History of Medicine, 2023, 9(1): 1600–1608
DOI: 10.17720/2409-5834.v9.1.2023.198

A History of Long-Term Proton Pump Inhibitors Reduces the Serum Calcium and Magnesium Levels Irrespective of Parathyroid Hormone

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Received: 20 January 2023 **Accepted:** 15 April 2023

Citation: M. Ali N, Mahmood HG, Alosami MH (2023) A History of Long-Term Proton Pump Inhibitors Reduces the Serum Calcium and Magnesium Levels Irrespective of Parathyroid Hormone. History of Medicine 9(1): 1600–1608. https://doi.org/10.17720/2409-5834.v9.1.2023.198

Abstract

Proton pump inhibitors (PPIs) are drugs used o reduce the stomach acidity caused by the treatment with anti-inflammatory drugs in some rheumatoid arthritis (RA) patients. The effect of these drugs on the parathyroid hormones (PTH) and related electrolytes (calcium, magnesium, and phosphate is not studied yet. The present study aims to accomplish this goal by measurements of the mentioned serum parameters in 70 RA patients treated with PPIs (PPI group) and comparing their results with 70 not treated with PPIs (No PPI group). The results showed a significant increase in serum calcium and magnesium levels in the PPI group compared with the No-PPI group. While no significant difference in the PTH level between groups. The severe RA group showed a significant increase in WBCs counts compared with the mild-moderate RA group indicating the role of inflammation as an indicator of severity. Serum calcium showed a significant correlation with the duration of the disease and a negative correlation with the disease activity. Serum intact-PTH has a significant correlation with serum inorganic phosphate, and inversely with serum calcium. Serum calcium has an inverse correlation with the ESR value. The results showed a significant correlation between calcium and hemoglobin. Receiver operating characteristic (ROC) for differentiation between severe and mild RF indicates that the increase in serum PTH level to a value higher than the cut-off value (55.50 pg/ml), indicates significantly that the patients may have a severe RA form in a sensitivity of 60.9% and specificity of 61.7%.

Keywords

Rheumatoid Arthritis, Parathyroid Hormone, Calcium, Magnesium, Severity.

Rheumatoid arthritis (RA) is a debilitating condition that affects millions of people worldwide. Both the frequency and incidence of RA, when adjusted for age, have increased worldwide since 1990. (Safiri et al., 2019). Joint pain, swelling, stiffness, and loss of function are all symptoms of RA, a chronic autoimmune inflammatory disease. Progressive disability, systemic problems, and even premature death have all been linked to RA (Kim & Suh, 2020). The joints are the primary targets of RA, a systemic inflammatory disease. The most common inflammatory joint disease, it causes cartilage and bone breakdown, which can lead to functional decline and disability if ignored. Degeneration of cartilage and joints, as well as functional impairment, are the results (Yap et al., 2018). Disability from RA is common and has negative effects on quality of life, ability to contribute to society, prognosis for the future, and economic losses (Hsieh et al., 2020). Genetic (Lin et al., 2020)

