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Sepsis and Fibroblast Growth Factor 21: A New Acute Phase Reactant?

Sepsis ve Fibroblast Büyüme Faktörü 21: Yeni Bir Akut Faz Reaktanı mı?

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ABSTRACT Objective: This study aimed to compare the levels of fibroblast growth factor 21 (FGF 21) in patients with acute metabolic decompensation, sepsis and non-infectious inflammatory status using infection parameters and scoring systems.

Materials and Methods: This cross-sectional study included 46 patients with sepsis and 29 patients with non-infectious inflammatory conditions in the case group. A total of 39 healthy volunteers were included in the control group. C-reactive protein, procalcitonin (PCT), sedimentation and FGF 21 levels were measured in all patients. Acute physiology and chronic health evaluation II and sequential organ failure assessment scores were also calculated.

Results: FGF 21 levels in the patients in the case group were significantly higher than those in the patients in the control group ($p<0.001$). A weak positive correlation was found between the FGF 21 and PCT levels ($r=0.292$, $p=0.011$). It was estimated that FGF 21 levels of 492.4 pg/mL and higher could predict the diagnosis of sepsis and non-infectious inflammatory status with 82.4% sensitivity and 80% specificity.

Conclusion: FGF 21 can be considered an acute phase reactant in cases of infection, rising like PCT but not increasing in every acute condition.

Keywords: Fibroblast growth factor 21, sepsis, mortality

ÖZ Amaç: Bu çalışmada akut metabolik dekompanzasyon olan sepsisli ve non-enfeksiyöz enflamatuvar durumlu hastaların fibroblast büyüme faktörü 21 (FGF 21) düzeylerini, enfeksiyon parametreleri ve skorlama sistemleri ile karşılaştırmak amaçlandı.

Gereç ve Yöntem: Kesitsel olarak dizayn edilen çalışmada olgu grubuna 46 sepsis tanısı olan hasta ile 29 non-enfeksiyöz enflamatuvar durum tanısı olan hasta ve kontrol grubuna da 39 sağlıklı gönüllü dahil edildi. Tüm hastaların C-reaktif protein, prokalsitonin (PCT), sedimentasyon ve FGF 21 düzey ölçümleri yapıldı. Akut fizyoloji ve kronik sağlık değerlendirme-II, sequential organ failure assessment skorlamaları hesaplandı.

Bulgular: Sepsis ve non-enfeksiyöz enflamatuvar durum gruplarındaki FGF 21 düzeyleri, kontrol grubuna göre anlamlı olarak daha yüksek bulundu ($p<0,001$). FGF 21 düzeyi ile sadece PCT düzeyi arasında zayıf pozitif bir korelasyon olduğu görüldü ($r=0,292$ $p=0,011$). FGF 21 ölçümlerinin 492,4 pg/mL ve üzerinde olmasının %82,4 sensitivite ve %80 spesifisite ile sepsis ve non-enfeksiyöz enflamatuvar durum tanılarını öngörebildiği gösterildi.

Sonuç: Sonuç olarak, FGF 21, enfeksiyöz tablolarda PCT gibi yükselmesi, ancak her akut tabloda artmaması nedeni ile akut faz reaktanı olarak kabul edilmesinden dolayı şüpheli bir parametre olarak değerlendirilebilir.

Anahtar Kelimeler: Fibroblast büyüme faktörü 21, sepsis, mortalite

Introduction

Sepsis is a systemic inflammatory response to infection, with high clinical mortality and increased incidence and clinical severity over the years (1). Sepsis is the most important cause of mortality in intensive care units (ICUs) and the mortality rate can reach up to 50% (2,3). The most effective method for reducing mortality is to initiate rapid treatment. Due to the diversity of clinical findings and different clinical courses in sepsis, delays are frequently encountered in diagnosis, and there is an increasing need for markers that provide early intervention and predict rapid clinical instability and also predict mortality (4,5). Therefore, new sensitive and specific markers are needed in this regard. In addition, the exact role of biomarkers in the treatment of septic patients has not been identified and this issue needs clarification (2,5,6).

