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Research Article

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The Role of Fibroblast Growth Factor-2 and Caspase-3 in Nontoxic Multinodular Goiter versus Normal Thyroid Tissue Cases from Baghdad, Iraq

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Abstract

Background: Nontoxic multinodular (MNG) disease is one of the most prevalent thyroid pathologies, especially in endemic areas like Baghdad, Iraq. ***Objective***: To determine the prognostic values of FGF-2 and active CASP-3 expression in cases of MNG to predict the possibility of cancer development. ***Methods***: Fifty patients were included in the study in a retrospective design and were obtained from Al-Yarmouk Teaching Hospital in Baghdad, Iraq. Paraffin blocks were obtained, and histological procedures for slide preparation for light microscopy were employed. Immunohistochemical procedures to detect the expression of FGF2 and active CASP-3 markers were applied. Statistical analysis to predict the extent, intensity, total score, and H-score of the immunohistochemical results was done. ***Results***: Analysis of cases showed an overexpression of the FGF2 marker in cases of MNG, and that was statistically significant. On the other hand, CASP-3 was downregulated in MNG cases, with an intensity of 0 in most instances, while a few cases showed intensities of 1+ and 2+, which were statistically significant. The H-score, on the other hand, was highly raised in MNG expressing FGF2; in contrast to CASP-3, which appeared very low in MNG tissues, and both results were of statistical significance. ***Conclusions***: Overexpression of FGF2 and low expression of active CASP-3 in cases of MNG confirm the benign behavior of the disease, but it does not exclude the possibility of cancer development. This expression can be regarded as prognostic for early detection of tumor transition in benign tissue.

Keywords: Active caspase-3; Fibroblast Growth Factor-2; Immunohistochemistry; Nontoxic multinodular goiter; Thyroid gland.

دور عامل نمو الأرومات الليفية-2 والكاسبيز-3 في حالات الغدة الدرقية متعددة العقد غير السامة مقابل حالات انسجة الغدة الطبيعية من بغداد، العراق

الخلاصة

الخلفية: مرض الغدة الدرقية غير السام (MNG) هو أحد أكثر أمراض الغدة الدرقية انتشارا، خاصة في المناطق المتوطنة مثل بغداد، العراق. **الهدف**: تحديد القيم التنبؤية لـ FGF-2 والتعبير النشط لـ CASP-3 في حالات MNG للتنبؤ بإمكانية تطور السرطان. **الطرائق**: تم تضمين خمسين مريضا في الدراسة بتصميم استعادي وتم الحصول عليهم من مستشفى اليرموك التعليمي في بغداد، العراق. تم الحصول على كتل بارافين واستخدام إجراءات نسيجية لتحضير الشرائح للمجهر الضوئي. تم تطبيق إجراءات مناعية كيميائية للكشف عن تعبير FGF2 وعلامات CASP-3 النشطة. تم إجراء تحليل إحصائي للتنبؤ بمدى وشدة ودرجة المجموع ودرجة H لنتائج الكيمياء المناعية النسيجية. **النتائج**: أظهر تحليل الحالات تعبيرا زائدا عن مؤشر FGF2 في حالات MNG، وكان ذلك ذا دلالة إحصائية. تم انخفاض التعبير عن CASP-3 في حالات MNG، مع شدة 0 في معظم الحالات، بينما أظهرت بعض الحالات شدات 1+ و2+، والتي كانت ذات دلالة إحصائية. أما درجة H، فقد ارتفعت بشكل كبير في MNG التي تعبر عن FGF2؛ على عكس CASP-3، الذي بدا منخفضا جدا في أنسجة MNG، وكانت كلتا النتيجتين ذات دلالة إحصائية. **الاستنتاجات**: يؤكد الإفراط في التعبير عن FGF2 وانخفاض التعبير عن CASP-3 النشط في حالات MNG السلوك الحميد للمرض، لكنه لا يستبعد احتمال تطور السرطان. وهذا التعبير عن العلامات يمكن اعتباره تنبؤيا للكشف المبكر عن انتقال الورم في الأنسجة الحميدة.

