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Original Article

Effects of fibroblast growth factor 21 serum level on clinicopathological findings in papillary thyroid carcinoma

Seyedarad Mosalamiaghili (MD) [1]
Hamideh Akbari (MD) [2]
Narges Lashkarbolouk (MD) [3, 4]
Ali Ariannia (MD) [5]
Mahshid Mehrjerdian (MD) [4]
Fatemeh Salamat [5]
Mahdi Mazandarani (MD) [3, 4*]

1. Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran
2. Clinical Research Development Unit (CRDU), Sayyad Shirazi Hospital, Golestan University of Medical Sciences, Gorgan, Iran
3. Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran.
4. Golestan university of medical Sciences, Gorgan, Iran
5. Cancer Research Center, Golestan University of Medical Sciences, Gorgan, Iran

*** Correspondence:**
Mahdi Mazandarani
Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

E-mail:
mahdi_mazandarani@yahoo.com
Tel: +98 1732202154

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Abstract

Background: This research examined the connection between circulating FGF21 and clinicopathological findings in papillary thyroid carcinoma.

Methods: This analytical cross-sectional research was conducted on patients with papillary thyroid cancer at the Seyyed Shirazi Endocrinology Clinic in Gorgan, Iran. Laboratory data, including demographics, ultrasonography and pathology reports, and FGF21 levels, were collected. The data was analyzed with SPSS 25. Normal distribution was evaluated by using Kolmogorov-Smirnov and Shapiro-Wilk tests. Group differences were evaluated with Chi-square, independent sample t-test and Mann-Whitney U tests. A p-value less than 0.05 was considered significant.

Results: In this research, 83% of patients were female, and the mean±SD age was 42.51±13.28 years old. The mean±SD and FGF21 concentrations in 49 patients were 716.41±458.7, the median was 489 pg/ml, and 24 (49%) patients were in the high FGF21 group. There was no statistically significant relation between FGF21 level and age (P=0.95), sex (P=>0.99), tumor size (P=0.68), tumor stage (P=>0.99), lymphadenopathy (P=>0.99), lymph node metastasis (P=0.24), triglycerides (P=0.93), total cholesterol (P=0.47), LDL (P=0.08), and HDL (P=0.08). However, FGF21 levels were significantly associated with fasting blood glucose (P=0.03), body mass index (BMI) (P=<0.0001), capsular invasion (P=0.001), lymphovascular involvement (P=0.0001) and Thyroid Imaging Reporting and Data System (TIRADS) score (P=0.02). In addition, high levels of FGF21 were found to be 78.95% sensitive and 70% specific for capsular invasion.

Conclusion: Our study demonstrated that FGF21 is associated with more severe papillary thyroid cancer clinicopathological features such as capsular invasion, lymphovascular involvement, TIRADS score, and BMI.

Keywords: Fibroblast growth factor, Thyroid neoplasm, Cell proliferation, Metastases, Papillary thyroid cancer.

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Fibroblast growth factors (FGF) and their receptors (FGFR) are identified in critical physiological activities of the human body, such as tissue regeneration, angiogenesis, regulation of lipids and glucose, and energy metabolism (1-4). The family of FGF ligands includes 18–22 components divided into paracrine and endocrine FGFs (FGF19, FGF21, and FGF23) (5, 6). Research has shown that abnormalities in FGF signalling pathways contribute to the development of certain cancers, such as papillary thyroid carcinoma (PTC), leading to the emergence of treatment options focused on these pathways. (6-9). FGF21 is produced in several organs and plays different roles in maintaining energy balance and regulating carbohydrate and lipid metabolism, and it has a bidirectional relation with thyroid hormones, including Triiodothyronine (T_3), which affects PTC pathogenesis; this factor reportedly induces tumorigenesis through activating mitogen-activated protein kinase (MAPK) signalling pathways (10, 11).

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Few studies discuss FGF21 serum levels in PTC. However, in a latter study, Kang Y et al. in 2019 conducted the relation between circulating FGF21 and thyroid cancer invasion, finding higher FGF21 serum levels in thyroid cancer patients than healthy controls. In addition, they showed that recombinant FGF21 led to thyroid tumor invasion (6).