For the follow-up of sepsis and infection in the clinic, indicators such as sedimentation, C-reactive protein (CRP), and procalcitonin (PCT) are used (7-9). In addition to these indicators, for intensive care patients, scoring systems have been developed for determining the severity of the disease, managing the treatment, grouping patients for clinical studies, and comparing the effectiveness of ICUs within themselves or between each other. These systems include the Acute Physiology and Chronic Health Evaluation-II (APACHE-II), Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology score II, Mortality Probability Model II, Therapeutic Intervention Scoring System 28, Logistic Organ Dysfunction System, and Multiple Organ Dysfunction score, among others (10,11). APACHE-II and SOFA are the most frequently used of these scoring systems (12,13).

Fibroblast growth factors (FGFs) are a large family of polypeptide growth factors that act as homeostatic factors in tissue repair and angiogenesis in the adult organism and maintain cell proliferation, migration, and differentiation during embryonic development (14,15). Recently, it has been demonstrated that some members of the FGF family have important roles in determining and regulating the functions of some hormonal tissues and organs as well as modulating various metabolic processes. One of the most studied members of this family is FGF 21. There are many findings in the literature showing that FGF 21 is increased in chronic metabolic conditions such as polycystic ovarian syndrome, non-alcoholic steatohepatitis (NASH), diabetes mellitus (DM), and chronic kidney failure (16-20). Studies showing that FGF 21 is also increased in cases such as acute metabolic

conditions such as sepsis and non-infectious inflammatory status have been published recently. However, these studies are generally based on animal experiments and there are limited numbers of human studies among them (21-23).

Our aim in this study was to compare the FGF 21 levels of patients with acute metabolic decompensation, sepsis, and non-infectious inflammatory status with infection parameters and scoring systems and to determine a threshold value so that high levels of FGF can be used in the diagnosis of these diseases and to determine severity.

Materials and Methods

Ethics committee approval for the study was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Keçiören Training and Research Hospital (decision no: 2012-KAEK-15/1061, date: 27.01.2016). Informed consents were taken from all participants. Seventy-five patients those aged 18 and over (n=75) hospitalized in the ICU of University of Health Sciences Turkey, Keçiören Training and Research Hospital for a period of six months (January 2017-June 2017) who diagnosed with sepsis and/or non-infectious inflammatory conditions were included in this study which was designed as a prospective observational study. Sepsis was defined according to the current criteria (For clinical operationalization, organ dysfunction can be represented by a 2 points or more increase in the SOFA score, which is associated with an in-hospital mortality greater than 10%) (1). Patients who had no suspected or documented infection but had two or more of the criteria of fever ($>38^{\circ}\text{C}$), hypothermia ($<36^{\circ}\text{C}$), leukocytosis ($>12,000\text{ mm}^3$), leukopenia ($<4000\text{ mm}^3$), tachycardia ($>90\text{ beats/minute}$), or tachypnea ($>20\text{ breaths/minute}$) were assigned to group 2 (24). The exclusion criteria for group 1 and group 2 were pregnancy, puerperium, refusal of the study by the patient or his/her conservator, and those with suspicion in the diagnosis of sepsis or non-infectious inflammatory conditions. Thirty-nine volunteers who had no acute signs or symptoms of infection and had applied to our hospital for any reason, without chronic metabolic diagnoses such as DM, hypertension, coronary artery disease, or cerebrovascular disease and without hematological or solid organ malignancies or any known inflammatory diseases (ulcerative colitis, etc.), and not diagnosed with any disease were assigned to the control group (group 3) (n=39).

Demographic and biochemical (liver and kidney functions, complete blood count, CRP, PCT) data of group 1 and group 2 patients within 24 hours of admission to the hospital were obtained from their records. The calculation SOFA and APACHE-II scores of all patients were recorded and serums obtained from fasting blood samples in the morning were stored at -80 °C for all participants to measure FGF 21 levels within first 24 hours. After the patient groups were formed, FGF 21 levels were measured from stored blood samples by sandwich assay ELISA [BioVendor Research and Diagnostic Products (antibody-coated 96-well plate human FGF 21)]. Samples were diluted one-to-one with 75 mL of saline. Testing proceeded with biotin and streptavidin. Absorbance measurements at 450 nm were performed on an ELx800 microplate reading device (BioTek Instruments, Inc.). For the measurement of FGF 21 levels according to the FGF 21 ELISA kit's instructions, serum samples were diluted 1:2 by buffer dilution before analysis. The standard curve range for the analysis is 30-1,920 pg/mL. Sensitivity was 7 pg/mL, and intraassay and interassay ranges were 3-4.1% and 3.6-3.9%, respectively.

