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Research Article

Evaluation of the relationship between inflammation and bone turnover by sclerostin and Dickkopf-1 (DKK-1) levels in patients with SIRS

SIRS tanılı hastalarda enflamasyon ve kemik döngüsü arasındaki ilişkinin sklerostin ve Dickkopf-1 (DKK-1) düzeyleri ile değerlendirilmesi

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Abstract

Introduction: In intensive care units (ICU), patients remain bedridden for a long time. In addition, severe infections are frequently seen in ICUs. Both prolonged immobilization and serious infections are associated with bone tissue loss. The Wnt pathway has recently been focused on evaluating bone tissue loss. The Wnt pathway participates in both infections and the formation of bone tissue. Wnt pathway inhibitors sclerostin and Dickkopf-1 (DKK-1) inhibit bone formation and increase osteoclastic activity. In this study, we aimed to examine bone turnover by the Wnt inhibitors sclerostin and DKK-1 and their possible associations with inflammation in SIRS patients.

Methods: We included 30 patients diagnosed with systemic inflammatory response syndrome (SIRS) in the study group and 16 in the control group. Serum sclerostin, DKK-1, white blood cell (WBC), and C-Reactive Protein (CRP) levels on the day of SIRS diagnosis (basal), the 7th, 14th, and 21stdays were evaluated in the study group, and the results were compared with the control group.

Results: When the control group was compared with the basal SIRS, there was a significant elevation in both sclerostin (p=0.003) and DKK-1 (p=0.001). Statistical analysis showed significant decreases in sclerostin levels between basal and the 7th, 14th, and 21st days (p=0.033, p=0.003, p=0.002, respectively). Similarly, significant decreases in DKK-1 levels between basal and the 7th and 21st days (p=0.015, p=0.001, respectively) and an insignificant decrease on the 14th day (p=0.191) was observed. Sclerostin was positively and significantly correlated with WBC and CRP in basal and 7th-day measurements and WBC in 7th and 14th days. DKK-1 is positively and significantly correlated with WBC in basal and 7th-daymeasurements, while DKK-1 negatively correlates with CRP in basal-7th-day measurements.

Conclusion: In this study, it was shown for the first time that the Wnt antagonists sclerostin and DKK-1 values are high in SIRS patients in ICU. Both biomarker levels decreased in parallel with the treatment. However, it could not be associated with disease severity and inflammatory marker levels. We believe that monitoring the change of Wnt antagonists will be useful in demonstrating bone turnover in patients with SIRS.

Keywords: Dickkopf-1, Intensive care unit, Sclerostin, Systemic inflammatory response syndrome, Wnt signaling pathway, Bone turnover

Öz

Giriş: Yoğun bakımlarda hastalar uzun süre yatağa bağımlı halde kalmaktadır. Ayrıca yoğun bakımlarda sıklıkla ağır enfeksiyonlar da görülmektedir. Hem uzun süreli immobilizasyon hem de ciddi infeksiyonlar kemik doku kaybı ile ilişkilidir. Son yıllarda, kemik döngüsünün değerlendirilmesinde Wnt yolağı üzerine yoğunlaşılmıştır. Wnt yolağı hem infeksiyonlarda hem de kemik dokunun formasyonunda rol alır. Wnt antagonisti olan sklerostin ve Dickkopf-1 (DKK-1), kemik yapımını azaltıcı ve osteoklastik aktiviteyi artırıcı etki yaparlar. Biz bu çalışmada, uzun süre yatağa bağımlı SIRS tanılı hastalarda, Wnt inhibitörleri olan "sklerostin ve DKK-1'in" seviyelerindeki değişimi aracılığıyla "kemik döngüsü ve bunun inflamasyonla olan ilişkisini" değerlendirmeyi amaçladık.

Yöntem: Çalışma grubuna SIRS tanısı alan 30 ve kontrol grubuna 16 hasta dahil ettik. Çalışma grubunda hastaların SIRS tanısı aldığı gün (bazal) ve takip eden 7., 14. ve 21. günlerde serum sklerostin, DKK-1, WBC ve CRP düzeylerini ölçtük, sonuçları kontrol grubu ile karşılaştırdık.

