



The role of lower dose steroid therapy with vitamin D replacement in patients with idiopathic granulomatous mastitis

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ABSTRACT

Objective: Low-dose steroid therapy has been recommended in idiopathic granulomatous mastitis (IGM) in various studies in the literature, but the therapeutic minimum dose has not been determined yet. Furthermore, vitamin D deficiency, the effect of which is accepted in autoimmune diseases, has not been previously examined in IGM. The aim of our study was to evaluate the efficacy of lower dose steroid therapy with adjustment of vitamin D replacement doses with measuring serum 25-hydroxyvitamin D levels in patients with idiopathic granulomatous mastitis (IGM).

Material and Methods: Vitamin D levels were evaluated in 30 IGM patients who applied to our clinic between 2017-2019. Vitamin D replacement was performed in patients with serum 25-hydroxyvitamin D level below 30 ng/mL and prednisolone was given to all patients at a dose of 0.05-0.1 mg/kg/day. Clinical recovery times of the patients were compared with the literature.

Results: Vitamin D replacement was given to 22 (73.33%) patients. Recovery time was shorter in patients receiving vitamin D replacement (7.62 ± 2.38 ; 9.00 ± 3.38 ; $p=0.680$). Average recovery time was 8.00 ± 2.68 weeks.

Conclusion: Treatment of IGM can be carried out with lower dose steroid therapy, leading to less complications and lower costs. Measuring serum 25-hydroxyvitamin D level and treating it with the appropriate dose may contribute to the healing process.

Keywords: Idiopathic granulomatous mastitis, lower doses of steroid therapy, vitamin D

INTRODUCTION

Idiopathic granulomatous mastitis (IGM) is a rare inflammatory breast disease of unknown etiology. This disease is clinically presented with erythematous mass, abscess or chronic fistulized sinus formation and may mimic the clinical characteristics of inflammatory breast carcinoma. Definitive diagnosis can only be made histopathologically by tru-cut or incisional biopsy, and the disease is accepted to be idiopathic after exclusion of all infectious and non-infectious causes of granulomatous disease (1-3).

Although surgery, drainage, corticosteroids and immunosuppressive drugs are used in the treatment of this disease, a clear consensus has not been reported yet (4-6). Recently, the healing effect of corticosteroids has been shown in this disease, but since it is rare, its therapeutic modality has not been determined. In different studies, different doses of steroids have been given, but the general opinion on corticosteroid dose has been as 0.4-0.8 mg/kg. However, long-term use of this dose has many side effects due to steroid such as glucose intolerance or Cushing's syndrome (7-10).

Recent studies have shown the effects of vitamin D not only on calcium metabolism and bone formation but also on the immune system. Vitamin D receptors are expressed in different tissues, such as the brain, heart, skin, bowel, gonads, prostate, breasts, and immune cells.

Therefore, it has increased its interest in the role of vitamin D in the treatment of inflammation and immune system (11-13). Vitamin D deficiency has occurred in the pathophysiology of various inflammatory diseases such as inflammatory bowel disease (IBD) and rheumatoid arthritis (RA), systemic lupus erythematosus (SLE),

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as well as in chronic low-grade inflammation associated with obesity, insulin resistance Type 2 diabetes (IDDM) and cardiovascular disease (14). Vitamin D deficiency is defined as a serum 25-hydroxyvitamin D level of less than 20 ng/mL (50 nmol/L), and insufficiency is defined as a serum 25-hydroxyvitamin D level of 20 to 30 ng/mL (50 to 75 nmol/L). In persons with vitamin D deficiency, treatment may include oral cholecalciferol (vitamin D₃) at 50.000 IU per week for eight weeks. After vitamin D levels normalize, experts recommend maintenance dosages of cholecalciferol (vitamin D₃) at 800 to 1.000 IU per day from dietary and supplemental sources (15,16).

In our study, we implemented low steroid dose to our patients as 0.05-0.1 mg/kg/day and evaluated the patients' responses to treatment and recovery times. In addition, we examined 25-OH vitamin D levels in these patients and performed vitamin D replacement in those with deficiency.

The primary purpose of this study was to evaluate the response to lower dose steroid therapy in patients with IGM, and the secondary aim was to evaluate the contribution of replacement therapy in the recovery process in patients with vitamin D deficiency in this disease.

MATERIAL and METHODS

This retrospective, non-randomized observational study covered 30 females with IGM who applied to the breast unit of our general surgery clinic between October 2017 and December 2019. Informed consent was obtained from the patients regarding the treatment to be given. Ethics committee approval was obtained from the ethics committee of our hospital. All patients were aged over 18 years and were not in pregnancy or breastfeeding. At first admission, anamnesis was taken and physical examination was made to all patients. Ultrasonography was performed on all of them as standard for imaging and all patients were diagnosed with IGM histopathologically by tru-cut biopsy.

The patients were also evaluated in terms of tuberculous mastitis and pyogenic infections. Tissue and abscess samples were sent to Polymerase chain reaction (PCR) testing for *Mycobacterium tuberculosis* (MT) and aerobic and anaerobic culture for other bacterial infections (17,18). All of the patients diagnosed with IGM were examined with vitamin D level, hemogram and C-reactive protein (CRP) in the blood.

Prednisolone (Prednol[®], Mustafa Nevzat, İstanbul, Türkiye) was started at 4 mg/day for the first week and continued for three weeks at 2 x 4 mg/day. After starting treatment, patients were called for control at the 1st and 2nd weeks, and then at the 1st, 2nd, 3rd and 6th months.