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INTRODUCTION

The most prevalent thyroid gland condition, multinodular goiter, affects about 7% of people worldwide [1]. It is defined by euthyroidism and unilateral or bilateral thyroid enlargement with morphologically and functionally altered follicles [2]. Nodular thyroid enlargement is primarily affecting females and results from several genetic factors, including circulating thyroid growth factors and mutagenesis, while environmental factors, such as iodine nutritional deficiency, dyshormonogenesis, stress, goitrogens, and infection, are secondary causes [3]. Particularly in endemic locations, nodular goiter presents a unique health problem [4]. When the prevalence of goitrous thyroid in children aged 6 to 12 is greater than 10%, it is classified as endemic; when it is 10% or lower, it is termed sporadic [5]. Studies show that thyroid dysfunction, both overt and subclinical, is prevalent in Iraq, where goiter is acknowledged as an endemic issue. According to a survey conducted in Iraq, goiter was more common in Baghdad City and less common in Basrah City [6]. According to research, up to 75–86% of cases of thyroid abnormalities, including goiter, are found in women, and they usually peak between the ages of 30 and

50 [7]. A thyroid nodule, which manifests as distinct swelling in an otherwise impalpable gland and is either seen as a single thyroid nodule or as a dominating nodule in a clinically multinodular gland of a multinodular goiter, poses a considerable diagnostic challenge for the treating surgeon [8]. 5% of thyroid nodules are malignant [9], with a higher prevalence in children, patients under 30 and over 60, and those with a history of radiation exposure [10]. Despite being regarded as a benign disease, numerous studies have evaluated the possibility that goiter could develop into thyroid cancer [11]. Thyroid cancer was discovered in 4-17% of surgical specimens with nodular goiters [12]. Even though fine needle aspirations (FNA) were used to assess these goiters, the results did not clearly identify the danger; additionally, it was not appropriate to take biopsies from every lesion. Patients with benign FNA and multinodular goiter have been found to have a considerable prevalence of thyroid cancer (46.3%), frequently papillary carcinoma [13]. Additionally, compared to single nodule illness, multinodular goiter has a significantly higher risk of papillary thyroid cancer, according to another research [14]. Evaluation of apoptosis in tissues depends on multiple markers; one of these biomarkers is active caspase-3, sometimes referred to as cleaved caspase-3, which is the gold standard biomarker for identifying apoptosis (programmed cell death) in biological research and pathology. Although a number of indicators may indicate that a cell is "stressed," the presence of active CASP 3 usually indicates that the cell has reached the "point of no return" and is actively destroying itself [15]. On the other hand, basic Fibroblast Growth Factor (bFGF), another name for Fibroblast Growth Factor 2 (FGF2), is a powerful signaling protein that functions as a multifunctional biological marker. It is mostly employed as a biomarker for angiogenesis, cancer progression, and stem cell pluripotency in clinical and research settings [16]. These markers have "prognostic" value in terms of anticipating the nodules' proliferative tendency or detecting early indicators of malignant change, even though MNG is a benign disorder. The expression of FGF2 and active CASP3 immunohistochemical markers on the thyroid tissues of multinodular goiter for estimation of disease process and detection of cancer possibility was the focus of our investigation.

METHODS

Study design and setting

This retrospective analysis was carried out on paraffin blocks of tissue specimens from nontoxic multinodular thyroid goiter (MNG) patients who underwent total/subtotal over the course of six months, from July 2025 to December 2025. Patients have been admitted to the general surgery department of the Al-Yarmouk teaching hospital in Baghdad, Iraq.

Patients' selection

Fifty patients (40 females and 10 males) were chosen according to the clinical picture and biochemical evaluation (serum TSH and T4). Patients' clinicopathological information, such as age and gender, has been collected.

Inclusion criteria

Every patient was euthyroid, and none of them had undergone thyroid-related therapy.

Exclusion criteria

Individuals who have previously received chemotherapy or radioactive iodine therapy were not included.