Bulgular: Kontrol grubu ile kıyaslandığında, çalışma grubundaki (SIRS) hastaların bazal ölçümlerinde hem sklerostin (p=0,003) hem DKK-1 değerlerinde istatistiksel olarak anlamlı yükseklik vardı (p=0,001). Çalışma grubunda; sklerostin değerlerinde, bazal ile karşılaştırıldığında 7., 14. ve 21. günlerde anlamlı ve progresif bir azalma olduğu gösterildi (sırasıyla p=0,033, p=0,003, p=0,002). Yine çalışma grubundaki DKK-1 seviyelerinde, bazal değer ile kıyaslandığında 7. ve 21. günlerde anlamlı (sırasıyla p=0,015, p=0,001), 14. günde anlamsız azalma görüldü (p=0,191). Korelasyon analizinde; çalışma grubunda sklerostin ile WBC arasında bazal - 7. gün, 7.-14. gün, sklerostin ile CRP arasında bazal - 7. gün pozitif korelasyon tespit edildi. DKK-1 ile WBC arasında bazal - 7. gün pozitif korelasyon vardı. Diğer taraftan DKK-1 ile CRP arasında bazal - 7. gün negatif korelasyon vardı.

Sonuç: Bu çalışmada, yoğun bakımdaki SIRS olgularında Wnt antagonistleri olan sklerostin ve DKK-1 değerlerinin yüksek olduğu ilk kez gösterildi. Her iki biomarker seviyeleri tedaviye paralel olarak azaldı. Bununla birlikte inflamatuar marker düzeylerindeki değişim ile ilişki bulunmadı. Wnt antagonistlerinin düzeylerindeki değişimin takip edilmesinin, SIRS tanılı hastaların kemik döngüsünün gösterilmesinde faydalı olacağı kanaatindeyiz.

Anahtar kelimeler: Dickkopf-1, Yoğun bakım ünitesi, Sklerostin, Sistemik inflamatuar yanıt sendromu, Wnt sinyal yolağı, Kemik döngüsü

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Key Points

1. Wnt antagonists sclerostin and DKK-1 values are high in severe infections like SIRS patients in ICU.
2. Sclerostin and DKK-1 levels decreased in parallel with the treatment in SIRS
3. Sclerostin and DKK-1 levels could not be associated with disease severity and inflammatory marker levels.
4. Monitoring the change of Wnt antagonists will be useful in demonstrating bone resorption in patients with SIRS. Still, it should be noted that the Wnt pathway is associated with many conditions such as stem cell biology, cancer, immobilization, and acute and chronic infections.

Introduction

Intensive care units are places where patients are hospitalized for a long time. Prolonged immobilization has long been associated with bone tissue loss [1,2]. In addition, serious infections are frequently seen in intensive care units. Systemic infection and inflammation have also been shown to cause bone tissue loss [3,4]. In recent years, some biomarkers have been focused on to show bone tissue loss. Today, some studies say sclerostin and Dickkopf-1 (DKK-1), which are Wnt antagonists, are accepted as biomarkers used in the prediction of osteoporosis [5].

The Wnt pathway engages in both infections and the formation of bone tissue [6-8]. While the Wnt pathway increases osteoblastic activity, it decreases osteoclastic activity and increases bone formation. Known as Wnt antagonists, sclerostin and Dickkopf-1 (DKK-1) are released from bone osteocytes, suppress the Wnt pathway, decrease bone formation, and increase osteoclastic activity [9,10]. It has been shown that sclerostin antagonists have positive effects on osteoporosis [11].

