Osmangazi Tıp Dergisi
Osmangazi Journal of Medicine 2021; 43(4):382- 387

Research Article / Araştırma Makalesi

The Effect of Glycemic Control on Inflammatory Parameters and Vitamin Levels in Patients with Rheumatoid Arthritis and Fibromyalgia

Fibromiyalji ve Romatoid Artritte Glisemik Kontrolün İnflamatuar Parametreler ve Vitamin Değerleri Üzerine Etkisinin İncelenmesi

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Abstract

The aim of this study is to compare the effect of glycemic control on both inflammatory parameters and vitamin levels in both rheumatoid arthritis and fibromyalgia. A total of 76 patients with type 2 diabetes mellitus and rheumatoid arthritis and 76 patients with type 2 diabetes mellitus and fibromyalgia were retrospectively evaluated in terms of the levels of 25 hidroxy vitamin D, vitamin B12, ferritin, folic asit, erythrocyte sedimentation rate, C-reactive protein, fasting blood glucose, hemoglobin A1c and complete blood count. C-reactive protein, ratios of platelet to lymhocyte and neutrophil to lymhocyte ($p<0.001$) and erythrocyte sedimentation rate ($p=0.002$) were significantly higher in patients with rheumatoid arthritis. However hemoglobin A1c, fasting glucose level, monocyte to lymhocyte ratio and vitamin levels were similar between patients with rheumatoid arthritis and fibromyalgia. Both groups were divided into two groups according to hemoglobin A1c being higher or lower than 7%. C-reactive protein ($p=0.037$) and monocyte to lymhocyte ratio ($p=0.050$) were significantly higher in rheumatoid arthritis patients with hemoglobin A1c≥7% than hemoglobin A1c<7%. However no significant difference was found in any parameter in fibromyalgia patients according to the level of hemoglobin A1c. Our study results showed that the levels of hemoglobin A1c was similar in patients with rheumatoid arthritis and fibromyalgia. And poor glycemic control accelerates inflammation in only rheumatoid arthritis, however it does not seem to effect vitamin levels.

Keywords: Diabetes mellitus, Fibromyalgia, Rheumatoid arthritis, Vitamin D

Özet

Bu çalışmanın amacı, romatoid artrit ve fibromiyaljili hastalarda, glisemik kontrolün hem inflamatuar belirteçler hem de vitamin değerleri üzerine etkisini karşılaştırmaktır. Hem tip 2 diyabeti olan hem de romatoid artriti olan toplam 62 hasta, hem tip 2 diyabeti hem de fibromiyaljisi olan 76 hastanın, 25 hidroksi vitamin D, vitamin B12, ferritin, folik asit, eritrosit sedimentasyon hızı, C-reaktif protein, açlık glukoz düzeyi, hemoglobin A1c ve tam kan sayımı değerleri retrospektif olarak değerlendirildi. Romatoid artritli hastalarda, fibromiyalji hastalarına göre eritrosit sedimentasyon hızı ($p=0.002$), C-reaktif protein, platelet/lenfosit ve nötrofil/lenfosit oranları ($p<0.001$) belirgin yüksek saptandı. Ancak hemoglobin A1c, açlık kan glukozu, monosit/lenfosit oranı ve vitamin değerleri her 2 grup arasında benzer bulundu. Her 2 grup da, hemoglobin A1c değerinin %7'den fazla veya düşük olmasına göre iki gruba ayrıldı. C-reaktif protein ($p=0.037$) ve monosit/lenfosit oranları ($p=0.050$) romatoid artritli hastalardan hemoglobin A1c değeri ≥%7 olan hastalarda belirgin olarak yüksek saptanırken, fibromiyaljili hastalarda hiçbir parametre, hemoglobin A1c değerine göre farklılık göstermedi. Bu çalışma sonucuna göre, fibromiyalji ve romatoid artritte, hemoglobin A1c değerleri benzerdir. Kötü glisemik kontrol fibromiyaljideki inflamatuar belirteçleri etkilemeyip, romatoid artritte inflamasyonu kötüleştirmekle birlikte, her 2 hastalık grubunda da vitamin değerlerini etkiliyor gibi görünmemektedir.

