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ORIGINAL ARTICLE – OPEN ACCESS

The Association Between Refeeding Hypophosphatemia and Serum Appetite-Regulating Hormone Levels in Critically Ill Patients: A Prospective, Observational, Single-Center Pilot Study

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ABSTRACT

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Objective: Refeeding hypophosphatemia (RH) is common in critically ill patients and is associated with high morbidity and mortality, but the influence on appetite-regulating hormones is unknown. This study aimed to determine the association between serum levels of phosphorus and specific appetite-regulating hormones in critically ill patients.

Materials and Methods: This study was performed prospectively in patients admitted to the intensive care unit (ICU). The study included patients aged ≥18 years who were admitted to the ICU and feeding at least 72 hours (h). Serum was obtained at baseline, 24 h, and 72 h later for concentrations of leptin, adiponectin, ghrelin, resistin, insulin-like growth factor 1 (IGF-1), and glucagon-like peptide 1 (GLP-1). Phosphorus levels were accepted at ≤2.4 mg/dL for RH.

Results: Of the 26 cases, 17 (65%) were male. The baseline phosphorus levels at baseline, 24 h, and 72 h were 3.58±0.94 mg/dL, 2.61±1.05 mg/dL, and 2.91±0.76 mg/dL, respectively. RH rate was developed 24 h, 72 h, and over time in 38%, 15%, and 42% patients, respectively. Adiponectin levels at 24 h were significantly different between patients who developed RH and those who did not develop RH. A positive correlation was observed between 24 h serum adiponectin level and 24 h phosphorus level. A positive correlation was found between baseline serum ghrelin level and baseline phosphorus level. No significant difference was found between RH and insulin, leptin, ghrelin, resistin, IGF-1, and GLP-1 at baseline, 24 h, and 72 h.

Conclusion: RH was found to be of high ratio in critically ill patients. Adiponectin level was found to be high at 24 h in patients with RH.

Keywords: Refeeding hypophosphatemia, appetite-regulating hormones, enteral nutrition, parenteral nutrition, critically ill patients

INTRODUCTION

Refeeding hypophosphatemia (RH) occurs after the reintroduction of feeding after a period of fasting is a potentially lethal condition. It is characterized by metabolic and biochemical changings (1). The predominant biochemical feature of refeeding syndrome is hypophosphatemia, and abnormal sodium and fluid balance may also be observed–changes in magnesium, potassium, glucose, protein, and fat metabolism (2). This is an important condition in critically ill patients undergoing refeeding whether orally, enterally, or parenterally after a period of starvation or fasting (3). Starvation and obesity cause some characteristic changes in appetite hormones; for example, leptin levels can drop in starvation and leptin can increase, and ghrelin can drop in obesity (4). This study hypothesized that increased catabolic hormones perhaps contributed to the frequency of hypophosphatemia. No study has explored the relationship between adipocytokine hormones and RH. This study aimed to investigate the relationship between appetite-regulating hormone levels and RH.

MATERIALS and METHODS

This study was performed prospectively in patients admitted to the medical and surgical ICU.

Inclusion Criteria

The inclusion criteria in this study included patients aged 18 years or older, needed ICU for at least 72 h, and received enteral and parenteral nutrition.

Exclusion Criteria

Patients were excluded from the study if they had the following: hypophosphatemia (≤2.4 mg/dl) at the beginning of the feeding, chronic renal impairment, diabetic ketoacidosis, hyperparathyroidism, gastric by-pass surgery, chronic liver disease, and disease of the bile ducts (except the operation for cholecystectomy).

Patient's demographic data, reason for ICU admission, Acute Physiology and Chronic Health Evaluation (APACHE-II) (5) and Sequential Organ Failure Assessment (SOFA) scores (6), Charlson Comorbidity Index score (7), Nutrition Risk Screening-2002 (NRS-2002) (8), type of feeding, length of hospital and ICU stay, amount of energy given within the first 3 ICU days, content of nutrition, electrolyte (Na, K, P, Ca, Mg) levels, and mortality rate were recorded, as well as initiation time, type of feeding route, and preparation of feeding started according to ESPEN guidelines (9).