Sclerostin and DKK-1 are inhibitors of the Wingless (Wnt)/β-catenin signaling pathway, which is one of three different pathways of Wnt signaling and plays a role in the regulation of bone metabolism [12]. These two Wnt antagonists block the process of osteoblast differentiation and bone formation [13]. Sclerostin is a glycoprotein primarily produced by mature osteocytes. In an in vivo model, transgenic mice overexpressing sclerostin have been shown to cause osteopenia through reduced osteoblastic activity, and thus, reduced bone formation [14]. Similarly, DKK-1 has been reported to inhibit osteoblastogenesis-chondrocyte differentiation, and excessive DKK-1 release results in osteopenia [15]. However, the Wnt signaling pathway plays a role in some fundamental processes for adult homeostasis, starting from the embryonic period. Furthermore, studies have shown that the Wnt pathway is associated with many conditions such as stem cell biology, cancer, and infection [7,16]. Therefore, "accepting Wnt antagonists as indicators of bone tissue loss" becomes controversial in the presence of severe infection.

In this study, we aimed to evaluate "bone turnover and its relationship with inflammation" in intensive care patients diagnosed with SIRS who were immobilized for a long time through the changes in the levels of sclerostin and DKK-1, which are Wnt inhibitors.

Methods

The study was conducted at Çanakkale Onsekiz Mart University Medical Faculty Hospital between June 2015 and January 2016. The study group included 30 adults over 18 diagnosed with SIRS, who were hospitalized in the intensive care unit. The control group included 16 patients hospitalized in the intensive care unit who did not have an active infection. After giving information about the study, written informed consent was obtained from the conscious patients and from the first-degree relatives of the unconscious patients. Those under 18 years of age, receiving steroid therapy, known osteoporosis, parathyroid tissue disease, and known bone metabolism disease were excluded from the study. The international sepsis guideline criteria [17] updated in 2012 were used to diagnose SIRS and sepsis (Table 1). The presence of at least two of the findings was accepted as SIRS, and the presence of documented or suspected infection in this picture was accepted as sepsis. One of the scoring systems, the APACHE II (Acute Physiology and Chronic Health Evolution II) score, was used to evaluate the severity of the disease and predict the outcomes [18].

Variables

Personal data of the patients (age, sex), APACHE II (Acute Physiology and Chronic Health Evolution II) scores [9] measured on the day of SIRS diagnosis, and primary diagnoses were recorded.

Laboratory measurements

After the diagnosis of SIRS in the study group, serum analysis was performed at four different times: day 0 (basal), day 7, day 14, and day 21. Serum sclerostin levels, serum DKK-1 levels, serum C-reactive protein (CRP) levels, and white blood cell counts (WBC) were recorded from all patients included in the study. The results were compared with the control group.

Serum sclerostin and DKK-1 analysis

Serum samples were frozen at -80 °C and stored until the end of the study and were collectively analyzed. ELISA kit (ELISA microplate strip washer [ELX50; BioTek Instruments, USA] and ELISA microplate reader [ELX 808; BioTek Instruments, USA]) was used to evaluate serum sclerostin and DKK-1 levels. The ELISA kits in which sclerostin and DKK-1 were studied belonged to MyBiosource, Inc. (San Diego, CA 92,195-3,308, USA). Analytical sensitivity for sclerostin and DKK-1 measurement was 1.0 ng mL^{-1}. The inter-analysis and intra-assay sensitivity of sclerostin and DKK-1 was less than 10%.

Table 1. Diagnostic criteria for sepsis infection, documented or suspected, and some of the following

General variables
Fever (> 38.3 °C)
Hypothermia (core temperature < 36°C)
Heart rate > 90 min^{-1} or more than two SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (> 20 mL kg^{-1} over 24 hours)
Hyperglycemia (plasma glucose > 140 mg dL^{-1} or 7.7 mmol L^{-1}) in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC count > 12,000 μL^{-1})
Leukopenia (WBC count < 4,000 μL^{-1})
Normal WBC count with greater than 10% immature forms
Plasma C-reactive protein more than two SD above the normal value
Plasma procalcitonin more than two SD above the normal value
Hemodynamic variables
Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP decrease > 40 mm Hg in adults or less than two SD below normal for age)
Organ dysfunction variables
Arterial hypoxemia (PaO_2/FiO_2< 300)
Acute oliguria (urine output < 0.5 mL kg^{-1} h^{-1} for at least 2 hours despite fluid resuscitation)
Creatinine increase > 0.5 mg dL^{-1} or 44.2 µmol L^{-1}
Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count < 100,000 μL^{-1})
Hyperbilirubinemia (plasma total bilirubin > 4 mg dL^{-1} or 70 µmol L^{-1})
Tissue perfusion variables
Hyperlactatemia (> 1 mmol L^{-1})
Decreased capillary refill or mottling