and environmental variables, such as smoking (Takeno et al., 2018) and obesity (Lin et al., 2020), are both thought to play a role in the etiology of RA (Dar et al., 2018). Women are two to three times more likely than males to get RA, which is one of the most common autoimmune disorders affecting 1-2% of the global population (Smolen et al., 2016). Fatigue, flu-like symptoms, swollen and sore joints, and morning stiffness are some of the more common early-stage RA symptoms, and these are accompanied by raised levels of C-reactive protein (CRP) and an elevated erythrocyte sedimentation rate (ESR) (Brzustewicz, E. et al., 2017a). Limitations in activity and a lower quality of life are a direct effect of RA's most prominent symptoms, which include pain, exhaustion, and physical impairment (Scott et al., 2010). Fatigue, flu-like symptoms, swollen and painful joints, morning stiffness, elevated CRP readings, and an elevated ESR are only some of the symptoms of RA (Brzustewicz, Edyta et al., 2017b). Symptoms, physical exam findings, risk factor analysis, family history, laboratory marker assessment (including increased CRP and ESR in blood, and identification of RA-specific autoantibodies), and joint ultrasound sonography are all used in conjunction to arrive at a definitive diagnosis of RA (Aletaha, Daniel & Smolen, 2018). In order to prevent further joint destruction, disability, and systemic indications of RA, the overarching treatment goal for patients with RA is to achieve full remission or at least dramatically lower disease activity within a span of around 6 months following diagnosis (Aletaha, Daniel & Smolen, 2018). Inhibition of prostanoid production is the primary mechanism by which NSAIDs exert their anti-inflammatory effects (Brune & Patrignani, 2015). The inflammation caused by RA disease is typically treated with non-steroidal anti-inflammatory medicines (NSAIDs), which are competitive COX inhibitors with varying degrees of selectivity for COX-1 and COX-2 (Crofford, 2013; Jahnavi et al., 2019). (Akgul et al., 2018). Slowing bone loss due to RA is a common goal of treatment, and disease-modifying antirheumatic medications (DMARDs) are generally acknowledged as a means to this end (Fautrel et al., 2018; Kцhler et al., 2019). Medication classes known as proton pump inhibitors (PPIs) include some of the most widely used drugs in the world (Levy et al., 2020). Prescription proton pump inhibitors are among the top 10 most prescribed drugs in the world (Targownik et al., 2007). utilized for a number of conditions involving stomach acid, including GERD, peptic ulcers, and non-ulcer dyspepsia (Freedberg et al., 2017). While proton pump inhibitors (PPIs) play an indispensable role in clinical practice, their long-term usage has been related to a number of health issues, such as chronic kidney disease, bone fractures, dementia, and vitamin and mineral shortages (Nehra et al., 2018). Recent research has shown that PPIs have a significant effect on the gut microbiome, perhaps as a result of suppressing stomach acid in the lower gastrointestinal tract (Naito et al., 2018). Although there is some mechanistic evidence linking long-term PPI usage to RA via intestinal dysbiosis, there is still a lack of definitive epidemiological evidence. A positive connection was discovered between PPI use and RA risk in a previous study's falsification studies (Jena et al., 2013). Women who used PPIs frequently had a greater chance of developing RA, and this risk increased with the length of time that PPIs were used. Large prospective trials are still needed to corroborate our findings because this study was an observational investigation (Yuan et al., 2020). It is important to note that the availability of PPI varies widely from nation to country, with some countries classifying them as "prescription-only medications" and many others allowing them to be purchased without a doctor's prescription. Low magnesium levels have been linked to ventricular arrhythmias in some patients (Del-Pino & Sanz, 2023.(

Calcium, the body's most abundant mineral, plays an important role in numerous metabolic pathways (Anderson, 2017). Low vitamin D levels have been linked to impaired calcium absorption (Ross et al., 2011). Increases in serum calcium have been linked to an uptick in the risk of conditions including heart attack and stroke (Larsson et al., 2017; Reid et al., 2017). Prior research established a negative relationship between circulating pro-inflammatory chemicals and both calcium status markers and blood calcium level (Poddar et al., 2016). Moreover, recent research has shown that serum calcium levels can influence fluctuations in ACPA levels (Ali et al., 2022). There are hundreds of enzymes in the human body, and over 80% of all metabolic activities are controlled by magnesium (de Baaij et al., 2015; Geiger & Wanner, 2012). Despite this, research to date shows that magnesium shortage is a major factor in chronic low-grade inflammation, which is a risk factor for a wide range of clinical disorders (Nielsen, 2018). Magnesium's contributions to biology span numerous fields, from cardiovascular contraction/relaxation to insulin resistance to lipid metabolism and the control of oxidative stress (Rosique-Esteban et al., 2018). The parathyroid glands, a quartet of tiny glands situated behind the thyroid gland, are solely responsible for maintaining an appropriate calcium balance in the body and are the primary sites of PTH expression (Corbetta, 2019). PTH is the body's primary regulator of calcium homeostasis, and because calcium plays

such a crucial role in physiology, its effects can be felt throughout the entire organism (Abboud et al., 2011). As a result of PTH's actions, vitamin D generation and intestinal calcium reabsorption are both boosted. Moreover, PTH promotes calcium reabsorption by enhancing tubular reabsorption in the kidneys and bone resorption (Mackenzie-Feder et al., 2011). Low levels of PTH, calcium, and phosphorus may aggravate RA illness by increasing the production of proinflammatory cytokines. Hence, vitamin D does not act on its own to regulate inflammatory cytokines in RA (Sakyi et al., 2022). Many studies have found a correlation between reducing the calcium-phosphorus ratio and pre-existing PTH levels in the body during a variety of disorders, including RA and others (Ganguly, 2017). Both calcium and phosphorus are well recognized as essential micronutrients with a demonstrated role in the control of various physiological processes. Bone health and mineralization, as well as vascular contraction, vasodilation, glandular secretion, muscular contraction, glycogen metabolism, and neurotransmission, are all regulated by calcium (Pereira et al., 2013).