Blood sampled from study patients for serum leptin, ghrelin, resistin, GLP-1, IGF-1, and adiponectin levels were recorded at baseline, 24 h, and 72 h. The association between serum appetite-regulating hormone levels and serum phosphorus levels before feeding and 24 h and 72 h after feeding were analyzed. The patients were divided into two groups: the RH group (whose serum phosphorus levels dropped to ≤2.4 mg/dl after refeeding) and the no-RH group (whose serum phosphorus levels were >2.4 mg/dl) (10, 11). Patients were given Pulmocare®, Multifiber plus®, Impact glutamine®, Diason®, and Nutrena® for EN and Oligo Clinomel, Kabiven periferal, and Compounder TPN for PN.

Methods of Study of Hormones and Kits

- **Leptin:** Diasorce® trademark kit processed using ELISA
- **Ghrelin:** Phoenix® trademark kit processed using enzyme immunoassay
- **Resistin:** eBiovance® trademark kit processed using ELISA
- **Adiponectin:** Biovendor® trademark processed using ELISA
- **GLP-1:** Ray-Bio® kit® processed using enzyme immunoassay
- **IGF-1:** Ray-Bio® kit® processed using enzyme immunoassay
- **Insulin:** Processed using electrochemiluminescence immunoassay (ECLIA) Cobas e700.

Venous blood was collected into serum tubes. After separation, the serum was aliquoted into Eppendorf tubes. Trypsinogen inhibitory aprotinin was used to keep these hormones containing protein, and they were kept in a –80 °C freezer until use.

Statistical Analysis

Basic statistical analyses were performed using SPSS 22.0. Continuous variables with normal distribution are presented as mean±SD. Statistical analysis for the parametric variables was performed using the Student t test between the two groups. The Mann–Whitney U test was used to compare nonparametric variables between the two groups. The relationship between categorical variables was investigated using the chi-square test and Student's t test. P-value <0.05 was accepted as statistically significant. The relationship between serum phosphorus levels and the levels of appetite-regulating hormones was analyzed using Spearman correlation analysis.

RESULTS

The patients' clinical and demographic characteristics were shown in Table 1. This study included 26 patients (17 men and 9 women), with a mean age of 63±18 years. The mean age of the RH developed group was 56±17 years, and the group that did not develop RH was 66±19 years, and no significant difference was found (p=0.201). RH developed in three men (37%) and five (63%) women. The patient's mean APACHE II score was 20±7 and SOFA score 7±3 when admitted at the ICU. No significant difference was found between the SOFA and the groups in whom RH developed and those who did not develop RH (p=0.156).

Of the patients, 13 (50%) were fed enterally, and the remaining 13 (50%), parenterally. Of the enterally fed patients, three had gastric residue and one was to have a tracheostomy operation, so feeding was interrupted for these patients. The time to start feeding was 40 (10–60) h in the RH developed group, while it was 24 (8–76) h in the group that did not develop RH (p=0.041).

The most common reasons for ICU were malignancy, neurological disorders, and sepsis. The ICU mortality rate was 39%, and no significant difference was found between the RH developed group and the not RH developed group in the ICU mortality rate (p=0.069).

The baseline, 24 h, and 72 h phosphorus levels were 3.58±0.94 mg/dL, 2.61±1.05 mg/dL, and 2.91±0.76 mg/dL, respectively. The phosphorus levels have been demonstrated in the RH developed group and the group that did not develop RH (Fig. 1).

RH rate was developed 24 h, 72 h, and over time in 10 (38%), 4 (15%), and 11 (42%) patients, respectively (Fig. 2).

The amount of nutrient energy, energy content, electrolytes, and blood parameters was evaluated. The amount of baseline, 24 h, and 72 h energy was 1195±298 kcal, 1533±406 kcal, and 1427±510 kcal, respectively. The RH developed group was similar to the group that did not develop RH at baseline, 24 h, and 72 h for energy.

Serum adiponectin levels at 24 h in the group that did not develop RH were significantly higher than in the developed group (p=0.003), and a positive correlation was observed with the phosphorus level. The association between serum appetite-regulating hormone levels and RH in critically ill patients is shown in detail in Figure 3.

No statistically significant difference was found between the RH developed group and the group that did not develop RH for serum leptin, ghrelin, resistin, GLP-1, and IGF-1 levels at baseline, 24 h, and 72 h. Baseline, 24 h, and 72 h serum appetite-regulating hormone levels in critically ill patients are shown in detail in Figure 3.