SD standard deviation, WBC = white blood cell; SBP = systolic blood pressure; MAP = mean arterial pressure; INR = international normalized ratio; aPTT = activated partial thromboplastin time

Ethical approval

Local Ethics Committee Approval for this study was obtained from Çanakkale Onsekiz Mart University Clinical Research Ethics Committee (Decision no: 2014-25, decision date: 24.12.2014).

Statistical analysis

The data were analyzed using the IBM SPSS version 19.0 (SPSS Inc., Chicago, IL, USA) statistical analysis program within Çanakkale Onsekiz Mart University. Patient data were presented as mean and standard deviation for age and APACHE II, while sex and initial diagnosis were presented as percentage and frequency (%). Sclerostin, DKK-1, WBC, and CRP values obtained were presented as means and standard deviation. In the statistical evaluation, the basal day values of the control and study groups were compared first, and the independent sample t-test was used for the comparison between the groups. Secondly, within-group values of the study group were compared, and paired samples t-test was used for statistical comparison of within-group values. Finally, the correlation of sclerostin and DKK-1 with changes in infection markers, WBC, and CRP was assessed. First, the differences between basal-7^{th} day, 7^{th}-14^{th} day, and 14^{th}-21^{st} day of all four markers were calculated. The calculated differences were then compared with the Spearman correlation test. The results were transferred to tables and graphs.

Results

A total of 37 patients were included in the study group, but three who started steroid treatment and four who died during follow-up were excluded. Sixteen patients were included in the control group. Age, sex, initial diagnosis, and APACHE scores of the patients are shown in Table 2.

Table 2. Patients demographic data

Property		Study group	Control group	p-value
Sex	Male	18 (60%)	9 (56%)	*0.03*
	Female	12 (40%)	7 (44%)	*0.012*
Age		63.0±15.7	69.1±8.9	0.122
APACHE II Score		19±7	13.9±5.4	*0.004*
Primary diagnosis	Cardiac diseases	13 (43.3%)	4 (25%)	*0.001*
	COPD	8 (26.7%)	7 (44%)	0.638
	Traumatic injuries	4 (13.3%)	0	*<0.001*
	Cerebrovascular disease	2 (6.7%)	3 (19%)	0.559
	Other	3 (10%)	2 (12%)	0.403

APACHE II: Acute Physiology and Chronic Health Evaluation II, COPD: Chronic Obstructive Pulmonary Disease, Data are presented as mean±standard deviations. In statistical analyses, the Mann-Whitney U test was used.

Laboratory test results

Table 3 shows the mean±standard deviations of sclerostin, DKK-1, WBC, and CRP taken from the patients at basal, 7th, 14th, and 21st days and compared with the control group. When basal sclerostin and DKK-1 values measured on the day of SIRS diagnosis of the control group and the study group were compared, both values were significantly higher in SIRS patients. An intra-group comparison was made in the study group, and there was a significant decrease in the reduction at days 7, 14, and 21 when compared with the baseline sclerostin values. There was no significant difference between the 7th-14th day, 7th-21st day, and 14th-21st day (Figure 1). When the DKK-1 values were compared with the baseline, the decrease on the 7th and 21st days was significant, while the decrease on the 14th was insignificant. Additionally, while the change on the 7th-14th day was insignificant, there was a significant difference between the 7th-21st and the 14th-21st (Figure 2). When the change in WBC values over time was examined, all comparisons were significant except for the 14th-21st days. All CRP values were significant except for the 7th-21st and 14th-21st day comparisons.