Establishing an association between FGF21 and PTC is essential since PTC is the most prevalent form of thyroid cancer; monitoring disease course and finding possible treatment approaches benefit the patients. However, establishing this association is yet to be achieved. In this study, we aimed to consider whether serum FGF21 level is related to clinicopathological findings in PTC patients. This study is the first one with a Middle Eastern population that has conducted such a study.

Methods

Study design and participant's selection: This cross-sectional research was conducted from March 2020 to March 2021. The study included PTC patients referred to the Gorgan Endocrine Outpatient Clinics at Seyyed Shirazi Hospital in Gorgan, Iran, who were over 18 years old and had a confirmed PTC diagnosis through preoperative fine needle aspiration (FNA). Excluded criteria were participants with a history of thyroid surgery, concurrent malignancy, dyslipidemia, and diabetes.

Data collection: Demographic data and clinicopathological findings of patients such as Thyroid Imaging Reporting and Data System (TIRADS) score, tumor size, tumor stage (12), lymphovascular invasion, lymphadenopathy (LAP), extrathyroidal involvement, and lymph node metastasis, were collected. Two expert pathologists and radiologists, blinded to patients' information, were assigned to extract these clinicopathological data from patients' records. During the COVID-19 pandemic lockdown, patient follow-up was conducted through telemedicine methods. The interdisciplinary collaboration between surgery, and endocrinology was facilitated by telemedicine, emphasizing its importance in our research.

Diagnosis of thyroid malignancy is made by ultrasound and FNA. Ultrasound findings in these patients were based on the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS), divided by nature, echogenicity, shape, margins, and calcifications. FNA should be investigated when the TIRADS score is four or higher. Patient staging is classified according to the PTC TMN system, in which patients under 55 only have stages 1 and 2, and patients over 55 have four stages. Stage 1 in patients younger than 55 is equivalent to stages 1 and 2 in patients over 55. Stage 2 in patients younger than 55 equals stages 3 (without metastases) and 4 (with metastases) in patients over 55 (12).

All patients underwent physical examinations; height, weight, and body mass index (BMI) (as weight (kg)/ [height (m)] ^{2}) were recorded for them. After 8 hours of overnight fasting, venous blood samples of patients were taken in the morning. We measured the total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), fast blood sugar (FBS) levels by using standard biochemical kits (Pars Azmun® Co., Tehran, Iran). Serum fasting FGF21 levels were measured before the surgery using an ELISA kit (Hangzhou Eastbiopharm® Co., China).

Statistical analysis: By using Statistical Package for Social Sciences Version 25.0 (SPSS Inc, Chicago, IL.), date were analyzed. For the assessment of normal distribution, Kolmogorov-Smirnov and Shapiro-Wilk tests were applied. The mean±standard deviation or median with interquartile range (IQR) were used for continuous variables. We divided patients into low and high FGF21 serum levels. The cut-off level for this classification was considered the median FGF21 level according to a previous study (6). A Mann-Whitney U, independent sample t-test, and chi-square tests were used for evaluating differences between groups. In case of a significant relationship between high FGF21 and capsular invasion, we will assess the diagnostic performance of high FGF21 for capsular invasion. A significant p-value was considered less 0.05.

Ethics approval: We acquired informed consent from all patients in the study, and a copy of the consent is available for review by the journal's editor. The aim of this study was thoroughly elucidated to the participants, and they were guaranteed that their information would remain confidential. This study adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Golestan University of Medical Sciences under the ethical code IR.GOUMS.REC.1399.294.

Results

Forty-nine patients with PTC cancer participated in the study, and 83% were females. In the high FGF21 group, 40% were females, while in the low FGF21 group, the percentage of females was 43%. The average age of individuals in the high FGF21 group was 38.5 ±16, whereas in the low FGF21 group, it was 39±12.5. The total mean ± SD and median age were 42.51±13.28 and 39 years, respectively, and the age range of patients was 28-72 years.