Contents And Techniques

Participants

This case-control study was carried out between November 2022 and February 2023 at Baghdad Teaching Hospital in Baghdad, Iraq's Medical City. 140 rheumatoid arthritis patients in Iraq ranging in age from 18 to 45 were included in the current study. Seventy individuals were given proton pump inhibitors (PPI group), while the remaining 70 received standard care (No-PPI group). Synovitis in at least one joint and a score of 6 or more from scores in 4 domains (number and sites of affected joints, serologic abnormalities (RF and anti-CCP antibodies (ACPA)), acute-phase response (CRP and/or ESR), and symptom duration) were used to diagnose definite RA according to the arthritis criteria of the "American College of Rheumatology" and the "European League Against Rheumatism" (Aletaha, D. In order to ensure comparability, healthy controls were obtained from the same region as patients' friends and relatives. They matched the patients in terms of both age and gender. In order to determine the CDAI for RA, we used this online tool: https://www.mdcalc.com/clinical-disease-activity-index-cdai-rheumatoid-arthritis (CDAI). We used this online tool (https://www.mdcalc.com/simple-disease-activity-index-sdai-rheumatoid-arthritis) to determine the SDAI for RA.

As per the requirements of the Helsinki Declaration, the study was given the green light by the ethics committee (IRB) at the College of Medicine, University of Baghdad, Iraq (2022), which follows the International Standard for the Protection of Human Subjects in Research. Each participant, both patients and controls, provided written informed consent before participation.

The Rules for Being Left Out

Individuals having a known history of the following problems were not included in this analysis: other connective tissue diseases, vitamin D deficiency, thyroid and parathyroid disorders, malignant diseases, renal and hepato-biliary disorders, bone fractures, and diabetes mellitus. Calcium and vitamin D supplements, bisphosphonates, and diuretics were also not allowed in the study, as were patients who were already using them.

Assays

Everyone had five milliliters of venous blood collected after fasting overnight, then spun at 3000 rpm for 15 minutes to ensure complete coagulation at 37 degrees Celsius. The collected sera were frozen at -80 degrees Celsius for later study. The C-reactive protein in the serum was tested using a lateral flow immunoassay kit manufactured by Shenzhen Lifotronic Technology® Co. Ltd. in China. Spinreact® Co., Girona, Spain, supplied semi-quantitative kits for measuring RF via the latex agglutination method. By using kits supplied by Hotgen Biotech Co., Ltd., Beijing, China, we were able to perform a semi-quantitative anti-CCP assay.

Serum PTH concentrations were evaluated using a commercially available ELISA kit (Melsin® Medical Co, Jilin, China). It was a very sensitive kit, only needing 0.1 pg/mL as a detection threshold. All intra-assay CV% values were below 10%. We followed the manufacturer's instructions to a T.

Biostatistical analysis

The Shapiro-Wilk test was used as a numerical means of assessing normality. Analysis of Variance (ANOVA) test was employed to assess differences in scale variables between diagnostic groups and analysis of contingency tables (Chi-square, χ^2 test) to check the comparison between the categorical variables. Pearson's correlation coefficients were used to examine associations between scale variables to find out the correlation between nonparametric parameters with other variables. All statistical analyses were performed using IBM SPSS

windows version 25, 2017. figures and tables were plotted using the Excel software of Windows Office 2019.