Table 3. Laboratory tests results of sclerostin, DKK-1, WBC, and CRP levels

		Sclerostin (pg mL^{-1})	DKK-1 (pg mL^{-1})	WBC (count x10^3)	CRP (µg mL^{-1})
Control group		422±85	1.960±807	14.1±6.1	40.2±29
Study group	**Basal**	538±116	2.358±587	17.4±4.3	54.4±41
	Day 7	473±72	1.967±466	15.2±4.2	120.6±67.7
	Day 14	450±87	2.172±641	13.1±3.7	151.6±82.7
	Day 21	449±67	1.675±276	15.7±3.8	136.5±74.5
p 1 (control – basal)		[1]0.003	[1]0.001	[1]0.023	[1]0.001
p 2 (basal – 7th day)		[2]0.033	[2]0.015	[2]0.001	[2]0.001
p 3 (basal – 14th day)		[2]0.003	[2]0.191	[2]0.001	[2]0.001
p 4 (basal – 21st day)		[2]0.002	[2]0.001	[2]0.001	[2]0.001
p 5 (7th – 14th day)		[2]0.343	[2]0.258	[2]0.001	[2]0.009
p 6 (7th– 21st day)		[2]0.185	[2]0.001	[2]0.007	[2]0.363
p 7 (14th– 21st day)		[2]0.975	[2]0.002	[2]0.210	[2]0.412

WBC: White Blood Cell, CRP: C-Reactive Protein. Data are described as mean±standard deviations. p1: comparisons between the control group and study group basal measurements, p2: comparisons between the control group and study group 7th day measurements, p3: comparisons between the control group and study group 14th day measurements, p4: comparisons between the control group and study group 21st day measurements, p5: comparisons between the 7th and 21st day measurements of the study group, p6: comparisons between the 7th and 21stdaymeasurements of the study group, p7: comparisons between the 14th and 21st day measurements of the study group. [1]: Independent Sample t-test, [2]: Paired samples t-test