Procedures and outcome measurements

Three serial slices, each measuring four micrometers in thickness, were cut for each case. To assess the histological alterations, the first slice was placed on a regular slide and stained with hematoxylin and eosin (H & E). Normal-looking thyroid tissue adjacent to goitrous tissue served as control tissue for comparison in this study. The second and third slides were placed on positively charged slides. For the immunohistochemical staining study using anti-active CASP3 antibody (primary antibody from Elabscience, Cat. No. E-AB-22115) and anti-FGF2 antibody (primary antibody from ABNOVA, Cat. No. MAB16168). A secondary antibody detection kit (Elabscience, Cat. No. E-IR-R213, rabbit/mouse specific HRP/DAB) was employed. The slides were dewaxed by hydrating them gradually with xylene. The antigen was completely recovered after 20 minutes of pressure cooking with citrate buffer. The primary anti-active CASP3 and FGF2 antibodies were allowed to warm up at room temperature for 30 minutes after being diluted to a 1:200 ratio using background-lowering dilution buffer (Abcam, code ab64211). Chromogen staining and DAB were utilized after detection using labeled streptavidin-biotin from an Elabscience secondary detection kit. Hematoxylin was used as a counterstain after the slides were quickly hydrated and mounted with DPX [17]. Every thyroid tissue slide was evaluated without any prior knowledge. The following estimates were made for the staining intensity and % of FGF2 and Active CASP3: Four staining intensity levels were available: 0 for no staining, 1+ for weak staining, 2+ for moderate staining, and 3+ for strong significant staining. The following percentage indicated the degree of staining: Less than 10% of the cells stained favorably is represented as negative, 10–50% as weak positive, 51–80% as moderate positive, and more than 80% as strong positive [18]. The McCarty H-Score is calculated for the brown color observed in the immunohistochemical slides according to the following equation in order to assess the status of the disease condition [19, 20]:

H-Score = [1 *(% weak] + [2* (% moderate] + [3 * (% strong]

The intensity and percentage of marker expressions were compared with the normal-looking thyroid tissue adjacent to multinodular goitrous tissue in cases included in this study [20].

Ethical considerations

The study design/purpose was approved by the MMC Institutional Review Board and Human Anatomy Department (No. 653 on 11/6/2025), and written informed consent was obtained from all participants.

Statistical analysis

Data analysis was achieved using IBM® SPSS Statistics software for Windows, version 26 (2019), and described using Microsoft Excel® (2019) MSO. Continuous variables were presented as mean ±standard deviation (SD) or median (interquartile range, 25-75% IQR) when applicable. Numerical data were first assessed using box plots to verify normality and detect extreme outliers, which could then be excluded from calculations. Comparisons were performed using two-way analysis of variance (ANOVA). Categorical variables were expressed as frequency percentage. The chi-square test was used to compare categorical variables. Categorical versus numerical data were confirmed using t-test examination. Statistical significance was set at *a p-value* < 0.05 with a 95% confidence interval (CI).

RESULTS

Out of the 50 cases enrolled in the study, 40 were females (80%) with an average age of 35±5.4 SD years, and 10 were males (20%) with an average age of 40.8±4.8 years, which showed a statistically significant higher frequency of MNG in females but an older male patient age range (*p*=0.003), as shown in Figure 1.

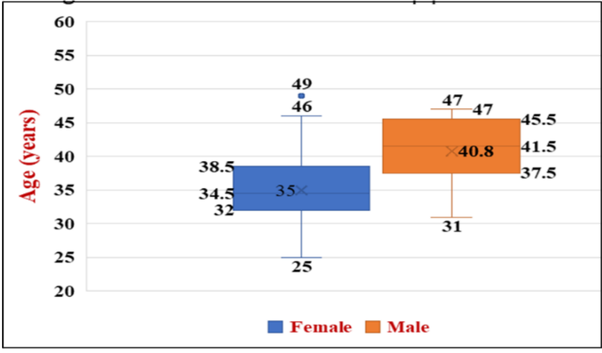

Figure 1: The age distribution among Iraqi patients with multinodular goiter (MNG).