Results

Baseline and clinical characteristics

The present study recruited 70 RA patients treated with PPI and 70 patients who take ordinary treatment (No-PPI). The baseline and clinical characteristics are presented in Table 1. There is no significant difference (p=0.733) in the mean age in the PPI group (32.03±7.28 years old) in comparison with the No-PPI group (31.60±7.58 years old). No significant difference in the distribution of the patient numbers between study groups (p=0.632). Fifty patients with PPI (21.4%) are obese, while twenty-one No-PPI patients (30%) are obese. In PPI patients, 22 patients (31.4%) were mild CDAI, 23 patients (32.9%) were moderate CDAI, and 25 patients (35.7%) were in a severe state. While in the No-PPI group, 24 patients (35.2%) were mild CDAI, and both moderate and severe CDAI patients groups have the same number of patients (23) and ratio (32.9%). There is no significant difference (p=0.918) among subgroups in PPI and No-PPI groups.

The duration of disease in PPI-treated patients was 34 patients (<3 years), 32 patients (3-7 years), and 4 patients (>7 years). While, the duration of disease in No-PPI treated patients was 42 patients (<3 years), 24 patients (3-7 years), and 4 patients (>7 years). There is no significant difference (p=0.542) between treatment groups in the duration of disease subgroups. Regarding drugs taken in patient groups, there is a significant increase (p<0.001) in the Humira taken by the PPI group in comparison with the No-PPI group. In contrast, a significantly higher number of No-PPI patients (47 patients) who took Enbrel drug compared with the PPI group (26 patients). No significant difference (p=0.454) was recorded in the number of patients who were treated with Methotrexate in the PPI group (52 patients) and the No-PPI group (48 patients).

Comparison of biochemical parameters between PPI and No-PPI groups

The results of the measured parameters in PPI and No-PPI groups are presented in Table 2. The results showed no significant difference (p<0.05) between groups in serum urea, creatinine, ALT, AST, ALP, albumin, inorganic phosphate, ESR, Hb, WBC count, and intact PTH. There is a significant decrease (p=0.008) in serum calcium in No-PPI patients (9.22±0.74 mg/dl) in comparison with the PPI group (8.91±0.64 mg/dl). Also, there is a significant decrease (p=0.037) in serum magnesium in No-PPI patients (1.89±0.07 mg/dl) in comparison with the PPI group (1.92±0.09 mg/dl).

Comparison of biochemical parameters in RA patients according to the severity

Table 3 presents the results of the measured biochemical parameters in the mild-moderate severity group in comparison with the severe group. All the measured parameters are non-significantly different (p>0.05) between the severity groups, except WBC count which showed a significant increase (p=0.031) in the severe RA group (5863.54±1604.77/mm^3) compared with the mild-moderate RA group (5282.07±1435.70 /mm^3).

Correlation between the measured biomarkers with other parameters

The correlations between the measured biomarkers with the patient's characteristics are presented in Table 4. Serum calcium showed a significant correlation with the duration of disease (r=-0.195, p<0.05), while a negative correlation with the disease activity (r=0.191, p<0.05). Serum albumin and magnesium have no significant correlation with any parameters of the characteristics of RA patients. Serum inorganic phosphate has an inverse correlation with BMI (r=-0.246, p=0.003). Intact PTH has a significant correlation with the presence of a family history of RA patients (r=0.202, p<0.05). No significant correlation between the measured biomarkers and the renal (urea and creatinine) and liver function tests (albumin, ALT, AST, and alkaline phosphate). The results indicated a significant inverse correlation between calcium and phosphate (r=-0.571, p<0.001). Serum intact-PTH has a significant correlation with serum inorganic phosphate (r=0.303, p<0.001), and inversely with serum calcium (r=-0.480, p<0.001). Serum calcium has an inverse correlation with the ESR value (r=-0.192, p=0.023). The results showed a significant correlation between calcium and hemoglobin (r=0.173, p=0.041).

Receiver operating characteristic (ROC) for differentiation between severe and mild RF

To determine the diagnostic sensitivity and specificity of the intact PTH for the diagnosis the severe RA patients with mild-moderate RA disease, the analysis of ROC was performed. The ROC curve of the analysis is plotted in Figure 1. While

the coordinates of the ROC results and the cut-off value of the concentration that produces the best sensitivity and specificity are presented in Table 5.

The results in Table 5 showed that the increase in serum intact-PTH level to a value higher than the cut-off value (55.50 pg/ml), indicates significantly (p=0.015) that the patients may have a severe RA form in a sensitivity of 60.9% and specificity of 61.7%. These results are enforced by the area under the curve (0.661, 95% CI=0.535-0.786) and the positive value of Youdin's J statistics that have a good positive value indicating the parameter should be increased to produce the calculated sensitivity and specificity.