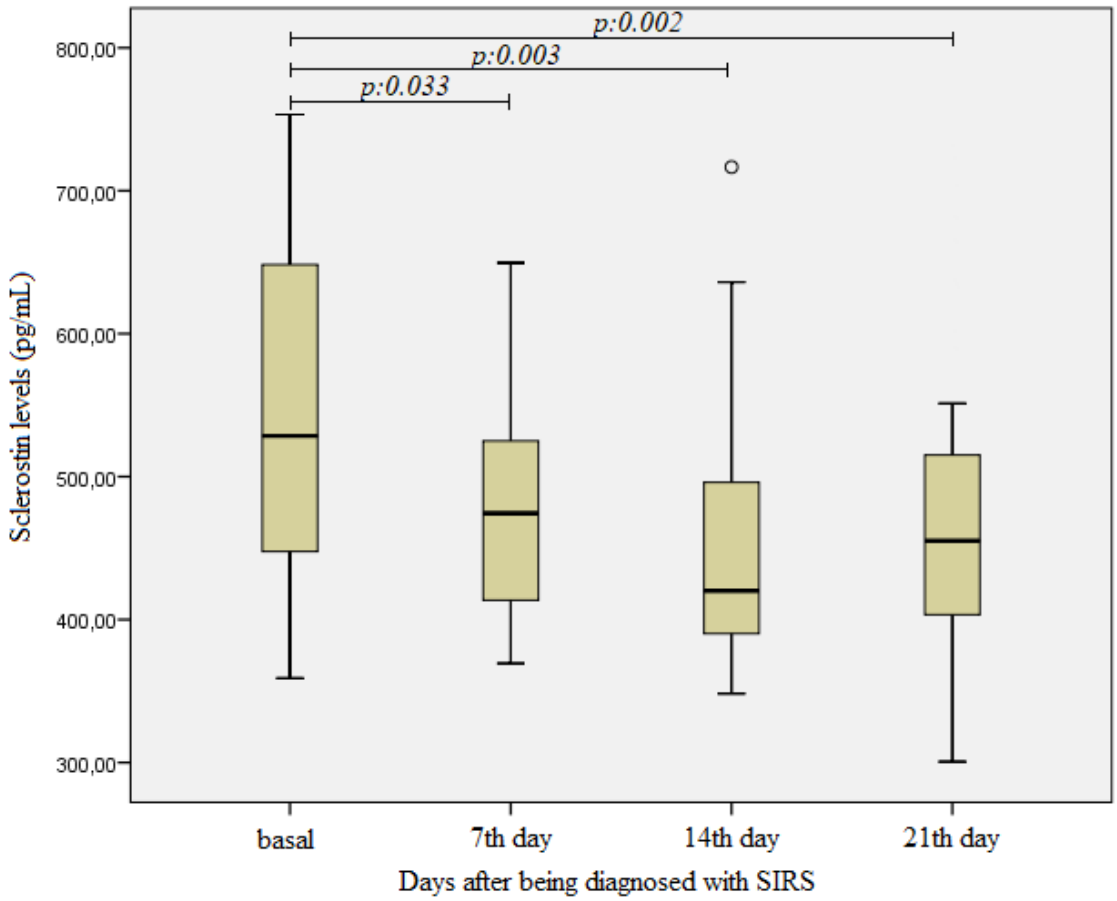

Figure 1. Change within days of sclerostin levels in the study (SIRS) group. Paired samples t-test was used for statistical comparison of study group values.

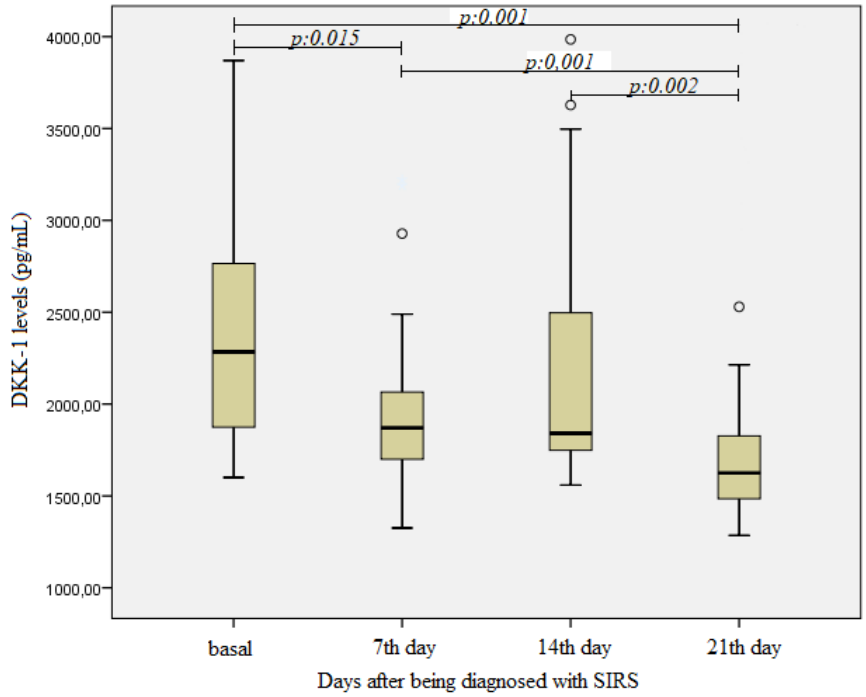

Figure 2. Change within days of DKK-1 levels in the study (SIRS) group. Paired samples t-test was used for statistical comparison of study group values.

Correlation between laboratory test results

The correlation of changes in the infection markers of sclerostin and DKK-1, WBC and CRP, over days is shown in Figure 3 and Table 4. When the graphical changes in Figure 3 and the statistical results are examined, it is seen that there is a positive correlation between sclerostin and WBC values only between basal-7th day, and there is no correlation between sclerostin and CRP. While there was a positive correlation between DKK-1 and WBC values only on the basal-7th day, there was a negative correlation between DKK-1 and CRP on the basal-7th day.