Sections from nontoxic MNG histologically appeared in routine H&E staining as heterogeneous follicles with variable size; the epithelium also has a variable cell type, from squamous to cuboidal, according to the status of the follicle. Colloid is cracked inside the follicles. There are clusters of red blood cells or hemosiderin where small blood vessels have ruptured inside a nodule. Some follicles get so large they burst, forming fluid-filled sacs or cysts as shown in Figure 2.

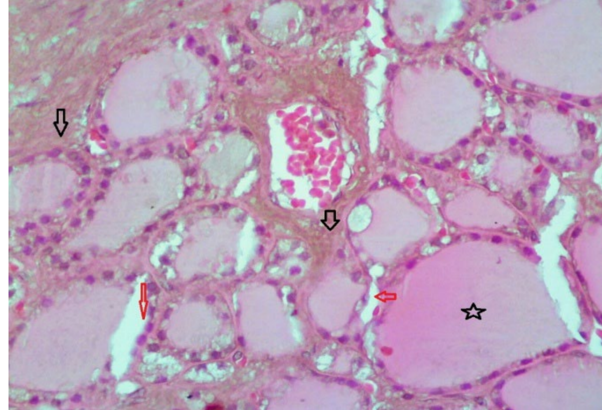

Figure 2: Photomicrograph of nontoxic MNG showing variable follicle size (star), cystic degeneration (red arrow), hemorrhage (black arrow) H & E 400X.

Immunohistochemical evaluation of FGF2-stained MNG thyroid tissues showed a varying stain intensity from 0 to grade 3+, where a cytoplasmic expression of the marker appeared in grade 1+ and 2+ and extended to nuclear staining in grade 3+ sections (brown color), as shown in Figure 3.

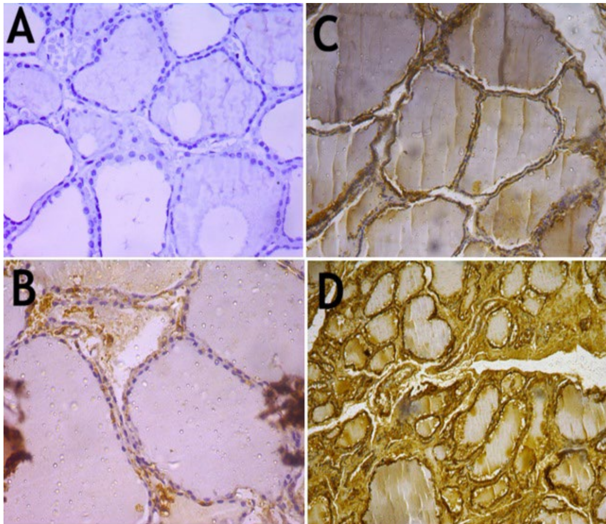

Figure 3: Photomicrograph of nontoxic MNG showing variable staining intensity of FGF2 immunohistochemical marker, A= o (no stain) as blue discoloration, B= 1+ (weak stain) as cytoplasmic expression of marker in follicular cells (brown discoloration), C= 2+ (moderate stain) as cytoplasmic expression of FGF2 marker in follicular cells (brown discoloration), D= 3+ (strong stain) include cytoplasmic and nuclear expression of FGF2 marker (brown discoloration). FGF2 immunohistochemistry 400X.

Expression of active CASP 3 appeared in MNG thyroid tissues, and intensity ranged from 0 grade to 2+ grade, where a cytoplasmic brown enhancement appears in the follicular cells of thyroid sections, as shown in Figure 4. By immunohistochemical examination of the thyroid nodular and normal surrounding tissue with the assigned

markers, the extent of staining was not that different in terms of statistical significance between the two areas for Active CASP 3 but was so for FGF2.