Table 1. Demographic characteristics and clinicopathological findings

Variables		FGF21 level		Total	P value*	OR(95% CI)
		High	Low			
Age (years)		38.5±16	39±12.5	39±13.5	0.952	1.01 (0.97-1.06)
Gender	**Female**	20 (40%)	21 (43%)	-	>0.99	1.05 (0.23-4.77)
	Male	4 (8%)	4 (8%)			
Tumour stage	**1,2**	23 (47%)	24 (49%)	-	>0.99	1.04 (0.06-17.68)
	3,4	1 (2%)	1 (2%)			
Tumour size (mm)		15±8.75	15±15.35	15±13	0.688	1.007 (0.96-1.05)
Capsular invasion	**Positive**	15	4	-	0.001	8.75 (2.26-33.79)*
	Negative	9	21			
Lymph node metastasis	**Positive**	5	2	-	0.247	3.026 (0.52-17.39)
	Negative	19	23			
Extra-thyroidal involvement	**Positive**	0	0	-	N.A.	N.A.
	Negative	24	25			
Lymphovascular involvement	**Positive**	12	1	-	0.0001	24 (2.78-206.96)
	Negative	12	24			
TIRADS score	**4**	10	19	-	0.021	4.43 (1.30-15.09)
	5	14	6			
LAP	**Positive**	9	9	-	>0.99	0.93 (0.29-2.99)
	Negative	15	16			
BMI (kg/m^2)		25.85±1.02	23.63±1.68	24.72±1.7	<0.0001	3.82 (1.83-7.97)
FBS (mg/dL)		95±24	113±30.5	99±28	0.032	0.96 (0.92-1.00)
TG (mg/dL)		140.5±109	138±100	139±101	0.936	1.00 (0.99-1.00)
Total cholesterol (mg/dL)		163±52.75	156±58	162±51.5	0.478	1.00 (0.99-1.00)
HDL (mg/dL)		36±9.55	44±19.5	39±14.5	0.087	0.94 (0.89-1.00)
LDL (mg/dL)		107.75±38.99	88.40±36.97	97.88±38.8	0.081	1.01 (0.99-1.03)

TIRADS, thyroid imaging reporting and data system; LAP, lymphadenopathy; BMI, body mass index; TG, triglyceride, FBS: Fasting blood glucose, LDL: Low density lipoprotein, HDL: High density lipoprotein, N.A.: Not Applicable. *Mann-Whitney U test and Chi-square test. Numerical data as mean ± standard deviation or median (interquartile range) and categorical data as frequency (percentage). OR: Odds ratio; CI: Confidence interval

No significant relation was found between age and sex with the high and low FGF21 groups. Most patients were Persian (23 patients, 46.9%), followed by Sistani (12 patients, 24.4%), Turkamen (10 patients, 20.4%), and other ethnicities (4 patients, 8.2%). No relation was found between race and FGF21 levels. All patients had total thyroidectomy, and those with lymph node metastasis underwent lymph node dissection. The median duration of follow-up was 15 months, with a range of 8 to 21 months, and all of our patients survived (100%). There were no

instances of local lymph node metastasis during the follow-up. Only one patient was found to have distant metastases, which was not enough for statistical analysis. In the high group, the average BMI of the patients was 25.85±1.02 kg/m2, whereas in the low group, it was 23.63±1.68 kg/m2. The total patient's mean BMI was 24.72±1.7 kg/m², and increasing BMI was significantly related among the high FGF21 groups (p-value <0.00). The frequency of increasing BMI was 3.82 times higher in patients with high FGF21 group compare to low FGF 21 group (OR = 3.82; 95% CI = 1.83-7.97). Table 1 reports the patients' demographic characteristics and clinicopathological findings. Twenty-four (49%) patients had high serum FGF21 levels, and 25 (51%) had low serum FGF21 levels. The mean±SD and median FGF21 levels were 716.41±458.7 and 489 pg/ml, respectively. In our study, 96% of patients had stage 1 and 2 PTC cancer, 2% of patients both groups were in stages 3 and 4. None of our patients had extrathyroidal involvement in both groups. The mean tumor size in PTC patients in both groups was 15 mm. There was no statically significant relation between tumor stage and tumor size with any of the groups.