Anahtar Kelimeler: Diyabet, D vitamini, Fibromiyalji, Romatoid artrit

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Received 25.12.2020 Accepted 17.02.2021 Online published 17.02.2021

Bakilan F, Ucan A, Ortanca B, The Effect of Glycemic Control on İnflammatory Parameters and Vitamin Levels in Patients with Rheumatoid Arthritis and Fibromyalgia, Osmangazi Journal of Medicine, 2021; 43(4):382-387 Doi: 10.20515/otd.844052

1. Introduction

Rheumatoid arthritis (RA) is an inflammatory disease which causes systemic complications (1). There is evidence that fibromiyalgia is also an inflammatory disease (2), however this inflammation is accepted as low grade (3). The C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) which are using for monitoring and diagnosis of RA, are classical markers of inflammation (4). And the ratios of monocyte to lymhocyte (M/L), neutrophil to lymphocyte (N/L) and platelet to lymhocyte (P/L) which are also the biomarkers of systemic inflammation (5), have been reported to be a predictors in rheumatoid arthritis (6). There are a few studies which investigates the inflammatory mediators in fibromyalgia. Ilgun et al showed that there were no association between fibromyalgia and both CRP and ESR (7). Karabas and Emre et al. also reported no relation with N/L and P/L. (8,9). Also the pathogenesis of type 2 diabetes mellitus (DM) is associated with inflammation (10). There are contradictory results about the relation between glycemic control and inflammatory parameters. Some of these studies reported a correlation between hemoglobin A1c (HbA1c) and CRP (11) while the others reported no correlation (12).

Moreover, systemic inflamation commonly effects epithelial cells, absorptive areas and villus structures of gastrointestinal tract (13) where almost all vitamins are also absorbed and usually coexists with gastrointestinal dysbiosis and intestinal hyperpermeability (14).

There are studies investigating the relation between poor glycemic control and inflammatory parameters or vitamin levels in diabetics patients. However we could not find any study which investigated the effect of glycemic control on inflammatory parameters and vitamin levels in both inflammatory diseases and low grade inflammatory diseases. In the light of above studies, we aimed to investigate the effect of glycemic control on both inflammatory parameters and vitamin levels in inflammatory diseases.

2. Materials and Methods

This study was a retrospective analysis of patients who had both type 2 diabetes mellitus (ICD-10: E11, E13 and subgroups) and rheumatoid arthritis or fibromyalgia, between January 2019 and April 2020 by searching the patient files and computerized database. The medical records of 76 patients who were diagnosed as rheumatoid arthritis by a specialist according to American College of Rheumatology (ACR) 1987 Criteria (ICD-10: M05, M06 and subgroups) were obtained. And the medical records of 2058 patients with fibromyalgia were obtained. 76 patients who were diagnosed as fibromyalgia by a physical medicine and rehabilitation specialist according to American College of Rheumatology (ACR) 1990 Criteria (ICD-10: M79 and subgroups) were randomly selected from 2058 patients. Randomly selection was performed with “random.org” (online random number generator).

American College of Rheumatology 1990 Fibromyalgia Criteria is widespread pain with tenderness at eleven or more of the eighteen tender points more than three months (15). The diagnosis of type 2 diabetes and rheumatoid arthritis was confirmed from the patient files. Almost all diabetes patients and all rheumatoid arthritis patients were using one or more medication (For type 2 diabetes: insulin / oral anti-diabetic medication, for rheumatoid arthritis: disease modifying anti rheumatic drugs (DMARD) / steroids / anti tumor necrosis factor agents (Anti-TNF)). But the other diabetes patients who took only dietary treatment, had fasting blood glucose values higher than $\geq$ 126 mg/dl or HbA1c values were higher than $\geq$ 6.5%.

Inclusion criteria were: patients with rheumatoid arthritis or fibromyalgia in addition to type 2 diabetes were included to this study. Exclusion criteria were as follows: patients with no confirmation of type 2 diabetes or rheumatoid arthritis, antinuclear antibodies positivity and hematological diseases, infectious diseases, malignancy, patients who had vitamin supplementation and patients who do not have any blood tests in patient files.

The medical records of 152 patients were reviewed for gender, age, antidiabetics medication (oral antidiabetics or insulin), medication of rheumatoid arthritis, complete blood count, ESR, CRP, rheumatoid factor, anti-cyclic citrullinated peptide antibodies (anti CCP), HbA1c, fasting glucose level and vitamin levels (25 hidroxy vitamin D, vitamin B12, ferritin, folic asid). The ratio of neutrophil to lymphocyte (N/L) and platelet to lymphocyte (P/L), monocyte to lymphocyte (M/L) were taken from complete blood count. The level of HbA1c < 7% was accepted as good glycemic control (16).

The study was carried out with the approval of the Council of Ethics of the Faculty of Medicine of Eskisehir Osmangazi University with the decision no 28 dated 03.11.20.

Statistical analysis

The distribution of continuous variables were tested with "Shapiro-Wilk test" and each descriptive statistic was mean ± standart deviation (SD) or median (25%-75%). Non-normally distributed variables were performed using the "Mann Whitney U test". Normally distributed variables were performed with "independent samples t-test". The categorical variables (i.e., insulin and antidiabetics usage) were evaluated with "Chi-square tests" and also presented as : numbers (n) and percentages (%). A p value <0.05 was considered as statistical significant. All analyses were performed using the SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

One hundred and thirty eight (101 female, 37 male) patients with the mean age of 58.69±10.44 (between 24-79 years) who met the criteria were included to the study. 14 patients with rheumatoid arthritis was excluded due to unconfirmed disease.

