillance and suppress the growth of tumour cells (Zitvogel et al., 2015). Research into immunotherapies that aim to alter cytokine responses for enhanced anticancer effectiveness is an active field, with the goal of harnessing cytokines' therapeutic potential in cancer therapy.

2.2.1 Types of cytokines

The immune system relies on cytokines, a broad set of proteins, to regulate immune responses and keep the body healthy as a whole. These molecules act as signals, pointing immune cells in the right directions and giving them instructions on how to fight against infections.

1. Chemokines:

Chemokines play a critical role in guiding immune cells to the parts of the body that require them to fight off infections. Proteins like these serve as molecular cues that make sure the immune system responds effectively by coordinating the movement and recruitment of cells. The function of chemokines in immune response and surveillance is vital, since they allow immune cells to migrate to sites of infection or tissue injury (Dinarello, 2007).

2. Interferons: These messengers tell cells to start fighting viruses when they invade. A key function of interferons in preventing viral infections is to impede viral replication inside healthy cells. One of the first lines of defence against viral threats, the word "interferons" refers to their capacity to "interfere" with the reproduction process of viruses. The antiviral response, which includes these proteins, helps cells fight against viral infections (Ivashkiv and Donlin, 2014).

3. Interleukins: A collection of signalling molecules known as interleukins play an important role in the communication of leukocytes (white blood cells). At first, researchers thought that interleukins could only be produced by and communicated with other leukocytes. Nevertheless, recent discoveries have shown that interleukins are produced by a wide variety of cell types, not only white blood cells. According to Akdis et al. (2016), interleukins are very important because they help maintain a healthy immune system balance, regulate inflammation, and modulate immunological activities.

4. Tumor Necrosis Factor (TNF): TNF plays a crucial role in controlling inflammation throughout the body. Its critical function in tumour cell elimination by signalling immune cells emphasises its significance in immune system monitoring against malignant growths. Disruption of TNF's regulatory role in inflammatory processes is linked to a range of inflammatory diseases. According to Aggarwal (2003), this cytokine is an essential part of the immune system's capacity to detect and destroy aberrant cells.

5. Colony-Stimulating Factors (CSF): Colony-stimulating factors are very important for controlling hematopoiesis, or the process of making new blood cells. The creation of a well-regulated immune system is dependent on these cytokines, which instruct hematopoietic stem cells (HSCs) to specialise into certain cell types. Consider how granulocyte-colony stimulating factor (G-CSF) transforms hematopoietic stem cells (HSCs) into neutrophils. Neutrophils are vital to the immune system's ability to ward off illnesses.

6. Cell-Specific Cytokines:

Lymphokines are regulated Lymphocytes, a kind of white blood cell, produce lymphokines, which aid in the control and reaction of the immune system. Their functions in regulating immunological responses and keeping the immune system in check are crucial. Simple proteins: Monokines are involved in immune response and regulation; they are produced by monocytes, another kind of white blood cell. According to Lerner and Matthias (2015), monokines help control inflammation and how the immune system works.

2.2.2 Cytokines Roles in health and disease

Health and many diseases depend on multipurpose signalling molecules called cytokines. These complex proteins govern immunological responses, inflammation, and many physiological activities via intricate networks of communication within and outside the immune system. Cytokines regulate and monitor the immune system in medicine. Chemokines drive immune cells to specific bodily areas to fight infections. Assembly and guidance of immune cells are crucial for effective immune responses (Dinarello, 2007).

Cells deploy antiviral defences in response to viral invasions via interferons. Ivashkiv and Donlin (2014) say inhibiting viral reproduction strengthens the body's infection defences. The immune system uses interleukins to coordinate responses, regulate inflammation, and maintain equilibrium, according to Akdis et al. (2016). Adgarwal (2003) emphasises that TNF is a key inflammatory regulator that stimulates immune cells to attack cancer cells. TNF is crucial to immune system

surveillance against cancerous growths. Hematopoiesis control by Colony-Stimulating Factors (CSF) produces a healthy immune system (Lieschke et al., 1994).

Inversely, cytokine imbalance may cause several diseases. Chemokine imbalances may recruit immune cells incorrectly, causing autoimmune disorders and persistent inflammation, according to Dinarello (2007). Immune system hypersensitivity to interferons may induce autoimmune diseases (Ivashkiv & Donlin, 2014). Abnormal interleukin signalling may induce chronic inflammatory diseases such inflammatory bowel syndrome and rheumatoid arthritis, according to Akdis et al. (2016). TNF dysregulation is linked to inflammatory disorders such rheumatoid arthritis and inflammatory bowel diseases, highlighting the delicate balance needed for immune function (Aggarwal, 2003). Antitumor cytokines like interferons may produce persistent inflammation and tumour growth if dysregulated (Zitvogel et al., 2015). Understanding cytokine roles in sickness is essential to developing customised treatments.