The correlation between serum appetite-regulating hormone levels and baseline, 24 h, and 72 h phosphorus levels was analyzed. A positive correlation was found between baseline serum ghrelin levels and baseline phosphorus levels (r=0.652, p<0.001). A positive correlation was observed between 24 h serum adiponectin level and 24 h phosphorus level (r=0.673, p<0.001) (Table 2).

DISCUSSION

This pilot study investigates the relationship between refeeding hypophosphatemia and appetite-regulating hormones in the ICU.

Critically ill patients have a higher incidence of RH because of the presence of multiple causal factors (3). The incidence of refeeding

Table 1. Patients' demographic and clinical characteristics

Variables	Total (n=26)	RH developed (n=11)	RH did not develop (n=15)	p
Age (years) ±SD	63±18	58±17	66±19	0.201
Gender, n (%)				
Male	17 (65)	5 (46)	12 (80)	0.063
Female	9 (35)	6 (54)	3 (20)	
APACHE II ±SD	20±7	21±6	20±7	0.608
SOFA (min.–max.)	3 (0–9)	2 (0–6)	4 (0–9)	0.156
Charlson Comorbidity Index (min.–max.)	3 (0–8)	3 (0–8)	3 (0–7)	0.807
Type of feeding route, n (%)				
Enteral	13 (50)	5 (55)	8 (53)	0.664
Parenteral	13 (50)	6 (45)	7 (47)	
Reason for ICU admission, n (%)				
Malignancy	9 (35)	4 (36)	5 (33)	
Sepsis	5 (19)	1 (9)	4 (27)	
Neurological disorders	5 (19)	3 (28)	2 (13)	
Trauma	3 (11)	1 (9)	2 (13)	
Intoxication	2 (8)	1 (9)	1 (7)	
Respiratory failure	1 (4)	0	1 (7)	
Gastrointestinal bleeding	1 (4)	1 (9)	0	
Length of ICU stay, day (min.–max.)	12 (2–90)	10 (2–90)	14 (2–55)	0.405
Beginning of feeding time (hours) (min.–max.)	24 (8–76)	40 (10–60)	24 (8–76)	**0.041**
NRS-2002 score ±SD	4±0.86	4±0.83	4±0.90	0.686
ICU mortality, n (%)	10 (39)	2 (20)	8 (80)	0.069

SD: Standard deviation; Min: Minimum; Max: Maximum; RH: Refeeding hypophospatemia; APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; NRS-2002: Nutrition Risk Screening-*2002*; ICU: Intensive care unit

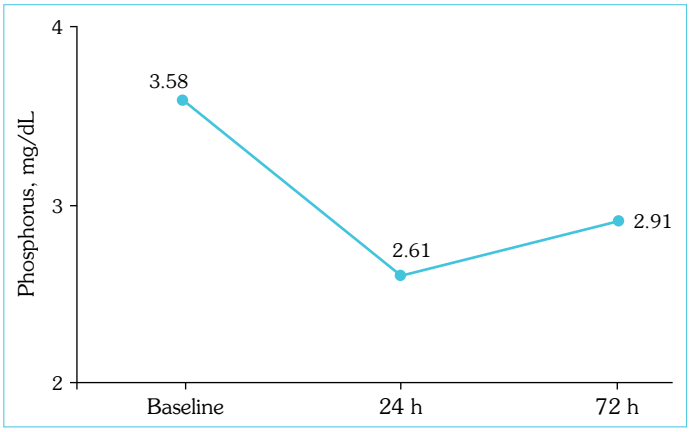

Figure 1. Phosphorus levels of RH developed group and the group that did not develop RH

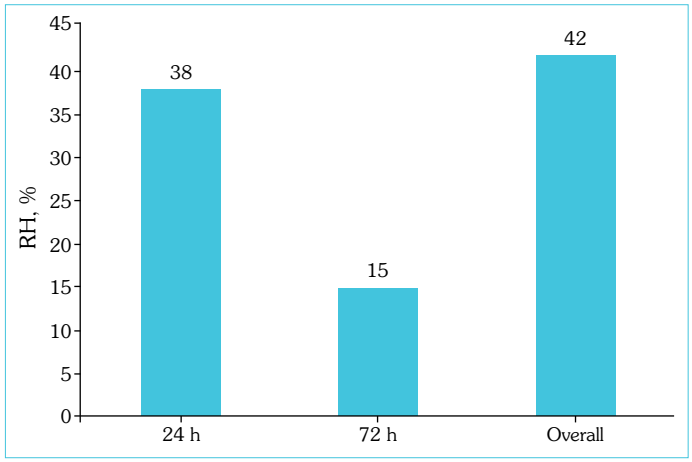

Figure 2. RH rate at 24 h, 72 h, and overall

syndrome (RS) depends on patient population. Olthof et al. (10) performed a retrospective study of caloric intake on outcome during the management of RS. Of 337 enrolled patients, 124 (36.8%) developed RS. Similarly, in our study, RS was found to be 31%.