Table 4. Correlation of "calculated differences between basal-7th days, 7th-14th days, 14th-21st days" between sclerostin, DKK-1, WBC, and CRP values in the study group (SIRS patients)

	basal-7th day		7th-14th day		14th-21st day	
	r value	**p-value**	**r value**	**p-value**	**r value**	**p-value**
Sclerostin-WBC	[1]*0.402**	[2]*0.029*	[1]0.093	[2]0.626	[1]0.071	[2]0.709
Sclerostin-CRP	[1]0.133	[2]0.484	[1]0.113	[2]0.554	[1]0.101	[2]0.594
DKK-1-WBC	[1]*0.440**	[2]*0.010*	[1]0.199	[2]0.293	[1]0.120	[2]0.528
DKK-1-CRP	-[1]*0.402**	[2]*0.028*	[1]0.211	[2]0.264	[1]0.111	[2]0.559

[1]: Pearson's correlation coefficient, [2]: Paired samples t-test, *: Positive correlation

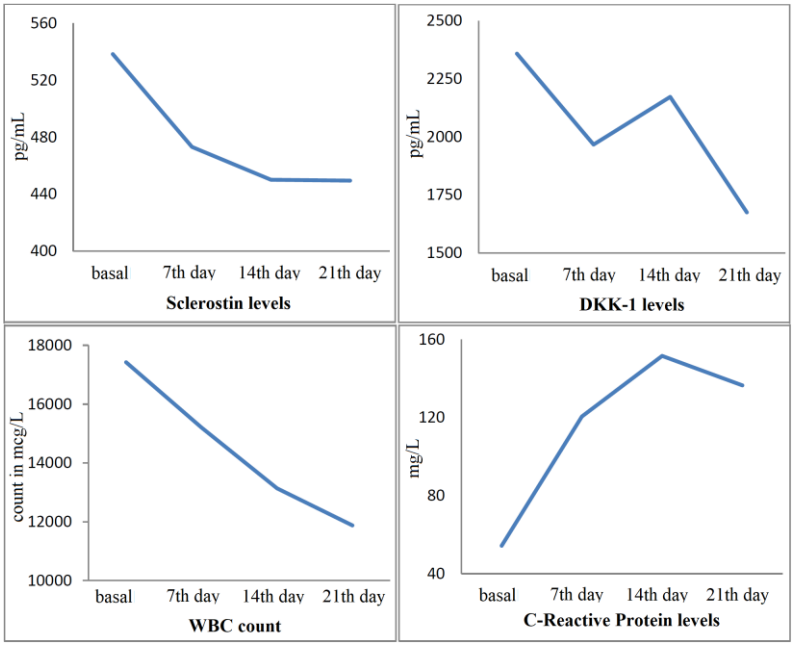

Figure 3: Graphical display of the change within days of mean values of sclerostin, DKK-1, WBC, and CRP values in the study group (SIRS patients)

Discussion

In our study, when patients with and without SIRS were compared, both sclerostin and DKK-1 values were higher in those diagnosed with SIRS. Serum sclerostin and DKK-1 levels were measured on admission to the intensive care unit (basal) and on the 7th, 14th, and 21st days following the patients diagnosed with SIRS. There was a progressive decrease in sclerostin values on days 7, 14, and 21 when compared with the baseline. Again, although DKK-1 values decreased, this decrease was significant on the 7th and 21st days (p=0.015 and p=0.001, respectively) and insignificant on the 14th day (p=0.191) when compared with the baseline value.

As the duration of intensive care unit immobilization increased, an elevation in the levels of both biomarkers was expected, but different results were obtained in our study. Although the stay was prolonged, sclerostin and DKK-1 levels decreased over time. This is likely to be related to the level of infection.

When the relationship of sclerostin and DKK-1 levels with infection is evaluated in the literature, it is seen that chronic infections/metabolic diseases are mostly emphasized. However, the results obtained are different from each other. Serum sclerostin levels were significantly reduced in HIV-infected patients compared to healthy controls. It has been suggested that untreated HIV and/or systemic inflammation may be a major regulator of serum sclerostin [19]. Different results were obtained in HCV, another viral disease. González-Reimers et al. [20] reported that serum sclerostin levels were higher in HCV patients than in healthy subjects. Again, HIV-positive patients had significantly higher serum DKK-1 levels [21]. While Pietrzyk et al. reported that increased circulating sclerostin levels reflect slower bone turnover in patients with chronic renal failure receiving dialysis [22], Neto et al. reported that patients with grade 3-4 renal failure who were not yet on dialysis had higher sclerostin and lower DKK1 levels [23]. In children with sickle cell anemia, chronic inflammation has been shown to correlate with elevated DKK-1 levels but not with sclerostin [24]. On the other hand, a recent study published in 2022 stated that DKK-1 levels decreased in chronic obstructive pulmonary disease (COPD) patients and showed a positive correlation with lung function [25]. These different results obtained in sclerostin and DKK-1 levels in the presence of chronic infection may be related to the fact that the Wnt pathway is affected by many factors, not only infection but also cancer. For example, DKK-1 has been suggested to be involved in the pathogenesis of osteoarthritis, metabolic bone disease (osteoporosis and Paget's disease), multiple myeloma-associated bone disease, and prostate cancer bone metastases [26].