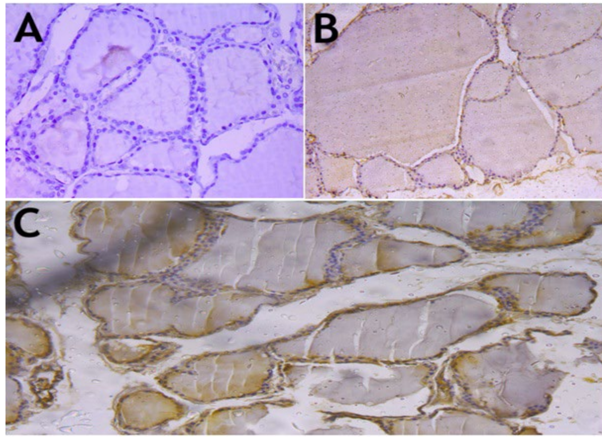

Figure 4: Photomicrograph of nontoxic MNG showing variable staining intensity of active CASP 3 immunohistochemical marker, A= o (no stain) as blue discoloration, B= 1+ (weak stain) as cytoplasmic expression of marker in follicular cells (brown discoloration), C= 2+ (moderate stain) as cytoplasmic expression of active CASP 3 marker in follicular cells (brown discoloration), Active CASP 3 immunohistochemistry 400X.

The intensity of staining was significantly different, on the other hand, for both markers. Null expression (0) was reversely presented for an active CASP 3 (higher in nodular tissue) and FGF2 (higher in normal surrounding tissue). Weak intensity (1+) showed the same affinity for both markers, being higher in normal surrounding tissue than in nodular tissue. Moderate intensities were significantly higher in normal surrounding tissue for active CASP 3 but in nodular tissue for FGF2. Strong marker intensities were noticed only for FGF2 in nodular tissue; none of the samples showed strong expression for Active CASP 3 in either tissue. This led to the result that the total marker staining score was also of significant statistical difference for both markers. These results are summarized in Table 1 and Figure 5.

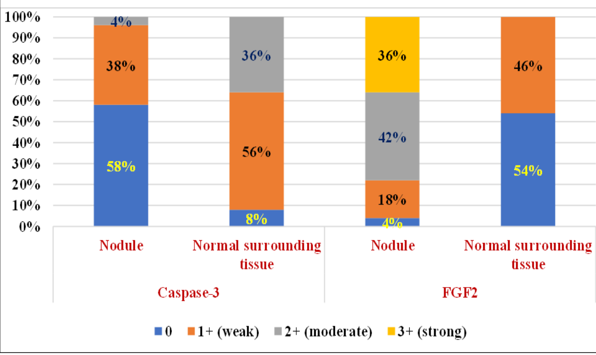

Figure 5: Intensity stating for Active CASP 3 & FGF2 in thyroid nodules and normal surrounding tissue of Iraqi patients with multinodular goiter (MNG).

These values brought the total immunohistochemical score (H-score) to a statistically significant difference between the nodular and surrounding normal tissues for both markers. Active CASP3 had more expressions surrounding normal tissue, while FGF2 had almost triple the expression in nodular tissue (Table 2).

Table 1: Extent, intensity and total score of immunohistochemical staining with Active CASP 3 & FGF2 in thyroid nodules and normal surrounding tissue of Iraqi patients with multinodular goiter (MNG)

Tissue Type		Marker					
		Active CASP 3		*p*-value	FGF2		*p*-value
		Nodule	Normal surrounding tissue		Nodule	Normal surrounding tissue	
Extent (%)		77.8±10.2	76.2±10.3	0.031	82±8.8	78.2±10.7	<0.0001
Intensity (%)	0	58	8	<0.0001	4	54	<0.0001
	1+ (weak)	38	56		18	46	
	2+ (moderate)	4	36		42	0	
	3+ (strong)	0	0		36	0	
Total score		0.36±0.5	0.96±0.5	<0.0001	1.73±0.7	0.37±0.4	<0.0001

Values are presented as mean±SD and percentage.

