TJEM TURKISH JOURNAL OF ENDOCRINOLOGY AND METABOLISM

ORIGINAL ARTICLE
Turk J Endocrinol Metab. 2022;26(2):67-72

The Association Between Somatostatin Receptor Ligand and Vitamin B12 in Patients with Acromegaly

ABSTRACT

Objective: Vitamin B12 deficiency causes hematologic and neuropsychiatric disorders, thus it is important to evaluate it in risky situations. In this study, we aimed to evaluate the association between somatostatin receptor ligands and vitamin B12 in patients with acromegaly.

Methods: Patients who were followed up with the diagnosis of acromegaly in the Endocrinology and Metabolism outpatient clinic of Cerrahpaşa Medical Faculty were evaluated. Patients were divided into groups according to their somatostatin receptor ligand use status. The groups were evaluated according to their vitamin B12 levels, demographic data, and biochemical parameters.

Results: One hundred fifty-two patients were evaluated. Thirteen patients had vitamin B12 deficiency. The majority (11/13) of patients with vitamin B12 deficiency were using somatostatin receptor ligands. In addition, the number of patients with vitamin B12 deficiency who received lanreotide autogel treatment was significantly higher compared with patients who did not use somatostatin receptor ligands ($P = .011$). Vitamin B12 levels were higher in patients who received lanreotide autogel treatment than in patients who did not use SRL treatment ($P = .040$). There was a negative correlation between vitamin B12 levels and lanreotide autogel use time and the cumulative lanreotide autogel dose.

Conclusion: It is important to evaluate vitamin B12 levels in the follow-up of patients with acromegaly receiving somatostatin receptor ligand therapy because these patients have lower levels of vitamin B12 compared with patients who do not use somatostatin receptor ligand therapy.

Keywords: Acromegaly, lanreotide autogel, octreotide LAR, vitamin B12

Serdar Şahin[1]
Tuğçe Eşkazan[2]
Ebru Çiçek[3]
Yeliz Yağız Özoğul[3]
Emre Durcan[1]
Cem Sulu[1]
Hande Mefküre Özkaya[1]
Ali İbrahim Hatemi[2]
Pınar Kadıoğlu[1]

[1]*Division of Endocrinology, Metabolism and Diabetes, Department of Internal Medicine, Cerrahpaşa Faculty of Medicine, İstanbul University Cerrahpaşa, İstanbul, Turkey*
[2]*Division of Gastroenterology, Department of Internal Medicine, Cerrahpaşa Faculty of Medicine, İstanbul University Cerrahpaşa, İstanbul, Turkey*
[3]*Department of Internal Medicine, Cerrahpaşa Faculty of Medicine, İstanbul University Cerrahpaşa, İstanbul, Turkey*

Corresponding author:
Pınar Kadıoğlu
✉ kadioglup@yahoo.com

Received: December 5, 2021
Accepted: April 10, 2022

Cite this article as: Şahin S, Eşkazan T, Yağız Özoğul Y, et al. The association between somatostatin receptor ligand and vitamin B12 in patients with acromegaly. *Turk J Endocrinol Metab*. 2022;26(2):67-72.

DOI: 10.5152/tjem.2022.22030

Introduction

Acromegaly is a chronic disease caused by excessive growth hormone (GH) secretion and consequently increased levels of insulin-like growth factor I (IGF-I).[1] In most cases, acromegaly is caused by a pituitary adenoma, which causes somatotroph cell-derived GH and IGF-1 hypersecretion.[2] Hypersecretion of GH causes high levels of IGF-1, leading to somatic overgrowth, multiple comorbidities, mortality, and physical disfigurement.[1] Morbidity and mortality in patients with acromegaly are mostly due to tumor compression, the elevation of GH/IGF-1, and secondary effects of treatment.[3,4] Mortality is 2-fold higher in patients with acromegaly due to the presence of diabetes, hypertension, cardiovascular, cerebrovascular, respiratory disorders, and malignancy.[5-7]

The primary treatment in patients with acromegaly is surgery, and the transsphenoidal route is generally preferred.[1] Biochemical control rates after surgery range from 32% to 85% in patients with acromegaly.[8] Medical treatment is recommended for patients who cannot be controlled after surgery and surgery is not appropriate. Among the medical treatments, somatostatin receptor ligands (SRLs) (octreotide, lanreotide, and pasireotide), cabergoline, pegvisomant, and combination therapies are included.[9] Among the medical treatments, first-generation SRLs [lanreotide autogel and octreotide long-acting release (LAR)] are recommended first.[9] Common adverse effects of first-generation SRLs include abdominal cramps, flatulence, and diarrhea. In addition, local skin irritation, pain at the injection site, and hair loss are among the rarer adverse effects.[1]