Information about DM medication of 39 (63%) patients with rheumatoid arthritis and 74 (97%) patients with fibromyalgia was obtained. 50 (80%) patients were using at least one DMARD, 33 (53%) patients were using steroid treatment, 3 (5%) patients were using anti-TNF treatment and 8 (12%) patients were using salazopyrin, only 1 (0.1%) patients were using azotiopurine. CRP, P/L, N/L (p<0.001) and ESH (p=0.002) were significantly higher in patients with rheumatoid arthritis. However HbA1c, fasting glucose level, monocyte to lymhocyte ratio and vitamin levels were similar between patients with rheumatoid arthritis and fibromyalgia (p>0.05) (Table 1).

Table 1. Comparison of parameters between rheumatoid arthritis and fibromyalgia

Patients with Type 2 Diabetes Mellitus (n=138)	Rheumatoid Arthritis (n=62)	Fibromyalgia (n=76)	p value
Age**	58.08 ± 11.21	59.19 ± 9.82	0.534
Gender (female/male) n(%)	43 (69.3%) / 19 (31.7%)	58 (76,3%) / 18 (23.7%)	0.359
Insulin usage (yes/no)	9 (23.1%) / 30 (76.9%)	13 (17.6%) / 61 (82.4%)	0.482
Oral Antidiabetics usage (yes/no)	33 (84.6%) / 6 (15.4%)	58 (78.4%) / 16 (21.6%)	0.426
HbA1c**	7.26 ± 1.92	7.31 ± 1.79	0.891
Fasting blood glucose**	149.23 ± 68.86	150.42 ± 76.35	0.925
CRP**	18.56 ± 24.42	3.67 ± 4.14	**p<0.001**
ESR**	24.22 ± 13.28	15.94 ± 10.66	**0.002**
Neutrophil/lymphocyte rate**	3.17 ± 3.01	1.87 ± 0.73	**p<0.001**
Platelet/lymhocyte rate**	151.08 ± 85.86	112.05 ± 34.87	**p<0.001**
Monocyte/lymhocyte rate**	0.30 ± 0.12	0.25 ± 0.37	0.325
25 hidroxy vitamin D**	21.60 ± 13.02	19.62 ± 10.12	0.392
Vitamin B12**	338.55 ± 146.18	375.39 ± 172.91	0.267

Ferritin*	48.80 (15 - 97.90)	29,0 (18 – 51.50)	0.105
Folic acid**	7.84 ± 4.84	7.48 ± 2.48	0.679

**median (25-75%) **mean ± standard deviation (HbA1c: Hemoglobin A1c, CRP: C reactive protein, ESR: Erythrocyte sedimentation rate)*

55 rheumatoid arthritis patients who had HbA1c records, were divided into two groups according to HbA1c value. CRP (p=0.037) and monocyte to lymhocyte ratio (p=0.050) were significantly higher in patients with HbA1c ≥ 7% (Table 2).

Table 2. Comparison of inflammatory parameters and vitamin levels according to HbA1c in patients with rheumatoid arthritis

Patients with Rheumatoid Arthritis (n=55)	HbA1c < 7% (mean ± standard deviation) (n=32)	HbA1c ≥ 7% (mean ± standard deviation) (n=23)	p value
CRP	12.69 ± 16.84	27.10 ± 31.49	**0.037**
ESR	23.10 ± 12.73	25.05 ± 14.83	0.629
RF	121.83 ± 218.89	181.16 ± 250.52	0.478
Anti-CCP	158.74 ± 114.45	73.14 ± 88.37	0.173
Neutrophil/lymphocyte rate	3.42 ± 3.98	3.02 ± 1.55	0.647
Platelet/lymhocyte rate	155.36 ± 100.10	148.66 ± 74.45	0.787
Monocyte/lymhocyte rate	0.27 ± 0.12	0.34 ± 0.11	**0.050**
25 hidroxy vitamin D	17.78 ± 7.93	26.79 ± 17.36	0.059
Vitamin B12	343.86 ± 147.63	306.67 ± 134.76	0.478
Ferritin*	64.56 (12.17 – 99.25)	98.77 (7,0 – 159,5)	0.897
Folic acid	7.18 ± 4.27	7.76 ± 4.58	0.772

**median (25-75%) (CRP: C reactive protein, ESR: Erythrocyte sedimentation rate, RF: Rheumatoid factor, Anti-CCP: anti-cyclic citrullinated peptide antibodies)*

Also 73 fibromyalgia patients who had HbA1c records, were divided into two groups according to HbA1c value, however no significant difference was found in any parameter (Table 3).