Discussion

The first notable finding is the difference between the PPI group and the No-PPI patients' serum calcium and magnesium levels, which is shown in Table 2. Hypochlorhydria, decreased intestinal calcium absorption, and a consequent negative calcium balance caused by PPIs could theoretically enhance the risk of osteoporotic fracture (Yu et al., 2008). As calcium solubility is influenced by the pH of the solution, calcium absorption may also be influenced by the pH of the stomach. a substantial decrease in serum levels of calcium, vitamin D, and inorganic phosphorus in PPI users with high alkaline phosphatase activity. When compared to those who did not take PPIs, all DXA scan scores were considerably lower for PPI users (Shandookh et al., 2022). PPIs have been directly linked to decreased intestinal calcium absorption, according to a single study, however the findings were inconsistent (Hardy et al., 1998). Recently, PPIs were discovered to be a unique risk factor for osteoporotic fracture (Roux et al., 2009). PPIs may promote bone health by decreasing bone resorption by blocking the osteoclastic H+-ATPase pump, according to in vitro research (Zaidi, 1990). However, additional clinical investigations revealed conflicting findings about PPIs' impact on bone resorption in people (Kocsis et al., 2002). Treatment with PPIs and a low intake of magnesium-rich foods disrupt the internal environment of the gut and increase the risk of colon magnesium malabsorption (Gommers et al., 2019). Long-term PPI use can result in hypomagnesemia, which increases the risk of bone fractures, arrhythmias, and cramping in the muscles (Hess et al., 2012.(

The comparison of Mild-Moderate RA and Severe RA Ca and Mg in the control group was shown in Table 3's results. The PPIs have a significant impact on bone mineral density, and long-term PPI use is frequently linked to the development of lumbar spine osteoporosis and osteopenia (Shandookh et al., 2022). The effective absorption of calcium is thought to need an acidic environment in the stomach lumen. But, when the pH is acidic, these proteins release the ionized calcium, which then becomes soluble and can be quickly absorbed. Recent epidemiological studies have demonstrated that individuals with gastroesophageal reflux illness who get long-term treatment with proton pump inhibitors (PPIs) have a considerably increased risk of osteoporosis and pathological hip fracture (Targownik et al., 2008). Higher dietary magnesium intake was linked to a lower prevalence of RA, which may be explained by magnesium's ability to suppress inflammation by preventing the production of proinflammatory genes (Shahi et al., 2019). Regardless of the cause, inflammation can cause significant systemic changes in the distribution and metabolism of trace metals (Chavan et al., 2015). Like in earlier studies (Cortйs & Moses, 2007; Lucia et al., 2011), the current investigation discovered lower serum magnesium levels in RA participants compared to controls. Similar to earlier studies, the current investigation found that RA individuals had lower serum calcium and higher serum phosphorus levels than controls (Ramavataram, 2012). On the other side, RA patients have lower serum calcium levels because to enhanced calcium metabolism and excretion rates (Annamalai & Kumar, 2018). Another explanation for the decreased calcium level is the impact of circulating proinflammatory chemicals and hormones that change calcium metabolism (Poddar et al., 2016). Symptoms of the patient, examination findings, risk factor evaluation, family history, joint ultrasound sonography, evaluation of laboratory markers such high CRP and ESR levels in the blood, and the identification of RA-specific autoantibodies are commonly used to make a diagnosis of RA (Aletaha, Daniel & Smolen, 2018.(

The severe RA group's WBC counts significantly increased as compared to the mild-moderate RA group, which is another significant finding in Table 3. An important role in the formation and progression of the autoimmune disease RA is played by immune cells in the synovial membrane, including resident and infiltrating immune cells (Siouti & Andreakos, 2019). According to Rossini, Maurizio et al. (2011)b, the serum level of PTH in RA patients was 40% greater than that of controls and was

linked to bone deterioration. Furthermore, more recent research has connected RA's bone damage to greater PTH levels. Serum levels of DKK1 are markedly elevated in RA patients, correlate with PTH, and are linked to an increased risk of osteoporosis and bone erosions. Yet this conclusion needs to be confirmed in a bigger, more carefully chosen sample (Rossini, Maurizio et al., 2015). Our results imply that the evolution of bone erosions in RA may be positively impacted by therapies to stop bone loss or reduce PTH levels (Rossini, M. et al., 2011a.(