Vitamin B12 (Vit B12) is essential for DNA synthesis and neurologic functions. Active and passive mechanisms play a role in the absorption of Vit B12. When supraphysiologic amounts of Vit B12 reach the small intestine, it is directly absorbed passively from the jejunum and ileum. Gastric intrinsic factor (IF) is required for the activation mechanism, and the absorption of the physiologic amounts of Vit B12 in foods occurs in this way.[10] Vitamin B12 deficiency can

Copyright: Copyright @ Author(s) – Available online at https://www.turkjem.org/
This journal is licensed under a Creative Commons (CC BY-NC-SA) 4.0 International License.

lead to hematologic and neuropsychiatric disorders.[10] One of the rare adverse effects of SRL is Vit B12 deficiency.[11] Therefore, Vit B12 deficiency may be important in patients with acromegaly using SRLs. However, there are insufficient data on this subject in the literature. In this study, we aimed to evaluate the association between SRLs and Vit B12 deficiency in patients with acromegaly.

Material and Methods

The medical records of patients with acromegaly who were followed by the Endocrinology and Metabolism outpatient clinic of İstanbul University Cerrahpaşa, Cerrahpaşa Medical Faculty, were retrospectively reviewed. Patients who were diagnosed as having acromegaly and whose Vit B12 levels were evaluated were examined. Patients whose Vit B12 levels were not evaluated; those with a lack of regular follow-ups; patients with a diagnosis of chronic pancreatitis, atrophic gastritis, malabsorption, and inflammatory bowel disease; patients who did not use somatostatin therapy regularly; and those with a history of gastrointestinal surgery were excluded from the study. Patients with histologic confirmation through endoscopic biopsy were considered to have atrophic gastritis. Upper gastrointestinal endoscopy was performed on patients for reasons such as anemia, weight loss, reflux symptoms, and medical treatment-resistant dyspepsia, dysphagia, and persistent vomiting.

All parameters of the patients were analyzed according to the period in which Vit B12 levels were evaluated. Patients' age, sex, Vit B12 level, Vit B12 deficiency status, alcohol consumption, smoking status, proton pump inhibitor (PPI) use, metformin use, use of cabergoline and pegvisomant, total disease duration, GH, IGF-1, insulin-like growth factor-1-upper limit of normal (IGF-1-ULN) values, biochemical control status, hemoglobin, hematocrit, mean corpuscular volume (MCV), white blood cell (WBC), platelet count, and abdominal imaging were retrospectively analyzed. Octreotide LAR, lanreotide autogel cumulative dose and mean dose every 28 days, and treatment durations were calculated. We calculated the cumulative SRL average dose by multiplying the dose used by the time used.

Patients with IGF-1 values within the normal range according to age and sex and random GH values less than 1.0 g/L were accepted as having controlled disease activity.[1] In discordant cases, patients with no deterioration in clinical and laboratory parameters and patients with IGF-1 values repeatedly in the normal range in the follow-up period were accepted as having controlled disease activity. The levels of GH and IGF-1 were measured in the same laboratory (supplementary material). Vitamin B12 levels less than 180 pg/mL were accepted as a deficiency. Vitamin B12 was assayed using an electrochemilum inescence immunoassay on a Roche Cobas e601 system (Roche, Cobas e 601, Roche Diagnostics GmbH, Mannheim, Germany).

The patients were divided into 2 groups according to the use of SRLs: patients using SRLs and those not using SRLs. The 2 groups were compared according to age, sex, alcohol, and smoking status, Vit B12 levels, Vit B12 deficiency, biochemical parameters, biochemical control status, and PPI, metformin, cabergoline, and pegvisomant use. Also, patients were divided into 3 groups according to the use of SRLs. Group A consisted of patients who did not use SRLs, group B comprised patients using octreotide LAR, and group C constituted patients using lanreotide autogel. These 3 groups were compared in terms of age, sex, alcohol, and smoking status, Vit B12 levels, Vit B12 deficiency, biochemical parameters, biochemical control status, and PPI, metformin, cabergoline, and pegvisomant use.