The rate of capsular invasion was 62.5% among individuals with high FGF21 levels and 16% among those with low levels. There was a significant association between capsular invasion and both high and low FGF21 level groups, with patients having high FGF21 levels being at 8.75 times greater risk of capsular invasion compared to those with low levels (OR = 8.75; 95% CI = 2.26-33.79; p < 0.001). A high FGF21 level (>489 pg/ml) demonstrated 78.95% sensitivity and 70% specificity in detecting capsular invasion. The negative predictive value (NPV), positive predictive value (PPV), and accuracy were 84%, 62.5%, and 73.47%, respectively (figure 1) (table 2).

Table 2. Diagnostic performance of high FGF21 for capsular invasion

	Sensitivity (CI95%)	Specificity (CI95%)	PPV (CI95%)	NPV (CI95%)	Accuracy (CI95%)
Capsular invasion	78.95% (54.43-93.95)	70% (50.6-85.27)	62.5% (47.92-75.11)	84% (68.06-92.82)	73.47% (58.92-85.05)
Lymph node metastasis	71.43% (29.04-96.33)	54.76% (38.67-70.15)	20.83% (12.90-31.86)	92.00% (77.54-97.46)	57.14% (42.21-71.18)

NPV, negative predictive value; PPV, positive predictive value; CI, confidence interval

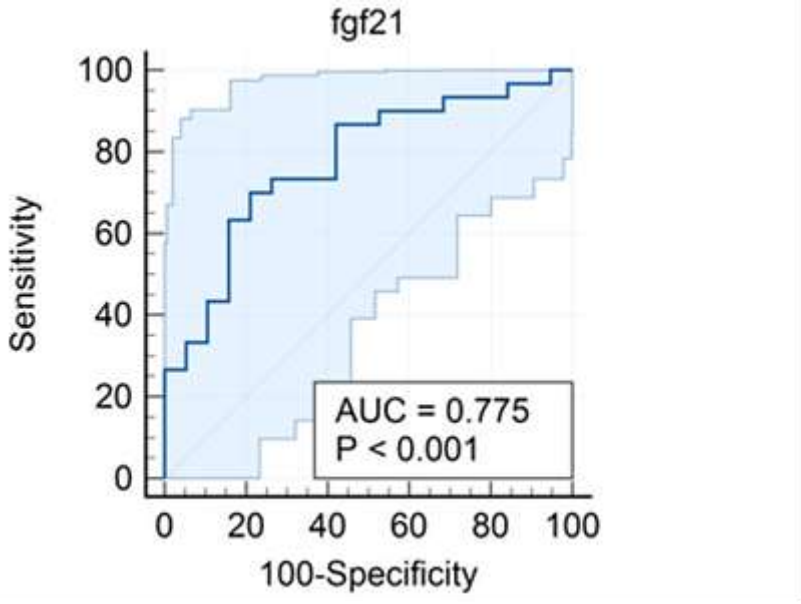

Figure 1. ROC curve for association of FGF21 with capsular invasion

The presentation of lymphadenopathy was 37.5% and 36% in the high and low FGF21 level groups. In the high-level group, lymph node metastasis was present in 20%, compared to 8% in the low-level group. In comparison, lymphovascular involvement was observed in 50% of the high-level group and 4% of the low-level group. We found no significant correlation between LAP and lymph node metastasis in the high and low FGF21 level groups (table 2). However, lymphovascular involvement was significantly linked to the high-level and low-level FGF21 groups (p-value <0.00). Lymphovascular involvement was notably more prevalent in the high FGF21 group than the low group, with the risk being 24 times greater in the high FGF21 group (OR = 24; 95% CI = 2.78-206.96).