The findings showed a strong negative link between body mass index and RF in the group of patients with obesity and rheumatoid arthritis, but a substantial positive correlation between body mass BMI and RF in the group of patients with rheumatoid arthritis (Mahdi et al., 2023). Lower levels of PTH, calcium, and phosphorus are linked to greater levels of proinflammatory cytokines, which could exacerbate the symptoms of RA. Ca, Cr, Fe, K, Mg, Mn, and Zn levels were noticeably reduced (Khadim & Al-Fartusie, 2023). In the intestine, magnesium absorption is impacted by calcium, and the opposite is also true (Workinger et al., 2018.(

The ROC curves are typically used to investigate potential future utility as a diagnostic biomarker for a particular disease. The parameter must, however, be unique to that illness in order for it to be used. In the current investigation, only PTH demonstrated good sensitivity, specificity, and AUC (Figure 1) for discriminating RA from controls, as shown in Table 5. Numerous studies assert that the sensitivity and specificity of the biomarker data gained from clinical research can be confirmed statistical exploration through ROC curves and logistic regression analysis (Grund & Sabin, 2010). This study is the first to apply ROC analysis in a sizable patient population, as far as we are aware. It was discovered that a 72% PTH reduction had the best ability to discriminate. We were unable to locate a patient subset for whom the AUC, sensitivity, or specificity had significantly improved (Foley et al., 2019.(

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Table 1. Baseline and clinical characteristics of the RA patients on PPI drugs and patients who take ordinary treatment (No-PPI).

Patients Characteristics	Study Groups		p-value
	PPI	No-PPI	
Age (years)			
<20	3(4.3)	3(4.3)	0.923
20-30	27(38.6)	31(44.3)	
30-40	29(41.4)	25(35.7)	
40-50	11(15.7)	11(15.7)	
Current Disease Activity Index			
Mild Activity	22(15.7)	24(17.1)	0.918
Moderate Activity	23(16.4)	23(16.4)	
Severe Activity	25(17.9)	23(16.4)	
BMI			
Normal (18.5-25)	24(34.3)	18(25.7)	0.632
Overweight (25-29)	31(44.3)	31(44.3)	
Obese >30	15(21.4)	21(30.0)	
Duration of disease (Yrs.)			
<3	34(48.6)	42(60.0)	0.542
3-7	32(45.7)	24(34.3)	
>7	4(5.7)	4(5.7)	
Duration of treatment with PPIs (Months)			
<12	55(78.6)	-	
12-24	10(14.3)	-	
24-36	5(7.1)	-	
Family history Yes/No	55/15	59/11	0.385
Humira Yes/No	25/45	2/68	<0.001
Enbrel Yes/No	26/44	47/23	0.001
Methotrexate Yes/No	52/18	48/22	0.454

Table 2. Comparison between PPI and Non-PPI in the measured parameters

Parameter	No-PPI	PPI	F or χ^2	p-value
Duration of D.Yrs	4.02±3.57	4.48±3.37	0.602	0.439
PPI duration months	-	12.24±8.65	-	-
B.Urea mg/dl	29.30±5.59	29.23±6.88	0.005	0.946
S.Cr mg/dl	0.52±0.15	0.15±0.12	0.047	0.828
AIT U/l	20.26±8.17	20.70±8.59	0.098	0.755
AST U/l	19.31±7.15	19.53±7.35	0.031	0.861
ALK.ph U/l	108.59±39.82	107.89±33.67	0.013	0.911
Ca mg/dl	8.91±0.64	9.22±0.74	7.233	0.008
Albumin g/dl	3.86±0.40	3.87±0.40	0.016	0.899
PO4 mg/dl	4.00±0.81	3.82±0.86	1.520	0.220
Mg mg/dl	1.89±0.07	1.92±0.09	4.416	0.037
ESR mm/hr.	33.40±17.54	33.54±18.62	0.002	0.963
Hb g/dl	10.94±0.99	11.01±0.89	0.170	0.680
WBC /mm3	5575.71±1502.79	5387.14±1533.22	0.540	0.464
Intact PTH pg/ml	51.56±21.47	53.76±20.79	0.379	0.539