Similar energy consumption is observed in both groups. When evaluated for RH, the time to start feeding may be effective as a risk factor. The risk of developing RH increases with the feeding of patients who were undernourished for a long time (12). In a retrospective study, the time to start feeding was found to be high in RH developed group (10). Similarly, it was found to be significantly higher in our study.

Numerous hormones play a role in regulating food intake and energy balance. These hormones secreted by adipose tissue are known

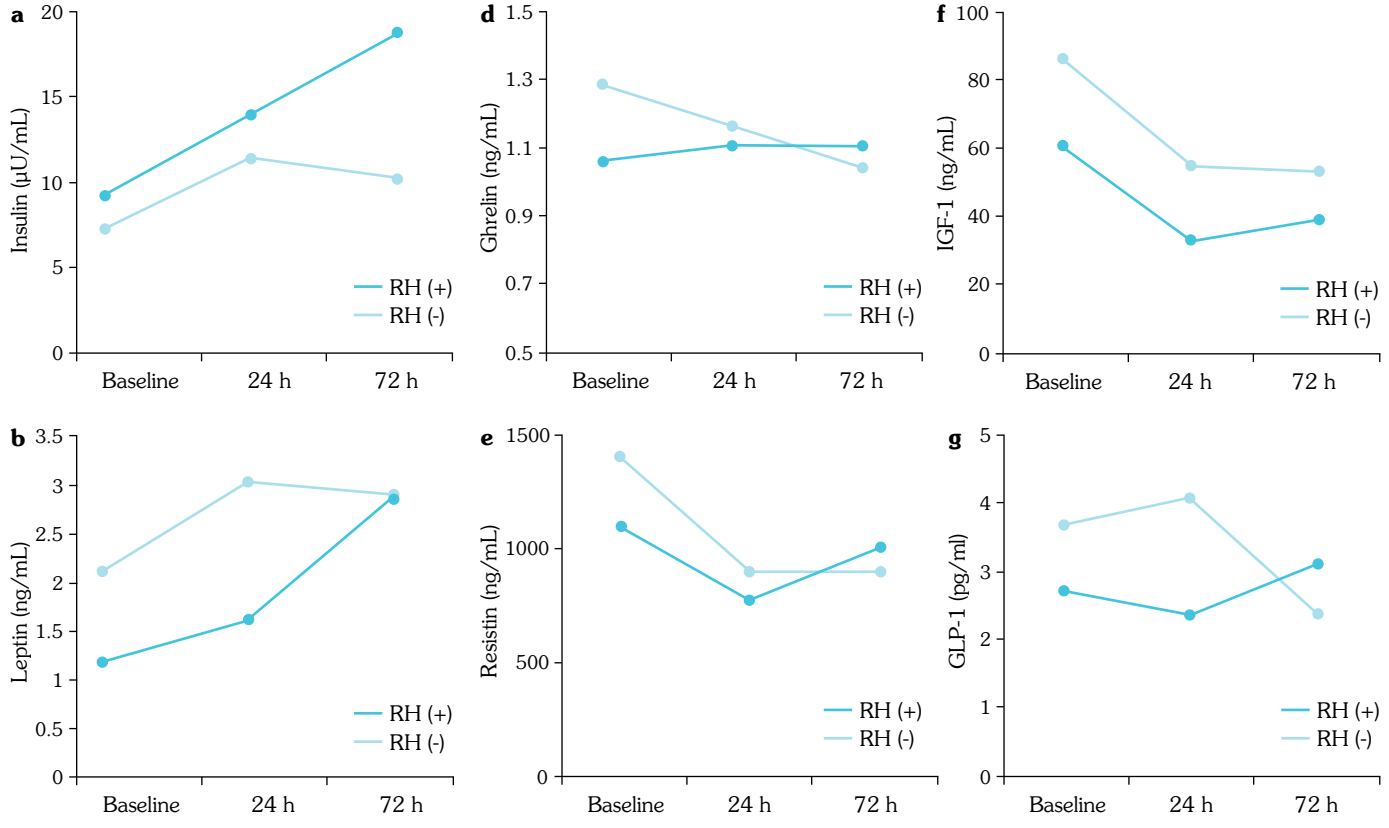

Figure 3. **For RH developed patients, the following results were determined at baseline, 24 h, and 72 h, respectively: insulin (a) (µU/mL, range), 12.13 (2.52–110.80), 15.19 (5.23–35.61), 14.53 (3.53–102.60); leptin (b) (ng/ml, range), 1.55 (0.001–15.27), 2.22 (0.001–30.09), and 2.34 (0.02–18.02); adiponectin (c) (ng/ml, range or ±SD), 33.78±15.25, 2515.62 (9.63–46.06), and 24.21 (3.33–62.00); ghrelin (d) (ng/ml, range), 1.085 (0.72–1.68), 1.093 (0.90–2.48), and 1.077 (0.55–1.34); resistin (e) (ng/ml, range), 1126.06 (518.03–4196.90), 943.67 (305.85–2070.78), and 920.69 (255.24–019.78); IGF-1v(f) (ng/ml, range), 63.60 (25–214), 33.70 (25–156), and 45.10(25–72.70); and GLP-1v(g) (pg/ml, range or ±SD), 2.33±1.99, 2.21 (0.20–5.06), and 2.28 (0.15–197.59)**

For patients that did not develop RH, the following were determined at baseline, 24h, and 72h, respectively: insulin (a) (µU/mL) (range), 6.12 (1.60–29.52), 10.35 (3.18–60.90), and 10.73 (2.45–448.1); leptin (b) (ng/ml, range), 2.03 (0.24–47.25), 3.04 (0.55–22.22), and 3.20 (0.48–38.02); adiponectin (c) (ng/ml, range or ±SD), 29.00±15.29, 25.85 (17.79–62.01), and 28.55 (11.89–69.08); ghrelin (d) (ng/ml, range), 1.230 (0.58–3.66), 1.216 (0.58–2.75), and 1.061 (0.58–2.42); resistin (e) (ng/ml, range), 1373.25 (190.55–4196.90), 771.43 (106.90–4196.90), and 942.72 (55.06–4196.90); IGF-1 (f) (ng/ml, range), 85.10 (25–138), 51 (25–113), and 50.90 (25–114); and GLP-1 (g) (pg/ml, range or ±SD), 3.35±2.88, 4.98 (0.18–38.56), and 2.50 (0.14–47.92)