Table 3. Comparison of inflammatory parameters and vitamin levels according to HbA1c in patients with fibromyalgia

Patients with Fibromyalgia (n=73)	**HbA1c < 7% (mean ± standard deviation) (n=43)**	**HbA1c ≥ 7% (mean ± standard deviation) (n=30)**	**p value**
CRP	3.44 ± 4.53	3.71 ± 3.41	0.864
ESR	16.09 ± 8.11	15.38 ± 14.63	0.856
Neutrophil/lymphocyte rate	1.80 ± 0.73	1.91 ± 0.67	0.525
Platelet/lymhocyte rate	110.61 ± 30.58	113.06 ± 39,0	0.764
Monocyte/lymhocyte rate	0.22 ± 0.05	0.31 ± 0.59	0.324
25 hidroxy vitamin D	19.43 ± 11.12	18.84 ± 7.98	0.817
Vitamin B12	351.85 ± 151.840	401.93 ± 197.76	0.242
Ferritin*	48.38 (19.5 – 53.25)	50.70 (18,0 – 68.25)	0.758
Folic acid	7.78 ± 2.42	7.17 ± 2.57	0.432

**median (25-75%) (CRP: C reactive protein, ESR: Erythrocyte sedimentation rate)*

4. Discussion

In this study, we investigated the effect of glycemic control on both vitamin levels and inflammatory parameters. Rheumatoid arthritis was selected for first group due to the underlying mechanism “inflammation”. Also, in recent studies, it has been reported that fibromyalgia also progresses with a systemic inflammation (2), but this inflammation is low grade (3). Fibromiyalgia was selected for second group due to this “low grade inflammation”. Our study results showed that, all inflammatory parameters were higher in RA patients compared to FM patients, as expected. However HbA1c and vitamin levels were similar in both groups. It is already known that rheumatoid arthritis is associated with diabetes mellitus and insulin resistance (17) Also fibromyalgia is associated with diabetes mellitus and high levels of HbA1c. Tishler et al. found that patients with both diabetes and fibromyalgia had significantly higher levels of HbA1c than diabetes patients without fibromyalgia (18).

When we evaluated in terms of glycemic control: the level of inflammatory parameters such as CRP and monocyte to lymphocyte ratios were higher in rheumatoid arthritis patients with poor glycemic control; however in fibromyalgia patients, no inflammatory parameters change according to glycemic control. Inflammation in rheumatoid arthritis is characterised by higher levels of cytokines such as interkeukin-6 and TNF-α which also induce insulin resistance and diabetes mellitus (17). And using glucocorticoid in RA, can disrupt glucose metabolism (19). And also the pathogenesis of diabetes mellitus type 2 is associated with immune system and CRP, interleukin-1β and interleukin-6 has been reported to be elevated (20). Both type 2 diabetes mellitus and rheumatoid arthritis are associated with immune system and inflammation. We believe these two disease may effect each other, poor glycemic control accelerates inflammatory processes in rheumatoid arthritis. We attribute the lack of this effect in fibromyalgia to being inflammation low grade. Similar to our study CRP was found higher in 83 rheumatoid arthritis patients with a poor glycemic control (HbA1c > 6%) than 213 patients with a good glycemic control, and also it was reported that any relation was not found between usind DMARD and HbA1c. (21). In our study 80% of RA patients were using DMARD. The relationship between DMARD and HbA1c could not be evaluated due to the small number of patients who did not use DMARD.

In the literature, vitamin D has been investigated mostly among the vitamins in patients with diabetes, fibromyalgia and rheumatoid arthritis. In many studies the levels of vitamin D was found lower in both fibromyalgia (22) and rheumatoid arthritis (23). However, there are conflicting results about vitamin D and glycemic control. In some studies it was reported that vitamin D deficiency is associated with poor glycemic control (24) and insulin resistance (25), in others no associaton was reported (26). In our study, any relation was not found between vitamin D deficiency and glycemic control. Also there was not found any relation between HbA1c and other vitamins. Similar to our study results, Karatoprak et al. reported no association between glycemic control and vitamin B12 and folic asid levels (27).

The limitations of our study are its retrospective design, the small sample size and the lack of control group which has only diabetes not rheumatologic disease. Further prospective studies are needed with higher numbers of patients. To the best of our knowledge, it is the first study which compares inflammatory parameters and vitamin levels according to glycemic control in fibromyalgia and rheumatoid artritis, this is the strength of our study.

In conclusion, the levels of HbA1c was similar in patients with rheumatoid arthritis and fibromyalgia. And poor glycemic control accelerates inflammation in rheumatoid arthritis, however glycemic control does not seem to effect vitamin levels. Specialist need to have awareness of rheumatoid arthritis with diabetes mellitus in clinical practise and provide more aggresive intervention for both inflammation and glycemic control.

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