Table 2: H-score for Active CASP 3 & FGF2 immunohistochemical markers in thyroid nodules and normal surrounding tissue of Iraqi patients with multinodular goiter (MNG)

Marker	Site	H-score (%)	Interpretation	*p*-value
Active CASP 3	Nodule	46	Low/Normal	<0.0001
	Normal surrounding tissue	128	Moderate	
FGF2	Nodule	210	High	<0.0001
	Normal surrounding tissue	46	Low/Normal	

DISCUSSION

The study highlights classic epidemiological data often seen in thyroid pathology, specifically Multinodular Goiter (MNG). The results suggest a clear divergence between the genders in terms of both prevalence and timing of onset. Gender predominance (the 4:1 ratio): the fact that 80% of our cases were female aligns perfectly with global endocrine data [21]. Thyroid disorders, including MNG, are significantly more common in women. This disparity is often attributed to the role of estrogen and progesterone. Estrogen has been shown to have a proliferative effect on thyroid cells. Another suggestion is women often face higher iodine demands during pregnancy and menstruation, which can trigger the compensatory thyroid growth that leads to nodule formation [22]. The statistically significant (p= 0.003) age difference between the two groups is the most

intriguing aspect of our findings. Women in our study are experiencing symptoms of MNG during their prime reproductive and career years, with an average age of 35 years. This implies that women may benefit from starting thyroid nodule screening earlier [23]. The average age of males in our sample was 40.8 years, which was substantially older. When MNG or thyroid nodules develop in men, they frequently show up later or with larger nodules in various clinical settings. A thyroid nodule in a male patient may have a marginally higher statistical risk of cancer than in a female patient, even though MNG is less common in men. Because of this, the "older male" population is crucial for meticulous diagnostic follow-up (such as FNA biopsy) [24]. The following are some assessments of the histology results from our investigation: Inactive, "resting" follicles under colloid pressure are indicated by squamous epithelium. Active, hyperplastic follicles are indicated by cuboidal epithelium. Dense, concentrated protein is the cause of cracked colloid, which is usually a harmless artifact. Hemosiderin is a benign biomarker of previous internal bleeding [25]. One sign of the end-stage degeneration of big, overextended follicles is the creation of cysts. These results are all related to nontoxic multinodular goiter (MNG) [26]. The molecular balance between cell survival (FGF2) and programmed cell death (Caspase-3) in Multinodular Goiter (MNG) is fascinatingly shown by the immunohistochemistry (IHC) profile. Our findings imply that the environment in the "nodular" area both stimulates growth and inhibits death, which accounts for the formation and persistence of these nodules. One important discovery is that nodular tissue has a much greater intensity and total score of FGF2 than normal tissue. Follicular cell proliferation and angiogenesis are both strongly stimulated by FGF2. Only nodular tissue exhibits "strong (3+)" intensity, indicating that FGF2 is the "engine" propelling the nodules' growth. FGF2 is especially elevated in the diseased areas, most likely as a reaction to local stresses or genetic changes in those follicles, as evidenced by the fact that null expression was higher in normal tissue [27]. The "executioner" protein of apoptosis is called caspase-3. Our findings indicate that in nodular tissue, "Null" expression is stronger, and its intensity has significantly decreased. A nodule must cease dying in addition to dividing more quickly (FGF2) in order to expand. Normal thyroid cells appear to maintain a healthy "turnover" rate, as seen by the higher moderate intensity in normal tissue. The weak expression of active CASP 3 in the nodules, rather than its robust expression in either tissue, suggests that the nodules are "apoptosis resistant." The "heterogeneous follicles" we saw earlier can amass over decades due to this resistance [28]. The statistical significance of the combined score for both markers demonstrates that MNG represents a metabolic shift rather than only a morphological alteration. High FGF2 combined with low active CASP 3 causes net tissue gains in nodular tissue. In healthy tissue, homeostasis (stability) will be confirmed by low FGF2 and a steady level of active CASP 3 [29]. The molecular "push and pull" that characterizes multinodular goiter is quantitatively confirmed by the change in the H-score (McCarty H-Score). An important sign of autonomous growth is the discovery that FGF2 expression is almost three times higher in the nodular tissue than in the surrounding normal tissue. FGF2 functions as a strong mitogen, which explains the mechanism of this triple expression. Localized FGF2 overexpression in MNG sets off a series of follicular cell division events. The fact that it is three times the quantity of normal tissue indicates that the nodules are hyper-proliferating rather than merely increasing [30]. Moreover, FGF2 has a strong angiogenic effect. This relates to our histology results of "ruptured small blood vessels"; the nodule's neovascularization—the development of brittle, leaky new capillaries that are prone to bleeding—is probably caused by the elevated FGF2 levels [31]. The normal tissue is preserving its integrity through active apoptosis (programmed cell death), but the nodules have "turned off" this safety mechanism, as evidenced by the substantially higher H-score for Active CASP 3 in the surrounding normal tissue compared to the nodules. Active CASP 3 removes damaged or unnecessary cells from a healthy thyroid. These "heterogeneous follicles" we saw appear to be almost immortalized, as seen by the decreased expression in the nodules; they keep growing because they refuse to die [32]. Our result indicates that not only are fewer cells undergoing apoptosis in the nodules, but the mechanism of death itself is weaker (lower intensity) in the remaining cells because the H-score takes intensity into account [33]. In the context of our investigation, the low H-score for Active CASP 3 and the high H-score for FGF2 explain why the benign nodules are expanding and do not go away rather than indicating cancer. But when considering thyroid illness, this particular biochemical imbalance offers a "fertile ground" where cancer may eventually arise. This is the breakdown. The molecular environment that our H-scores produce is important in cancer research, even though they reflect a benign activity. The gland's "quality control" is diminished when active CASP 3 is poor, as in our nodular tissue. A low-apoptosis environment may enable a cell with genetic mutation to live rather than die. Cells are forced to divide quickly by high FGF2 levels. There is a tiny chance of a DNA copying error occurring each time a cell divides. These mistakes might build up over many years [34]. However, Thompson et al. demonstrated that increased FGF-2 expression was not only linked to the neoplastic state but also accompanied thyroid hyperplasia [19]. Increased FGF2 expression is frequently linked to more aggressive goiter formation and an increased risk of recurrence following partial thyroidectomy. FGF2 expression is higher in thyroid carcinomas (such as papillary thyroid carcinoma) than it is in MNG. Consequently, a nodule's exceptionally high FGF2 levels may indicate a higher likelihood of malignant transformation [35]. On the other hand, low