as adipokines. The amount in the circulation is affected by the decrease in adipose tissue after prolonged fasting. Adipokines are thought to have potential functions in critically ill patients. Ghrelin was found to improve tissue perfusion in severe sepsis, and resistin has proinflammatory properties. Therefore, adipokine levels are important during critical illness (13).

No reliable measurement was found to predict RS. Leptin, ghrelin, and insulin growth factor-1 (IGF1) are potential biomarkers (14).

In one study, phosphate concentration decreased by 30% 12–36 h after parenteral nutrition therapy was initiated. In this condition, it is thought to be associated with increased leptin and increased IGF-1 (15).

Current studies showed that serum leptin levels were low in critically ill patients. Leptin is effective in glucose balance, immune factor, growth, and development. It is involved in the pathogenesis of hypertension, atherosclerosis, and cancer. While it is high at the beginning of the critical illness, it decreases afterwards. This suggests that it may play a role in the pathogenesis and/or outcome of the critical disease (16). In our study, serum baseline leptin levels were low and increased with refeeding. Also, serum leptin levels were lower, but nonsignificant, in the RH developed group than in the group that did not develop RH.

A study conducted in the ICU found a relationship between decreased ghrelin levels and gastrointestinal dysfunction (16). In our study, ghrelin levels tended to decrease in the group that did not develop RH.