This study was approved by the Local Ethics Committee of Cerrahpaşa Faculty of Medicine. The study adhered to the tenets of the Declaration of Helsinki.

Statistical Analysis

The Statistical Package for the Social Sciences version 22.0 software (IBM Corp.; Armonk, NY, USA) was used. The distribution of variables was evaluated using the Kolmogorov–Smirnov test. In normally distributed variables, continuous data are given as means ± standard deviation (SD), in non-normally distributed variables, continuous data are given as median (IQR) and categorical data are given as numbers and percentages. In the comparisons of 2 groups, the Mann–Whitney *U* test was performed in the analysis of quantitative, non-normally distributed, and independent data. The independent samples *t*-test was used in the analysis of quantitative, normally distributed, and independent data. In the comparison of 3 groups, for the analysis of quantitative independent data, we used analysis of variance (ANOVA) for data with normal distribution, and in post hoc analysis, we performed the Bonferroni test. We used the Kruskal–Wallis test for data with non-normal distribution, and the Mann–Whitney *U* test for the analysis of quantitative independent data. Bonferroni correction was then performed to account for errors due to the multiple comparisons among groups A, B, and C. The chi-square test, and, if chi-square conditions were not met, Fisher's test was performed in the analysis of qualitative independent data. Statistically significant results were considered as $P < 0.05$. The confidence level was set at 95%.

Results

In our study, 160 patients with acromegaly were assessed. Three patients were excluded due to atrophic gastritis, one due to terminal ileum resection, and 4 due to irregular SRL treatment use. One hundred fifty-two patients with acromegaly were evaluated, 71 (46%) of whom were male and 81 (54%) were female. All data were evaluated according to the period in which the patients were assessed for Vit B12. The mean age of the patients was 45.3 ± 11.8 years, and the mean age at the time of diagnosis was 41.1 ± 12.0 years. The median duration of the disease was 32.5 [range, 16.0-54.7] months. The median Vit B12 level was 289.5 [range, 242.0-374.0] pg/mL; 13 (8.5%) patients had Vit B12 deficiency. Fifty-nine (38.8%) patients were not using SRLs, and 93 (61.2%) patients were using SRLs. Of the patients using SRLs, 59 (38.8%) were using octreotide LAR and 34 (22.4%) were using lanreotide autogel. The cumulative octreotide LAR dose was 990.0 [range, 365.0-1990.0] mg, and the median octreotide LAR dose was 25.0 [range, 20.0-30.0] mg/28 days. The cumulative lanreotide autogel dose was 2400.0 [range, 1064.9-3757.2] mg, and the median lanreotide autogel dose was 101.5 [range, 90.0-114.0] mg/28 days. The median [IQR] hemoglobin, hematocrit, MCV, WBC, and platelet count values were 13.0 [range, 12.0-14.0] g/dL, 39.0% [range, 36.1-41.0], 85.0 [range, 82.0-87.2] fL, 6800 [range, 5800-8300] µL, and 249,000 [range, 200,000-292,000] µL, respectively. The alcohol consumption and smoking data of 111 patients were obtained. Seven (6%) patients consumed alcohol, and 36 (32%) patients smoked. One (7%) of 13 patients with Vit B12 deficiency smoked, none of them consumed alcohol. None of the patients with Vit B12 deficiency had vegan or vegetarian eating styles.

Anemia was present in 53 (34.9%) patients. Of these, 15 (28.3%) were microcytic and 38 (71.7%) were normocytic; there was no macrocytic anemia. Eight (61.5%) of 13 patients with Vit B12 deficiency had anemia. Four (50%) of these patients had microcytic anemia and

4 (50%) had normocytic anemia. None of the patients had macrocytic anemia. Thirty-three (21.7%) patients were using cabergoline, 3 (2.0%) were using pegvisomant, 11 (7.2%) were using PPIs, and 27 (17.8%) patients were using metformin. One (7%) of 13 patients with Vit B12 deficiency was using PPIs; none were using metformin. Abdominal imaging was present in 102 (67.1%) patients. Of these patients, 97 (63.8%) had abdominal ultrasonography, 3 (2%) had abdominal magnetic resonance imaging, and 2 (1.3%) had abdominal computed tomography imaging. No patients had any findings of pancreatitis. Fifty-three patients had upper gastrointestinal system endoscopy. None of these patients had any findings of atrophic gastritis. Of the 13 patients with Vit B12 deficiency, 7 (53%) had abdominal imaging, and none had signs of pancreatitis. Upper gastrointestinal endoscopy and endoscopic biopsy were performed in all patients with Vit B12 deficiency. Only 1 patient underwent antrum biopsy, the others had both antrum and corpus biopsies. Atrophic gastritis was not detected in any patients with Vit B12 deficiency. General features of patients with Vit B12 deficiency are presented in Table 1.