Statistical Analysis

SPSS 15.0 (SPSS Inc.) was used for the analysis. The distribution of the data was assessed using a one-sample Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as mean and standard deviation, skewed-distributed continuous variables were expressed as median (minimum-maximum), and categorical variables were expressed as number and percentage. Categorical variables were compared with the chi-square test. Non-normally distributed data were compared with the Mann-Whitney U test. Correlation analyses between continuous variables that did not fit the normal distribution were analyzed with the Spearman test. The power of FGF 21 measurements to predict sepsis and non-infectious inflammatory conditions diagnosis was evaluated by receiver operating characteristics (ROC) analysis. The results were evaluated in a confidence interval of 95% and at a significance level of p<0.05.

Results

There were 34 females in the patient group (19 in group 1, 15 in group 2) and 19 females in the control group in our study. Group 1, group 2, and group 3 had similar characteristics in terms of gender and age distribution (Table 1).

FGF 21 levels in group 1 and group 2 were significantly higher than in group 3 (p<0.001) (Figure 1). There was no significant difference between group 1 and group 2 in terms of FGF 21 level, CRP level, PCT level, APACHE-II score, APACHE-II mortality, or SOFA score (Table 2).

As a result of the correlation analysis between FGF 21 levels and APACHE-II, SOFA, PCT, and CRP values, there was a positive correlation only between FGF 21 levels and PCT levels (r=0.292, p=0.011, r²=0.085). According to the ROC analysis, FGF 21 level was found to significantly predict sepsis and non-infectious inflammatory conditions (area under the curve: 0.884, 95% confidence interval: 0.824-0.944, p<0.001). FGF 21 measurements of 492.4 pg/mL and above could predict sepsis and non-infectious inflammatory conditions with 82.4% sensitivity and 80% specificity (Figure 2).

Discussion

According to the results of our study, FGF 21 level has been shown to significantly predict sepsis and non-infectious inflammatory conditions. FGF 21 measurements of 492.4 pg/mL and above could predict sepsis and non-infectious inflammatory conditions with 82.4% sensitivity and 80% specificity. In addition, a weak correlation was found between FGF 21 level and inflammatory markers and PCT level.

In addition to inflammatory markers, a number of scoring systems have been frequently used in ICUs in recent years in the follow-up of sepsis and non-infectious inflammatory status due to rapid clinical instability. However, there is still a need for new parameters to help make decisions faster. For this purpose, studies investigating a large number of parameters are common in the literature (3,5,6,9). One of

Table 1. Basic demographic data and FGF 21 levels of sepsis, non-infectious inflammatory status, and control groups

	Group 1 (sepsis) (n=46)	Group 2 (non-infectious inflammatory status) (n=29)	Group 3 (control) (n=39)	p-value
Age (years)	76 (47-92)	72 (18-87)	67 (53-82)	0.001
Gender (%)	19 (41.3%) females	15 (51.7%) females	19 (48.7%) females	0.639
FGF 21 (pg/mL)	1970 (66-2402)	1696 (222-2255)	330 (65-1028)	0.001

FGF 21: Fibroblast growth factor 21

these parameters is FGF 21. One reason why FGF 21 is investigated is that it has an important role in determining and regulating the functions of some hormonal tissues and organs, as well as controlling processes such as various glucose, fat, and ketone metabolisms (15). On the other hand, unlike other members of the FGF family, FGF 21 has no heparin binding sites, so it shows its effects systemically in a hormone-like manner and thus can be easily detected in the blood (21).