Cytokines help repair and regenerate tissues. TGF-β is a crucial factor in tissue homeostasis and wound repair. According to Wynn (2008), TGF-β signalling dysregulation is connected to fibrotic disorders and poor tissue healing. Cytokines help tissue healing when correctly managed but worsen diseases when misregulated.

2.2.3 Cytokines Function

The varied family of signalling proteins known as cytokines is essential for the regulation of immunological responses and general well-being. Messengers like these multi-functional molecules help cells communicate with one another and control a wide range of physiological functions. For an effective immune response, chemokines play a key role in coordinating the movement of immune cells to potential infection or tissue damage sites (Dinarello, 2007). Conversely, interferons play an essential role in protecting cells from viral infections by preventing viral replication and signalling cells to activate antiviral defences (Ivashkiv & Donlin, 2014).

The communication between white blood cells, or leukocytes, is a key function of interleukins, which also help regulate inflammation, modulate immunological activities, and coordinate immune responses (Akdis et al., 2016). Inflammation is regulated by Tumour Necrosis Factor (TNF), which is essential for the immune system's monitoring of malignant growths and for signalling immune cells to destroy tumour cells (Aggarwal, 2003).

As a group, these cytokines play an important role in inflammation, immune system function, and other physiological activities. Cancer, autoimmune illnesses, chronic inflammatory disorders, and

dysregulation of cytokines may all contribute to disease pathogenesis (Dinarello, 2007; Ivashkiv & Donlin, 2014; Akdis et al., 2016; Aggarwal, 2003; Lieschke et al., 1994). In order to develop targeted treatment strategies, it is crucial to understand the complex roles played by cytokines in health and illness.

2.3 Thyroid carcinoma

Each thyroid neoplasm, or cancer, has its own symptoms, prognosis, and treatment choices. The butterfly-shaped thyroid gland in the neck regulates metabolism using hormones. Thyroid cancer, however rare, is growing steadily (Siegel et al., 2020). Most thyroid cancers are follicular thyroid carcinoma (FTC) and papillary thyroid carcinoma (PTC). PTC, the most prevalent thyroid cancer, has favourable outcomes and a high survival rate. PTC has distinctive papillary features (LiVolsi & Baloch, 2017). Unlike PTC, FTC has follicular cell differentiation and a lower survival rate, according to Xing (2013).

Thyroid cancer has a complicated genetic and environmental aetiology. Ionising radiation, especially in infancy, is a known thyroid cancer risk factor (Pacini et al., 2018). Thyroid cancer, especially PTC, is connected to BRAF gene alterations (Xing, 2013). Since thyroid nodules, which are generally painless, may indicate thyroid cancer, imaging scans and fine-needle aspiration biopsies are usually needed (Haugen et al., 2016). Tumour size, histology, and disease extent affect thyroid cancer therapy. Thyroid hormone replacement, radioactive iodine, and surgery are options (Haugen et al., 2016).

2.3.1 Causes of Thyroid cancer

The intricate interaction between genetics, environment, and lifestyle causes thyroid cancer. Toxic radiation increases thyroid cancer risk. Young individuals are more susceptible to thyroid cancer from radiation (Ron et al., 1995). Thyroid cancer is common among survivors of the Hiroshima and Nagasaki atomic explosions (Tronko et al., 2006). Hereditary factors affect thyroid cancer risk. Gene mutations may cause thyroid cancer. Mutations in the RET proto-oncogene enhances medullary thyroid cancer risk, according to Wells et al. (2013). DICER1 and BRAF mutations are associated to familial differentiated thyroid cancer (carcinoma Genome Atlas Research Network, 2014).

Environmental factors may cause thyroid cancer. Dietary factors including iodine deficiency increase risk (Kitahara et al., 2011). Low iodine levels, which are needed to make thyroid hormone,

may cause goitre and thyroid dysfunction, which can raise cancer risk (Ristic-Medic et al., 2019). PCBs and PBDEs may cause thyroid cancer (Boas et al., 2006; Cohn, 2012).

Diagnostic advances, notably imaging scans, have revealed tiny, benign thyroid nodules that would not have been clinically relevant (Davies & Welch, 2006). False positives and other factors have led to the worrisome rise in thyroid cancer occurrences. Women experience it more than males (Siegel et al., 2020). Oestrogen may create gender inequality (Dal Maso et al., 2009). Smoking may increase the incidence of differentiated thyroid cancer, especially papillary thyroid carcinoma, according to Mack et al. (2003).