The Comparison of SRL Treatment (+) vs. SRL Treatment (−)

No significant difference was found among the groups in terms of sex and age. There was no significant difference between the groups in terms of alcohol consumption and smoking. Vit B12 deficiency was present in 11 (11.8%) patients in the SRL treatment (+) group and 2 (3.4%) patients in the SRL treatment (−) group, which was not statistically significantly different. In addition, the median Vit B12 level was 288.0 [range, 223.0-373.0] pg/mL in the SRL treatment (+) group and 297.0 [range, 246.0-375.0] pg/mL in the SRL treatment (−) group; the difference was not statistically significant. Hemoglobin and hematocrit values were significantly lower in the SRL treatment (+) groups. However, no significant difference was found in terms of the presence of anemia. There was no statistical significance between the groups in terms of MCV levels. In terms of disease duration, the median value was 40.0 [range, 23.5-70.0] months in the SRL treatment (+) group and 23.0 [range, 12.0-37.0] months in the SRL treatment (−) group, which was statistically significantly different ($P < .001$). There was no difference between the groups in terms of GH, IGF-1, IGF-1-ULN, and disease control. No significance was found between the groups in terms of the use of PPIs, metformin, and pegvisomant, whereas the use of cabergoline was significantly higher in the group using SRLs ($P < .001$).

In the correlation analysis, a negative correlation was found between Vit B12 levels and the duration of SRL use ($P = .$, $r = -0.232$). However, no correlation was found between Vit B12 levels and age, and total disease duration.

The Comparison of Groups A (SRL Treatment −), B (Octreotide LAR +), and C (Lanreotide Autogel +)

There was no statistically significant difference between the groups in terms of sex and age. Disease duration was found to be significantly shorter in group A (SRL treatment −) compared with group B (octreotide LAR +) ($P < .001$). There was no significant difference between the groups in terms of alcohol consumption and smoking. In terms of Vit B12 deficiency, the number of patients with Vit B12 deficiency was found to be significantly higher in group C (lanreotide autogel +) than in group A (SRL treatment −) ($P = .011$). Although there was no statistically significant difference, the number of patients with Vit B12 deficiency was higher in group C (lanreotide autogel +) than in group B (octreotide LAR +). When analyzed in terms of Vit B12 levels between the groups, Vit B12 levels were found to be significantly lower in patients using lanreotide autogel (group C) than in patients not using SRL treatment (group A) ($P = .040$). There was no significant difference between the groups in terms of anemia and MCV. Although there was a significant difference in terms of hemoglobin and hematocrit ($P = .050$ and $P = .039$, respectively), the statistical significance disappeared in pairwise comparisons. There was no significant difference between the groups in terms of pegvisomant, PPI, and metformin use. However, the use of cabergoline was found to be significantly lower in group B than in the other groups ($P < .001$ and $P < .001$, respectively). There was no significant difference between the groups in terms of GH, IGF-1, IGF-1-ULN, and disease control. The comparisons of groups A, B, and C are presented in Table 2.

In the correlation analysis, a negative correlation was found between Vit B12 levels and cumulative lanreotide autogel dose ($P = .048$, $r = -0.342$), the duration of lanreotide autogel use ($P = .035$, $r = -0.363$) in group C (lanreotide autogel). However, no correlation was found between Vit B12 levels and age, total disease duration, and dose (mg/28 days). In group B, there was no significant correlation between Vit B12 levels and these parameters (Table 3).

Discussion

Studies are reporting low levels of Vit B12 in patients with acromegaly receiving somatostatin analogs treatment, but there are no robust studies in the literature on this issue. In an early study conducted by Plockinger et al. 10 patients with acromegaly treated with subcutaneous octreotide were prospectively evaluated. In patients with normal Vit B12 levels at the initiation of octreotide treatment, Vit B12 levels decreased over time.[12] In another study on octreotide LAR treatment, this situation could not be demonstrated.[13] In our study, Vit B12 levels were found to be significantly lower in patients who received SRL (octreotide LAR + lanreotide autogel) therapy compared with patients who did not receive SRL therapy. Although we do not know the Vit B12 level before SRL treatment, the difference between the groups in terms of Vit B12 levels may have reduced the effect of SRL treatment on Vit B12 levels. Although our study has a retrospective design, it may be important because it evaluates 3 treatment groups simultaneously in patients with acromegaly. However, this issue may be clearer with larger and prospective studies.