Among all participants, 41% had a TIRADS score equal to 4, whereas 59% had a TIRADS score equal to 5. Additionally, 58% of the high-level and 24% of the low-level groups had a TIRADS score of five, and TIRADS score was significantly related to the high and low FGF21 level groups (p- value: 0.02), and TIRADS score was 4.43 times greater in high FGF 21 group compare to low FGF21 group (OR = 24; 95% CI = 1.30-15.09). In the high group, the mean FBS level was 95±24 mg/dL, and in the low group was 113±30.5 mg/dL. The mean total FBS level was 99 ± 28 mg/dL and the relation between FBS and FGF21 level was found (p- value: 0.03). In our research, the total TG was 139±101 mg/dL, the level of cholesterol was 162±51.5 mg/dL, HDL was 39±14.5 mg/dL, and LDL was 97.88±38.8 mg/dL. Furthermore, there was no difference in the lipid profiles of both groups, and significant relation was not seen between low and high FGF21 level groups and lipid profiles, including TG, total cholesterol, HDL, and LDL.

Discussion

Thyroid cancer is the most common malignant tumor of the endocrine system, and papillary thyroid cancer is the most common malignant tumor of the thyroid. Unfortunately, the incidence (169%), mortality (87%), and disability-adjusted life-years (75%) of thyroid cancer have significantly risen in the past two decades, and consequently, the burden of treatment patient support costs for the healthcare system and patients have inevitably increased (13, 14). Lately, various studies have been carried out on molecular pathways, including the role of the fibroblastic growth factor system in cancer.

As new medical findings support FGF21 as a new predictive factor for various pathologies (15-19), and FGF21 is a novel biomarker in PTC (6), we investigated the effects of FGF21 serum levels on preoperative tumor aggressiveness in patients with PTC. (9, 20, 21). FGF21, a member of a subfamily of FGFs, modulates the metabolism of glucose and lipids when released from the liver into the systemic circulation. In addition, fasting and upregulating peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC1α) induces FGF21. PGC1α is a primary coordinator of metabolic pathways that converts glucose to fatty acids in the liver. Because of the high metabolism of cancer cells, they may suffer nutrient starvation, which may explain the increased FGF21 levels in patients with more consistent PTC (22). On the other hand, thyroid hormones impact systemic metabolism; therefore, there is a relation between thyroid hormones and FGF21 expression. According to the study by Adams, hepatic FGF21 production is directly enforced via the T3 hormone by PPARα dependent mechanisms (23).

In this research, most patients had female gender (83.67%), and the mean age of our patients was 39±13.5 years. However, compared to the FGF21 level, none of them was statistically significant. Similar to our result, in research investigated by Abdullah and Huang mean ages of the participants were 40 and 43.2 years old. According to Sezar, Huang and Kang, most patients were females (83.2%, 75.7%, 85%) (6, 24-26). Our results indicated that the mean±SD and median FGF21 levels were 716.41±458.7 and 489 pg/ml, respectively, which differs from a similar study by Kang (227.2±184.0 and 184.1 pg/mL) (6).

Further analyses in the present study reported that a high FGF21 serum level was significantly related with capsular invasion (P < 0.00). Our high FGF21 group showed more capsule involvement rather than a similar study conducted by Kang (78.9% vs. 67.7), with the mean capsule invasion rate being the same in both studies (both 38.7%) (6). Chaigneau, also reported that 38.7% of the participants had a capsular invasion, which was in line with our result (27). Kang, investigated the expression of KLB, FGFRs, and FGF21 levels. They investigated the role of FGF21 in PTC cell lines (TPC-1 and BCPAP) treated with rFGF21 in tumor aggressiveness, which illustrated that FGF21-treated cells show more remarkable migration and invasion compared to the standard thyroid cell line. They also proved that FGF21 plays a vital function in the invasion and migration of cells by upregulating FGFR signalling by comparing the inhibition of the FGFR pathway with AZD4547 (an FGFR tyrosine kinase inhibitor). Thus, FGF21 role is more sensible in stimulating tumor progression and invasion by upregulating the FGFR signalling pathway (6).