Few studies show the relationship between acute infections and Wnt antagonists. However, a recent study in 2018 reported strikingly high levels of DKK-1 in the blood of children with acute infections compared to healthy blood donors [27]. The results obtained in our study suggest that sclerostin and DKK-1 levels were high on the first day of the diagnosis of SIRS due to severe infection and decreased in parallel with the regression of the infection after treatment.

Another issue is the relationship between changes in inflammation marker levels and serum sclerostin and DKK-1 levels. Our study found a positive correlation between serum sclerostin/DKK-1 levels and WBC levels only in a certain time interval (both sclerostin and DKK-1 and WBC were significantly positive at basal-7th days). On the other hand, while CRP values increased compared to baseline, sclerostin and DKK-1 levels tended to decrease (we did not detect any correlation between sclerostin and CRP, DKK-1 and CRP were negatively correlated at basal-7th days). We interpreted these results as "the change in sclerostin and DKK-1 levels did not show a clear correlation with the change in inflammatory markers". In the studies of Mazon et al., one of the rare studies on this subject, there was no relationship between DKK-1 levels measured in acute infections and CRP, platelet, or white blood cell counts [26]. Therefore, although our study and the study of Mazon et al. showed sclerostin and DKK-1 levels increasing in acute infections, it is obvious that it would not be correct to associate it with inflammatory marker levels such as CRP and WBC. Patients followed in intensive care units have more than one disease, and many treatments are applied. Their effects on the levels of Wnt antagonists are not yet clear. For example, Castrillón et al. say that atorvastatin reduces DKK-1 levels [28]. In the light of all this information, it can be concluded that the levels of Wnt antagonists are affected in acute infection in clinical practice, but it does not reflect the change in inflammatory marker levels. However, the relationship between other inflammatory markers and Wnt antagonists has not yet been studied. More extensive studies are needed on this subject.

Limitations

The drugs used, age, and chronic diseases of the patients could not be standardized. Sclerostin and DKK-1 values may be affected due to additional diseases. The control group was not healthy individuals, and changes in Wnt inhibitors could not be calculated depending on the characteristics of the patients. In the control group, sclerostin and DKK-1 measurements were made only on the first day.

Conclusion

In this study, it was shown for the first time that the levels of sclerostin and DKK-1, which are Wnt antagonists, were high in SIRS patients followed up in the intensive care unit and decreased over time in parallel with the treatment. We believe monitoring Wnt antagonist levels will be useful in demonstrating bone turnover in patients with SIRS. However, it could not be associated with the change in inflammatory marker levels. The results are unclear due to our limited data, risk factors for additional diseases, and uncertainties. In future studies, it would be beneficial to include control patient groups in which changes in Wnt antagonist levels due to long-term immobilization were also measured. Different infection markers can be examined by studying their correlations with sclerostin and DKK-1 levels. In addition, studies are needed to standardize comorbidities and treatments that affect bone turnover, such as steroids.

Conflict of interest: The authors declared no potential conflicts of interest concerning this article's research, authorship, and/or publication.

Author Contributions		Author Initials
SCD	Study Conception and Design	HBA, UA, MA
AD	Acquisition of Data	HBA, UA
AID	Analysis and Interpretation of Data	HBA, UA, MA
DM	Drafting of Manuscript	HBA
CR	Critical Revision	HBA, MA

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