A study published by Gariani et al. (21) in 2013 is methodologically similar to our study but was conducted with fewer participants. They compared sepsis and systemic inflammatory response syndrome (SIRS) groups with healthy controls. According to the sepsis classification updated in 2016, the definition of SIRS is no longer used (1). However, group 2 in our study, comprising patients with non-infectious inflammatory status, can be considered as acceptably similar to the SIRS group in the study of Gariani et al. (21) As a result of their study, similar to our study, FGF 21 levels were

found higher in patients with sepsis and SIRS compared to healthy controls. Unlike our results, FGF 21 levels were found higher in the sepsis group than the SIRS group and FGF 21 level was found to be positively correlated with APACHE-II score, while no correlation was found with PCT level (21). We found a significant difference in FGF 21 levels between the case and control groups, but there was no difference between groups in terms of gender and age. Unlike the study of Gariani et al. (21), the fact that the level of FGF 21 was significantly higher in group 2 in our study may be due to our study having a larger number of participants. In a study published in 2018, the level of FGF 21 was shown to have sensitivity of 81.3% and specificity of 89.8% to predict 28-day mortality (23). The recently published study of Li et al. (4)

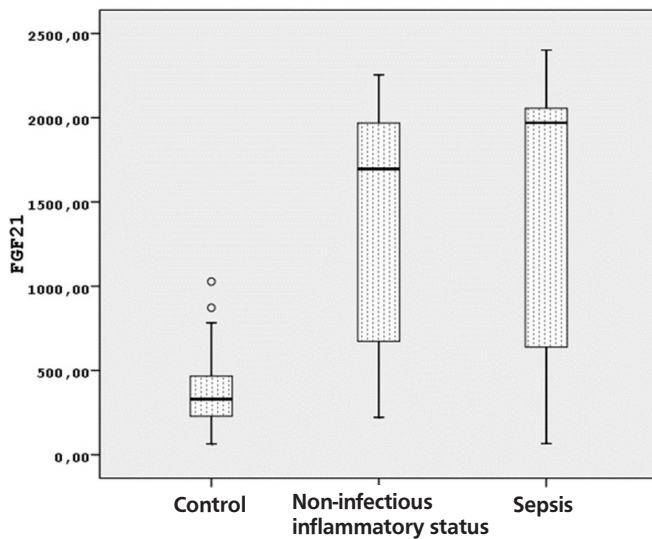


Figure 1. Distribution of FGF 21 (pg/mL) levels by groups
FGF 21: Fibroblast growth factor 21

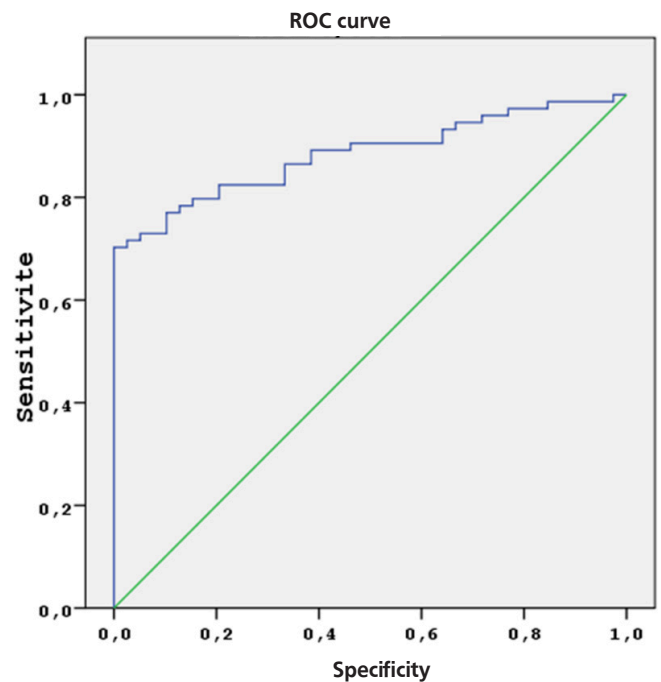


Figure 2. ROC curve of FGF 21 for prediction of patients' mortality
FGF 21: Fibroblast growth factor 21, ROC: receiver operating characteristics