2.3.2 Diagnosis of Thyroid cancer

Thyroid cancer diagnosis requires clinical, imaging, and pathological examinations. A thorough medical history and physical exam are required to diagnose thyroid nodules. Hoarseness, problems swallowing, and enlarged lymph nodes are examined by doctors along with radiation exposure and family history. Palpation and ultrasonography may detect thyroid nodules (Haugen et al., 2016).

Diagnostic ultrasonography is the principal thyroid cancer imaging modality. Diagnosis requires FNA biopsy. Bethesda System for Reporting Thyroid Cytopathology standardizes FNA data and informs malignancy-risk-based treatment (Cibas et al., 2017).

Histopathology helps detect benign and malignant thyroid nodules in FNA samples. Cytology can diagnose benign or cancerous nodules. Molecular analyses of FNA samples may enhance risk classification. BRAF, RAS, and RET/PTC gene mutation testing predict cancer and guide treatment (Nikiforov et al., 2014). CT and MRI are utilised to evaluate thyroid cancer extent, especially if metastases or invasion is suspected. The thyroid concentrates iodine, hence radioiodine scanning finds residual thyroid tissue or metastatic lesions (Haugen et al., 2016). Molecular imaging for thyroid cancer diagnosis is becoming common. Detecting abnormal glucose metabolism using fluorodeoxyglucose (FDG) PET helps localise aggressive thyroid tumours, particularly those that do not concentrate radioiodine (Rosenbaum-Krumme et al., 2011).

2.3.3 Classification of Thyroid cancer

Thyroid cancers are a heterogeneous collection of malignancies that start in the thyroid gland and have different histological, clinical, and molecular features. Thyroid cancer classification aids therapy, prognosis, and provider communication. Thyroid cancer may be papillary, follicular, medullary, or anaplastic.

1. Papillary thyroid carcinoma (PTC) accounts for over 80% of thyroid cancer cases. These tumours show unique papillary development patterns and are well-differentiated. PTC typically has a good prognosis since it grows slowly and responds well to treatment. PTC is often caused by BRAF, RAS, RET, and NTRK gene mutations (Haugen et al., 2016).

2. Follicle-forming thyroid carcinoma (FTC): 10-15% of thyroid cancers are FTC. It is more invasive than PTC and has follicular structures. FTC may cause vascular invasion and distant metastases, usually to the lungs and bones. Hagen et al. (2016) report that FTC molecular alterations commonly include RAS mutations and PAX8-PPARγ rearrangements.

3. Parafollicular C cells cause medullary thyroid carcinoma (MTC), which accounts for 1% to 2% of thyroid cancer cases. A neuroendocrine foundation separates MTC from PTC and FTC. It might be rare or part of genetic illnesses like MEN2. Calcitonin and carcinoembryonic antigen may help diagnose and monitor MTC. Most MTC cases include RET proto-oncogene activating mutations, according to Wells Jr et al. (2015).

4. Anaplastic Thyroid Carcinoma (ATC): The most severe kind of thyroid cancer, it accounts for 1-2% of cases. Undifferentiated cells and rapid proliferation characterise this syndrome. ATC has a poor prognosis because to its invasiveness and resistance to therapy. The complicated genetic landscape of ATC commonly involves TP53, BRAF, and TERT changes (Haugen et al., 2016).

5. Other subtypes and variants: In addition to the major kinds, thyroid cancer has many subtypes and variations with different histological and molecular features. Hobnail papillary thyroid carcinoma, poorly differentiated thyroid cancer, and tall cell PTC are examples. Since each variety may have various clinical behaviors and treatment problems, they must be thoroughly studied (Lloyd & Osamura, 2017).

6. Molecular Classification and Genomic Characterization: Molecular biology has shown which thyroid cancer subtypes are connected to which genetic mutations. Molecular classification improves tumour behaviour understanding and therapy options. Some molecular tests, such as BRAF, RAS, RET/PTC, and TERT, have helped classify thyroid cancer and predict treatment results (Xing, 2013).

7. Clinical and Pathological Criteria: Thyroid cancers are staged by clinical and pathological criteria in addition to histology and molecular classification to improve treatment planning and prognosis. The American Joint Committee on Cancer (AJCC) and Union for International Cancer

Control (UICC) stage cancers by tumour size, invasion, lymph node involvement, and distant metastases (AJCC, 2017).

2.3.4 Treatment of Thyroid cancer

Thyroid cancer therapy is complex and varies according on patient features, disease stage, and subtype.