Table 3. Biochemical parameters in RA patients according to the severity

Parameter	Mild-Moderate RA N=92	Severe RA N=48	p-value
B.Urea mg/dl	29.47±6.47	28.88±5.86	0.596
S.Cr mg/dl	0.52±0.13	0.51±0.14	0.927
AIT U/l	20.25±8.58	20.92±7.98	0.656
AST U/l	19.32±7.45	19.63±6.85	0.811
ALK.ph U/l	108.49±35.85	107.75±38.77	0.911
Ca mg/dl	9.01±0.74	9.15±0.64	0.249
Albumin g/dl	3.88±0.41	3.85±0.382	0.747
PO4 mg/dl	3.98±0.79	3.78±0.92	0.181
Mg mg/dl	1.90±0.08	1.91±0.07	0.398
ESR mm/hr.	31.97±16.56	36.35±20.41	0.172
Hb g/dl	10.97±0.98	10.99±0.87	0.910
WBC /mm^3	5282.07±1435.70	5863.54±1604.77	0.031
Intact PTH pg/ml	54.59±20.99	48.96±21.0	0.074

P: probability, N: number.
Severe RA group showed a significant increase in WBCs count compared wuith the mild-moderate RA group.

Table 4. Correlation between biochemical parameters with the patient's characteristics

Parameters	Ca	Albumin	PO4	Mg	Intact PTH
Age	0.104	0.084	-0.052	-0.140	-0.072
BMI	0.171*	0.023	-0.246**	-0.151	-0.028
Duration of Disease	0.098	-0.038	-0.055	-0.128	-0.025
Family history	0.039	-0.090	-0.097	-0.107	0.202*
Duration of treatment	0.191*	-0.095	-0.127	0.083	-0.096
Disease Activity	-0.195*	-0.022	0.040	-0.143	-0.068
B.Urea	-0.144	0.023	0.086	-0.020	0.079
S.Cr	0.016	-0.035	0.031	-0.092	-0.128
ALT	-0.012	-0.019	-0.040	-0.070	0.050
AST	0.087	-0.047	-0.053	0.079	0.024
ALK.ph	0.054	-0.144	0.024	0.041	0.020
Albumin	0.090	1	-0.014	-0.047	-0.063
Ca	1	0.090	-0.571**	0.046	-0.480**
PO_4	-0.571**	-0.014	1	0.061	0.303**
Mg	0.046	-0.047	0.061	1	-0.076
RF	0.011	0.063	-0.038	-0.082	-0.011
ESR	-0.192*	-0.015	0.131	-0.034	0.154
Hb	0.173*	-0.035	-0.126	0.004	-0.079
WBC	-0.046	0.053	0.022	-0.082	0.099

*: Significant correlation ($p<0.05$), **: Significant correlation ($p<0.01$).

Table 5. Receiver operating characteristic-area under curve (AUC) analysis of the intact-PTH in RA patients. CI: Confidence interval.

Parameter	Cut-off value pg/ml	Sensitivity %	Specificity %	Youdin J statistic	p-value	AUC	95% CI
Intact PTH	55.50	60.9	61.7	+0.29	0.015	0.661	0.535-0.786

P: probability, Youdin J statistic: Maximum height above the reference line (dashed line), AUC: area-under curve, CI: confidence interval.

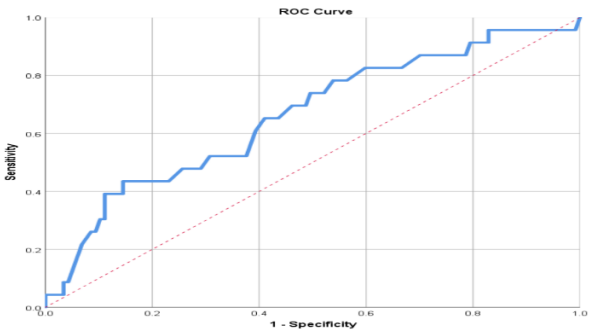

Figure 1. Receiver operating characteristic curves of the intact-PTH in RA patients.