As for other factors contributing to other clinicopathological factors of PTC, it was deduced from our

study results that FGF21 is also significantly related to lymphovascular invasion (P =0.00). This distinctive finding also confirms the FGF21 role in thyroid cancer cells migration, which has not been reported by Kang. (P =0.48). Although FGF21 was shown to have a substantial relation with extrathyroidal extension in the study by Kang, this could not be assessed in our study because none of our patients had extrathyroidal extension (6). Most of the patients were in stages 1 and 2, and there was no relation between the FGF21 level and the patient's stage. This could be related to the fact that patients had no extrathyroidal extension of PTC. Also, Tang, mentioned that most patients were also at stages 1 and 2 (28). Only seven (14.28%) patients had lymph node metastasis in our study. Although no relation was found between lymph node metastasis and the FGF21 level, five of them (71.4%) had a high level of FGF21.

Epidemiological data have found that obesity is related with worsening outcomes and increased risk for various types of malignancies, which include papillary and follicular cancers. According to studies, this relation is due mainly to an increase in inflammatory cytokines, dysregulating energy metabolism, and hyperinsulinemia in high BMI patients. As mentioned above, FGF21 has a vital role in modulating the carbohydrates and lipids metabolism. In our study, patients with higher BMI had high FGF21, with statistically significant relation. The relation between high BMI and PTC has been proven in studies; by considering the role of FGF21 in regulating metabolism, it is possible to understand its role in PTC by measuring the level of this factor in these patients (29, 30).

In a study by Zhao, measuring the association between obesity and PTC in 5114 patients, a significant relationship was found between patients with excess BMI and high risk of PTC (31). On the other hand, elevated FGF21 level is found in type 2 diabetes mellitus patients, higher BMI values, and other chronic conditions such as coronary heart, cirrhosis, metabolic syndrome, disease, hepatitis, chronic and acute renal dysfunction and fatty liver degeneration (22, 32, 33). Leptin has been associated with multiple cancers that FGF21 is associated with, like thyroid carcinoma and endometrial cancer (18, 34). Both are correlated with the AKT and EKR pathways but do not increase their total amounts. These pathways are involved in cell proliferation. Notably, not all FGF21-related cancers are leptin-related, making FGF21 a more comprehensive factor (35). Furthermore, studies have confirmed the association between BMI and clinicopathological features such as advanced tumor stages, lymph node metastasis, and extrathyroidal extension (36). Conversely, Paes gathered a study on 259 patients with PTC that mentioned the possibility of fewer nodal metastases in obese patients and tumors that were not aggressive in patients with higher BMI (37). However, other studies focus on this matter, but the consistency still needs to be improved (38, 39).

Ultrasound (US) is essential in assessing FNA- qualified trials. Using ultrasound can help avoid unnecessary surgical procedures that delay diagnosing and treating malignant lesions and asymptomatic benign nodules. For classifying thyroid nodules, we used TIRADS. Scores are assigned based on five models based on a combination of US characteristics, each including an estimated risk of malignancy. The features that suggest thyroid cancer are microcalcifications, a taller-than-wide shape, irregular margins, and hypoechogenicity. The studies mentioned that the TIRADS score has specificity and sensitivity for estimating the risk of cancer in a medical approach (40). Our study reported that 58% of high group and 24% of the low FGF21 group had a TIRADS score of five, and a high TIRADS score was significantly associated with high groups.

To our knowledge, there has yet to be previously published research on the role of serum level of FGF21 as a clinicopathological measurement of PTC in Iran and the Middle East. Our study has limitations. We determined the FGF21 levels in thyroid cancer patients in the limited group at the time of diagnosis. Studies with bigger patient groups that measure FGF21 in long-term follow-up are recommended to ensure the FGF21 level is an effective marker of clinicopathological findings. Our results support the role of serum FGF21 as a predictive biomarker of tumor invasiveness in thyroid cancer. Serum FGF21 levels in PTC patients are positively correlated with BMI, and targeting FGFR may serve as an alternative therapy to treat PTC patients.

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Authors' contribution: HA, S.M and MA. MA reposed the idea and designed the research. NL, MA. ME and A.A conducted document preparation and data collection. FS. SA performed analysis of data. MA, NL wrote the first draft

of the article, and all authors commented on first draft, and approved the final article.

Availability of data and materials: Data and materials supporting the findings of the article are available upon reasonable request.

Consent for publication: Informed consent was acquired from all patients included in this research.

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