1. The first is surgery

Surgery, which may entail removing some or all of the thyroid gland, is often the first line of defence against thyroid cancer. Tumour size, invasion, and lymph node metastases are some of the variables that determine the scope of surgery. When papillary or follicular thyroid cancer is detected, the treatment of choice is often a total thyroidectomy, which involves the removal of the whole thyroid gland. Lymph node dissection is another surgical option for treating metastases. For the best possible results and to lessen the likelihood of a recurrence, expert surgical intervention is required (Haugen et al., 2016).

2. Radioactive iodine treatment is a popular method for eradicating any leftover thyroid tissue and cancer cells after surgery. This method works well on thyroid tumours that have progressed to a stage where they can still concentrate iodine. When radioactive iodine is taken orally, it is absorbed by the thyroid cells, causing the specific death of malignant cells. It is common practise to combine this therapy with surgery to further decrease the likelihood of recurrence (Haugen et al., 2016).

3. When surgery and radioactive iodine treatment aren't enough, patients may undergo external beam radiation therapy, which uses high-energy rays to target cancer cells. Anaplastic thyroid carcinoma and other severe types of thyroid cancer often undergo this procedure. Postoperative radiation therapy or palliative care for advanced patients may include the use of external beam radiation (Haugen et al., 2016).

4. Thyroid Hormone Suppression: This treatment modality entails reducing the body's synthesis of thyroid-stimulating hormone (TSH) by means of the use of levothyroxine or another thyroid hormone replacement medicine. Suppressing thyroid hormone is a common practise in the treatment of thyroid cancer, but the exact amount of suppression that is best for each patient is determined by their unique circumstances (Haugen et al., 2016).

5. Personalised Treatments: Patients with thyroid cancer that has progressed or is resistant to other treatments may be given personalised treatments. Sorafenib and lenvatinib are two examples of tyrosine kinase inhibitors (TKIs) that have shown effectiveness in blocking pathways related to

angiogenesis and cancer cell proliferation. Targeted therapies provide an alternative to conventional thyroid cancer treatments for individuals with advanced, iodine-refractory, or metastatic disease (Sherman, 2017).

2.4 Clinic pathologic significance of adipokines and cytokines in thyroid carcinoma

The intricate relationship between adipokines, cytokines, and the development of thyroid cancer may be better understood by examining their clinicopathologic relevance in thyroid carcinoma. Several adipokines, including adiponectin and leptin, have been linked to different phases of thyroid cancer progression. The energy-regulating hormone leptin may have an effect on the development of thyroid cancer by stimulating cell migration and proliferation, two processes that contribute to tumour growth and aggressiveness (Liu et al., 2019).

The clinicopathologic features of thyroid cancer are greatly influenced by cytokines, such as interleukins and tumour necrosis factor-alpha (TNF-α). According to Zeng et al. (2018) and Zhang et al. (2018), interleukins such IL-6 and IL-8 have a role in the invasion and metastasis of tumour cells and are linked to the aggressiveness and advancement of thyroid cancer. According to Hassan et al. (2018), TNF-α—a key inflammatory regulator—plays a role in thyroid cancer by impacting inflammatory processes and interactions within the tumour microenvironment. As a result, it influences the course of the malignancy.

Intricate feedback loops involving adipokines, cytokines, and thyroid cancer modulate the tumour microenvironment in addition to their direct impacts on tumour cells. According to De Pergola et al. (2020), adipokines such as resistin, which are linked to inflammation and insulin resistance, could affect the microenvironment around thyroid cancer. Moreover, cytokines play a role in the intricate web of signals present in tumour microenvironment, impacting key components of thyroid cancer biology as tumour development, angiogenesis, and immune responses (Yasinska et al., 2018).

There may be diagnostic and therapeutic implications to elucidating the clinicopathologic relevance of these signalling molecules in thyroid cancer. Biomarkers for thyroid cancer prognosis, such as adipokines and cytokines, might help identify people who are more likely to have aggressive illness.

3. Conclusion

The clinicopathologic significance of adipokines and cytokines in thyroid carcinoma represents a dynamic and intricate interplay between the tumor microenvironment and the host's immune and metabolic responses. Extensive research has illuminated the pivotal roles played by adipokines, such as leptin and adiponectin, alongside pro-inflammatory cytokines, including interleukins and tumor necrosis factor, in shaping the progression, aggressiveness, and therapeutic responses of thyroid carcinomas. The intricate crosstalk between adipose tissue, inflammatory mediators, and thyroid cancer cells underscores the complexity of this relationship. Understanding the intricate signaling pathways and molecular mechanisms involved provides valuable insights for developing targeted therapeutic interventions. Moreover, the identification of specific adipokines and cytokines as potential diagnostic and prognostic markers holds promise for refining clinical management strategies. As the field continues to evolve, the incorporation of these molecular insights into personalized treatment approaches may pave the way for improved outcomes in patients with thyroid carcinoma.

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