levels of CASP 3 indicate that thyroid cells are living longer than they need to, which is causing the gland to grow. CASP 3 is utilized in clinical pathology to evaluate the "apoptotic index." High proliferative markers (such as Ki-67 or FGF2) in conjunction with noticeably low Casp-3 expression may suggest a higher likelihood of the goiter becoming "toxic" or turning into a tumor [36]. The current study's overall findings can be summed up as follows: a hyperplastic state is confirmed when a high FGF2/low Active CASP 3 profile is combined. FGF2 is frequently expressed significantly more highly in papillary thyroid carcinoma (PTC) than in benign MNG, but it is also examined in the context of thyroid cancer. Additionally, very low levels of active CASP 3 are linked to more aggressive tumor activity and treatment resistance in certain thyroid malignancies, which is why active CASP 3 and FGF2 are occasionally utilized as prognostic markers.

Study limitations

This study uses their control group from tissue adjacent to multinodular goiter tissue of the thyroid due to limitations in obtaining normal thyroid tissue from individuals or autopsies.

Conclusion

This study, which was conducted on a benign nontoxic multinodular goiter, explains the alteration in the immunostaining expression of FGF2 and active CASP3, which confirms the benign behavior of the disease. Despite this conclusion, the possibility of cancer development in these benign processes is not unexpected since there is a molecular drive for those cancerous changes based on overexpression of FGF2 and low expression of active CASP3, which underline the possibility of cancer appearance even after years of benign status of the thyroid gland.

Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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