Table 2. Inflammatory markers, APACHE-II scores, APACHE-II mortality, and SOFA scores in sepsis and non-infectious inflammatory status groups

	Group 1 (sepsis)	Group 2 (non-infectious inflammatory status)	p-value
CRP (mg/dL)	14.65 (1.26-32)	15.54 (1.13-35)	0.654
PCT (ng/mL)	4.56 (0.10-100)	4.47 (0.14-100)	0.794
APACHE II score	28 (9-51)	24 (11-39)	0.107
APACHE II mortality	63.9 (9.9-98.1)	53.3 (12.9-89.8)	0.113
SOFA	9 (2-18)	6 (1-15)	0.140

APACHE-II: Acute Physiology and Chronic Health Evaluation-II, CRP: C-reactive protein, PCT: procalcitonin, SOFA: Sequential Organ Failure Assessment

supports our study results; in their work, SOFA score and serum FGF 21 concentration were shown to be important markers of 28-day mortality in patients with sepsis.

We found a positive correlation between FGF 21 level and PCT level ($r=0.292$, $p=0.011$). PCT is a more specific marker in cases of infection than CRP and sedimentation levels (5,25). Due to the presence of infection in most of our patient population, there was a relationship between PCT and FGF 21, while no relationship could be detected between CRP and sedimentation. With a larger number of participants, we think that a relationship between CRP and sedimentation levels could be found, which are less specific in infection than PCT and FGF 21 levels.

Wang and Chen (26) suggested that PCT, compared to CRP, showed a more significant correlation with APACHE-II and SOFA scores, and that PCT was a better indicator in the evaluation of prognosis and severity in patients with sepsis. Based on this assumption, we compared APACHE-II and SOFA scores and the levels of markers in our study. We could not find a relationship between those scores and FGF 21 levels. Gariani et al. (21) showed a poor correlation between FGF 21 level and APACHE-II score. In a study published in 2018, there was a positive correlation between FGF 21 level and APACHE-II and SOFA scores. The APACHE-II scoring system gives more meaningful results in patients with postoperative and/or cranial pathology (23). When we compare the APACHE-II and SOFA scores with the FGF 21 levels, we see that the patient population in our study was hospitalized for internal medicine reasons, which may be why we did not find a correlation.

In animal studies, it has been suggested that FGF 21 injections can be considered as a possible pharmacological treatment in diseases such as DM, obesity, and NASH (27,28). FGF 21 was shown to be an acute phase protein that protects against the toxic effects of lipopolysaccharides and sepsis in a study on rats (22). Recently, FGF 21 was also found to provide anti-inflammatory effects by inhibiting some signals in macrophages (29). As a result of our research, FGF 21 elevation may be an anti-inflammatory response to sepsis and SIRS in humans. We believe that our study has prepared

a basis for pharmacological treatment based on FGF 21 that can be applied in humans in the future.

Our study has some limitations. First of all, the relatively limited sample prevents generalizing our study results. Second, low levels of free triiodothyronine (fT3) and free thyroxine (fT4) (euthyroid patient syndrome) are associated with disease severity and mortality in ICU patients, but we did not use thyroid function evaluations of the patient population in our study for analysis and we consider this a limitation (4,13). As other limiting factors, we did not evaluate the levels of tumor necrosis factor alpha, interleukin-6, or other inflammatory markers, and we did not use scoring systems other than the SOFA and APACHE-II scores. In addition, due to the small sample size, confounding factors known to increase FGF 21 levels such as DM or NASH could not be excluded.

Conclusion

In conclusion, FGF 21 can be considered as a suspicious acute phase reactant in cases of infection, as it is ascending similarly to PCT, but is not increased in every acute condition.

Ethics

Ethics Committee Approval: Ethics committee approval for the study was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Keçiören Training and Research Hospital (decision no: 2012-KAEK-15/1061, date: 27.01.2016).

Informed Consent: Informed consents were taken from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.T.E., E.B., Design: T.A., E.B., Data Collection and Process: S.D., Analysis or Interpretation: D.T.E., T.A., Literature Search: S.D., A.O.K., Writing: S.D., A.O.K.

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