There are no studies evaluating Vit B12 levels in patients with acromegaly who received lanreotide autogel treatment or did not receive SRL treatment. Therefore, it is not known whether the effect of lanreotide autogel and octreotide LAR treatment on vitamin B12 levels is different. However, in our previous study, we reported that the adverse effects of octreotide LAR and lanreotide autogel treatments on the upper gastrointestinal system were different.[14] In our study, we found a significant decrease in Vit B12 in patients who received lanreotide autogel treatment, but we did not see the same difference in patients who received octreotide LAR treatment. However, because our study was a retrospective design, it may be difficult to obtain a clear result. Prospective studies can shed light on this issue.

The mechanism by which somatostatin analogs cause Vit B12 deficiency is also unclear because there has not been much research on this issue. There are 2 opinions on this subject. First, somatostatin analogs can directly inhibit the release of IF, leading to Vit B12 deficiency.[12] The other view is that somatostatin analogs may cause Vit

Table 1. The General Characteristics of Patients with Vitamin B12 Deficiency

Patients number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Sex	Male	Male	Male	Female	Female	Female	Male	Male	Male	Female	Male	Male	Female
Age (years)	28	33	62	41	29	37	42	47	52	26	61	42	52
Treatment	Lanreotide autogel	Lanreotide autogel	Octreotide LAR	Octreotide LAR	Octreotide LAR	Lanreotide autogel	Octreotide LAR	Lanreotide autogel	None	Lanreotide autogel	Lanreotide autogel	Lanreotide autogel	None
Duration of treatment (months)	6	21	36	29	30	6	68	27	-	35	41	57	
B12 level (pg/mL)	131	177	138	168	160	140	175	179	133	171	130	128	166
Smoking	No	Yes	No	No	No	No	No	No	No	No	No	No	No
PPI	No	No	Yes	No	No	No	No	No	No	No	No	No	No
Endoscopy	Normal	Pangastritis	Normal	Antral gastritis	Normal	Normal	Normal	Normal	Antral gastritis	Pangastritis	Pangastritis	Pangastritis	Pangastritis
Endoscopic biopsy	Antrum: Mild, active, chronic gastritis *H. pylori* +	Antrum: Moderate, active, chronic gastritis *H. pylori* +	Antrum: Mild, active, chronic gastritis *H. pylori* –	Antrum: Moderate, active, chronic gastritis *H. pylori* +	Antrum: Mild, inactive, chronic gastritis *H. pylori* –	Antrum: Moderate, active, chronic gastritis *H. pylori* +	Antrum: Inactive, chronic gastritis *H. pylori* –	Antrum: Mild, active, chronic gastritis *H. pylori* +	Antrum: Inactive, chronic gastritis *H. pylori* –	Antrum: Mild, active, chronic gastritis *H. pylori* –	Antrum: Mild, active, chronic gastritis *H. pylori* +	Antrum: Mild, active, chronic gastritis *H. pylori* –	Antrum: Mild, active, chronic gastritis *H. pylori* +
	Corpus: Mild, active, chronic gastritis *H. pylori* +	Corpus: Mild, active, chronic gastritis *H. pylori* –	Corpus: Not evaluated	Corpus: Mild, active, chronic gastritis *H. pylori* +	Corpus: Mild, inactive, chronic gastritis *H. pylori* –	Corpus: Moderate, active, chronic gastritis *H. pylori* +	Corpus: Inactive, chronic gastritis *H. pylori* –	Corpus: Mild, active, chronic gastritis *H. pylori* +	Corpus: Inactive, chronic gastritis *H. pylori* –	Corpus: Mild, active, chronic gastritis *H. pylori* –	Corpus: Mild, active, chronic gastritis *H. pylori* +	Corpus: Mild, active, chronic gastritis *H. pylori* –	Corpus: Mild, active, chronic gastritis *H. pylori* +

PPI, proton pump inhibitors; *H. pylori, Helicobacter pylori*.