Table 2. Correlation analysis between serum appetite-regulating hormones and phosphorus levels over time

	Phosphorus Baseline		Phosphorus 24 h		Phosphorus 72 h	
	r	p	r	p	r	p
Insulin						
Baseline	0.090	0.660				
24 h			-0.106	0.607		
72 h					0.159	0.439
Leptin						
Baseline	0.140	0.494				
24 h			0.343	0.087		
72 h					-0.042	0.837
Ghrelin						
Baseline	**0.652**	**<0.001**				
24 h			0.287	0.156		
72 h					-0.048	0.816
Adiponectin						
Baseline	-0.293	0.147				
24 h			**0.673***	**<0.001**		
72 h					-0.103	0.617
IGF-1						
Baseline	-0.062	0.763				
24 h			0.171	0.404		
72 h					0.301	0.135
GLP-1						
Baseline	0.157	0.445				
24 h			0.337	0.092		
72 h					-0.310	0.124
Resistin						
Baseline	-0.092	0.654				
24 h			0.056	0.787		
72 h					0.086	0.678

A positive correlation was found between baseline serum ghrelin levels and baseline phosphorus levels. A positive correlation was observed between 24 h serum adiponectin level and 24 h phosphorus level. IGF-1: Insulin-like growth factor 1; GLP-1: Glucagon-like peptide 1; h: Hours

Adiponectin is an adipokine that is involved in glucose and lipid metabolism and is associated with insulin resistance and secreted by adipocytes. Compared to healthy individuals, adiponectin levels in the circulation are decreased in obese and diabetes mellitus patients. In a study conducted in the ICU, adiponectin levels decreased significantly on the 3rd and 7th day compared to healthy individuals (17). This study demonstrated higher serum adiponectin levels before refeeding and a decrease after refeeding.

IGF1 is one of the indicators of nutrition state. Therefore, low fasting serum IGF1 levels were expected; however, serum IGF1 was increased in refeeding. In 24 h after refeeding, the patients' developed RH was lower. It is thought that the nutritional state of the patients who developed RH was worse. Serum IGF-1 is less affected by inflammation in malnutrition. IGF-1 levels decrease more than 4 times in the hunger state, and its concentration increases with nutrition (18).

In a study conducted in the ICU, resistin levels in critically ill patients were found to be higher than in healthy controls (15). It was found higher in septic patients compared to non-septic patients. It correlated with the severity of the disease (13). In our study, resistin level tended to decrease at 24 h in both groups and was higher in the group with RH at 72 h. This condition may be related to severe clinical illnesses including RH.

In RS, protein and fat metabolism begins to turn to carbohydrate metabolism. This causes an increase in insulin secretion, causing glucose, and electrolytes to enter the cell. It causes dangerously low circulating electrolytes. RS shows clinical signs and symptoms

including multi-organ dysfunction (3). In our study, insulin level was found to be high in the group with RH at all times.

GLP-1 increases insulin synthesis, suppresses glucagon synthesis, inhibits gastric emptying, and plays a role in glucose homeostasis by reducing appetite. Loss of glucose homeostasis as a result of injury stress response and ongoing proinflammation is common in critically ill patients. In a study conducted in the ICU, GLP-1 level increased six times in critically ill patients compared to those in healthy individuals. Both chronic and acute inflammatory conditions, including sepsis, was concluded to increase circulating GLP-1 levels (19, 20). GLP-1 level tended to decrease in patients who did not develop RH, while it tended to increase in patients who developed RH.

This study has several limitations which included the following: the small patient populations, the heterogeneity of patients, and the single-center study. Mortality was high in the group that did not develop RH, but this may be due to high APACHE-II and SOFA scores.

In conclusion, adiponectin levels at 24 h in the group that did not develop RH were demonstrated to be significantly higher than those in the RH developed group in critically ill patients. The RH was found to be of high ratio in critically ill patients. A positive correlation was found between baseline serum ghrelin levels and baseline phosphorus levels.

This is a pilot study. Since there were no laboratory markers other than phosphorus value that could recognize RS, this study aimed to find alternative biomarkers. The number of patients was small; hence, generalizing the study with larger populations is recommended.

Ethics Committee Approval: The Erciyes University Clinical Reseach Ethics Committee granted approval for this study (date: 05.03.2013, number: 2013/195).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – ED, KG, MG, MS; Design – ED, KG, MG, MS; Supervision – MG, MS, KG, SM; Materials – ED, SM; Data Collection and/or Processing – ED, KG; Analysis and/or Interpretation – ED, KG, ŞT, NTÖ, SŞ, GGŞ; Literature Search – ED, KG, ŞT, NTÖ, SŞ, GGŞ; Writing – ED, KG, ŞT, NTÖ, SŞ, GGŞ; Critical Reviews – MS, MG, KG, ŞT.

Conflict of Interest: The authors have no conflict of interest to declare.

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