Table 2. The Comparison of Groups A, B, and C

	Group A (n = 59)	Group B (n = 59)	Group C (n = 34)	*P*
Sex F (%)/M (%)	30 (50.8)/29 (49.2)	35 (59.3)/24 (40.7)	16 (47.1)/18 (52.9)	NS
Age means ± SD (year)	45.8 ± 12.1	46.0 ± 10.4	41.9 ± 13.3	NS
Alcohol use (n [%])	2 (4.5)	2 (4.9)	3 (11.5)	NS
Smoking (n [%])	14 (31.8)	10 (24.4)	12 (46.2)	NS
The disease duration (month)	23.0 [12.0-37.0]	42.0 [24.0-115.0][a]	37.0 [17.0-47.7]	**<.001**
The duration of SRL use (month)	-	31.0 [15.5-75.0]	23.5 [11.0-36.5]	**.047**
B12 level median (IQR) (pg/mL)	297.0 [246.0-375.0][b]	290.0 [228.0-375.0]	268.0 [194.0-329.0]	NS
B12 deficiency (n [%])	2 (3.4)	4 (6.8)	7 (20.6)[c]	**.014**
Hemoglobin median (IQR) (g/dL)[d]	13.5 [12.6-14.4]	12.9 [11.9-13.7]	13.0 [11.9-14.0]	**.050**
Hematocrit median (IQR) (%)[e]	39.8 [37.2-42.9]	38.6 [35.4-40.2]	38.2 [35.8-41.0]	**.039**
MCV median (IQR)(fL)	85.0 [82.0-88.0]	84.6 [82.0-87.1]	84.0 [82.1-87.0]	NS
PPI use (n [%])	2 (3.4)	7 (11.9)	2 (5.9)	NS
Metformin use (n [%])	8 (13.6)	15 (25.4)	4 (11.8)	NS

[a]Group B vs Group A ($P < .001$).
[b]There was no statistically significant difference among the groups, but a significant difference was found between group A and group C in pairwise comparisons ($P = .040$).
[c]Group C vs Group A ($P = .011$).
[d,e]There was a significant difference in terms of hematocrit ($P = .048$) among the groups, but the significance disappeared in pairwise comparisons.
F, female; M, male; SRL, somatostatin receptor ligand; MCV, mean corpuscular volume; PPI, proton pump inhibitor; NS, not significant; IQR, interquartile range.

B12 deficiency by preventing acid secretion from gastrin-secreting cells, creating hypochlorhydria.[12,15] We cannot comment on this subject because our study is retrospective, but this issue needs large and prospective studies.

Vit B12 deficiency causes megaloblastic anemia by disrupting DNA synthesis. In addition to anemia, it can cause a decrease in all blood cells (pancytopenia).[16] In our study, none of the patients with Vit B12 deficiency had macrocytic anemia or pancytopenia. There was no difference between the groups in terms of MCV. There is little information on this subject in the literature. In the study by Plockinger et al[12] although Vit B12 deficiency was observed in patients receiving octreotide treatment, no hematologic change was detected in any patients.

Table 3. Correlation Analyses in Group B and Group C

Group B (octreotide LAR +) (n = 59)	B12 Level
The mean octreotide LAR dose (mg/28 days)	$P = .934$ $r = -0.011$
The cumulative octreotide LAR dose (mg)	$P = .140$ $r = -0.205$
The duration of octreotide LAR use	$P = .106$ $r = -0.224$
Age	$P = .460$ $r = 0.098$
The total disease duration	$P = .229$ $r = -0.159$
Group C (lanreotide autogel +) (n = 34)	
The mean lanreotide autogel dose (mg/28 days)	$P = .880$ $r = 0.027$
The cumulative lanreotide autogel dose (mg)	**$P = .048$** **$r = -0.342$**
The duration of lanreotide autogel use	**$P = .035$** **$r = -0.363$**
Age	$P = .804$ $r = 0.044$
The total disease duration	$P = .028$ $r = -0.376$

LAR, long-acting release.

There are several limitations to our study. The IF levels of the patients could not be evaluated because of our study's retrospective design, and Vit B12 levels before SRL treatment were unknown. The course of Vit B12 could not be evaluated in patients receiving SRL treatment. In addition, neurologic examinations of patients with Vit B12 deficiency could not be performed. However, this is the first study to evaluate lanreotide autogel treatment and evaluate 3 groups of patients who received octreotide LAR treatment, lanreotide autogel treatment, and no SRL treatment.

In conclusion, Vit B12 levels were found to be lower in patients who received SRL treatment than in patients who did not receive SRL treatment. Therefore, it is important to evaluate Vit B12 levels in the follow-up of patients with acromegaly receiving SRL treatment. The absence of atrophic gastritis in patients with Vit B12 deficiency suggests that SRL treatment causes Vit B12 deficiency by another mechanism. In addition, the effect of octreotide LAR and lanreotide autogel treatment on Vit B12 levels may be different. Therefore, prospective and larger studies are necessary on this issue.

Ethics Committee Approval: This study was approved by the Local Ethics Committee of Cerrahpaşa Faculty of Medicine (approval number: 142289).

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – P.K., H.M.Ö., S.Ş.; Design – P.K., H.M.Ö., S.Ş.; Supervision – P.K., H.M.Ö., A.İ.H.; Data Collection and/or Processing – S.Ş., T.E., E.Ç., Y.Y.Ö., E.D., C.S.; Analysis and/or Interpretation – P.K., H.M.Ö., S.Ş., A.İ.H.; Literature Search – P.K., H.M.Ö., S.Ş.; Writing Manuscript – S.Ş., P.K.; Critical Review – P.K., H.M.Ö., S.Ş.

Declaration of Interests: The authors declare that they have no conflict of interest.

Funding: This study received no funding.

References

1. Katznelson L, Laws ER, Melmed S, et al. Acromegaly: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;99(11):3933-3951. [CrossRef]
2. Melmed S. Acromegaly pathogenesis and treatment. *J Clin Invest*. 2009;119(11):3189-3202. [CrossRef]
3. Colao A, Ferone D, Marzullo P, Lombardi G. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. *Endocr Rev*. 2004;25(1):102-152. [CrossRef]
4. Melmed S, Casanueva FF, Klibanski A, et al. A consensus on the diagnosis and treatment of acromegaly complications. *Pituitary*. 2013;16(3):294-302. [CrossRef]
5. Holdaway IM, Bolland MJ, Gamble GD. A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. *Eur J Endocrinol*. 2008;159(2):89-95. [CrossRef]
6. Dekkers OM, Biermasz NR, Pereira AM, Romijn JA, Vandenbroucke JP. Mortality in acromegaly: a meta-analysis. *J Clin Endocrinol Metab*. 2008;93(1):61-67. [CrossRef]
7. Sughrue ME, Chang EF, Gabriel RA, Aghi MK, Blevins LS. Excess mortality for patients with residual disease following resection of pituitary adenomas. *Pituitary*. 2011;14(3):276-283. [CrossRef]
8. Agrawal N, Ioachimescu AG. Prognostic factors of biochemical remission after transsphenoidal surgery for acromegaly: a structured review. *Pituitary*. 2020;23(5):582-594. [CrossRef]
9. Melmed S, Bronstein MD, Chanson P, et al. A Consensus Statement on acromegaly therapeutic outcomes. *Nat Rev Endocrinol*. 2018;14(9):552-561. [CrossRef]
10. Oh RC, Brown DL. Vitamin B12 deficiency. *Am Fam Physician*. 2003;67(5):979-986.
11. Consortium SM. Use of somatostatin analogues in adult patients with acromegaly shared care guidelines. 2011:1-16.
12. Plöckinger U, Dienemann D, Quabbe HJ. Gastrointestinal side-effects of octreotide during long-term treatment of acromegaly. *J Clin Endocrinol Metab*. 1990;71(6):1658-1662. [CrossRef]
13. Fløgstad AK, Halse J, Bakke S, et al. Sandostatin LAR in acromegalic patients: long-term treatment. *J Clin Endocrinol Metab*. 1997;82(1):23-28. [CrossRef]
14. Sahin S, Icli TB, Durcan E, et al. The effect of somatostatin analogs and acromegaly on the upper gastrointestinal system. *Pituitary*. 2021;24(2):184-191. [CrossRef]
15. Krejs GJ. Physiological role of somatostatin in the digestive tract: gastric acid secretion, intestinal absorption, and motility. *Scand J Gastroenterol Suppl*. 1986;119:47-53. [CrossRef]
16. Green R, Allen LH, Bjørke-Monsen AL, et al. Vitamin B12 deficiency. *Nat Rev Dis Primers*. 2017;3(3):17040. [CrossRef]