In patients with improvement in the first month control, 4mg/day was continued for one week and the treatment was terminated. In patients without complete recovery, treatment was continued from 8 mg/day until observing clinical improve-

ment, then the dose was reduced and completed. The average steroid dose we administered to our patients was 0.05-0.1 mg/kg/day.

Vitamin D, hemogram and CRP levels were examined in the blood of the patients diagnosed with IGM. Patients with serum 25-hydroxyvitamin D levels below 30 ng/mL were given cholecalciferol (Devit-3[®] oral drop, Deva Drug, İstanbul, Türkiye) 50.000 IU/ week for eight weeks, followed by 800-1000 IU daily. Adequacy of treatment was evaluated quarterly.

In addition, in the clinical follow-up of the patients, abscess drainage was performed in the presence of an abscess detected with physical examination and ultrasonography. Surgical excision was performed in patients with isolated mass image and not causing deformity.

The resolution of the patient's complaints and the disappearance of the lesion in physical examination and ultrasonography were accepted as clinical improvement.

All data were analyzed using SPSS version 23. Continuous variables were expressed as mean ± standard deviation. Mann-Whitney U test and Student's t-test were used to compare nonparametric and parametric values, respectively, between the two groups.

Statistical significance was defined as a p value of <0.05.

RESULTS

The study included 30 female patients. There were 6 (20%) patients aged 20-30 years, 18 (60%) patients aged 31-40 years, and 6 (20%) patients aged 41-50 years. The menopausal status of 28 (93.33%) patients was premenopausal and 2 (6.67%) patients were postmenopausal.

While taking anamnesis, 22 (80%) patients described pain and 8 (20%) patients stated that they had no pain. During physical examination, masses were observed in 4 (13.3%) patients, and mastitis/abscess images in 26 (86.67%) patients. Mastitis was present in the right breast of 12 (40%) patients and in the left breast of 18 (60%) patients. In ultrasonography findings, irregular hypoechoic lesions were monitored in 3 (10%) patients, mastitis-like inflammatory appearance in 9 (30%) and abscess/mastitis findings in 18 (60%). According to the BIRADS classification, there were 3 (10%) patients with BIRADS 3, 24 (80%) patients with BIRADS 4 and 3 (10%) patients with BIRADS 5.

There was no growth in the bacterial culture of any of the patients, and MT PCR tests were negative. There were 18 (72%) patients with high CRP and 3 (11.54%) patients with high WBC, all of whom had moderate CRP and WBC elevation (Table 1). Abscess drainage was performed in 17 (56.67%) patients and excisional biopsy in 1 (3.33%) patient. Serum 25-hydroxyvitamin D levels were <20 ng/mL in 17 (56.66%) patients, 20 to 30 ng/mL in 5 (16.67%) patients and >30 ng/mL in 8 (26.67%) patients.

Table 1. Demographic information, clinical presentation, laboratory parameters and radiological findings of patients with IGM

	20-30 (n)	31-40 (n)	41-50 (n)
Age	6 (20%)	18 (60%)	6 (20%)
Menopausal status	Premenopausal (n) 28 (93.33%)	Postmenopausal (n) 2 (6.67%)	
Pain (n)	Yes (n) 24 (80%)	No (n) 8 (20%)	
Physical examination	Mass (n) 4 (13.3%)	Mastitis/Abscess (n) 26 (86.67%)	
Side	Right (n) 12 (40%)	Left (n) 18 (60%)	
Ultrasonographic findings	Irregular Hypochoic lesion (n) 3 (10.00%)	Mastitis-like inflammation (n) 9 (30.00%)	Coexistence of abscess and mastitis (n) 18 (60.00%)
BIRADS classification	BIRADS 3 (n) 3 (10.00%)	BIRADS 4 (n) 24 (80.00%)	BIRADS 5 (n) 3 (10.00%)
CRP	Normal (n) 7 (28%)	High (n) 18 (72%)	
WBC	Normal (n) 23 (88.46%)	High (n) 3 (11.54%)	

Table 2. Evaluation of the response to Vitamin D replacement

Serum 25-hydroxyvitamin D levels	Number of patients		Recovery time (week)		p
	n	%	Mean ± sd	Median	
<30 ng/mL (Patients given replacement therapy)	22	(73.33)	7.62 ± 2.38	7.00	0.680
<20 ng/mL	17	(56.66)	7.63 ± 2.26	7.00	
20-30 ng/mL	5	(16.67)	7.60 ± 2.97	8.00	
>30 (Patients without replacement therapy)	8	(26.67)	9.00 ± 3.38	8.00	

Kruskal Wallis test.

Vitamin D replacement was given to 22 (73.33%) patients, 8 (26.67%) patients were not replaced.

Recovery time was shorter in patients receiving vitamin D replacement but was not statistically significant (7.62 ± 2.38; 9.00 ± 3.38; p= 0.680) (Table 2). All patients participating in the study were given low-dose steroid therapy, and the average recovery time was 8.00 ± 2.68 weeks and average follow-up time was 16.60 ± 5.83 months.

DISCUSSION

The etiopathogenesis and treatment model of IGM is not fully illuminated, and delays in diagnosis and treatment may lead to

long-term pain, cosmetic and psychosocial problems. The underlying pathogenesis of IGM is unknown despite being an autoimmune disease. Pathological features of IGM include chronic granulomatous inflammation without necrosis.

Granulomas typically contain lymphocytes, plasma cells, epithelioid histiocytes, multinucleated giant cells, and rarely neutrophils, and granulomatous lesions can be observed in breast lobules or terminal ducts in any breast quadrant (9).

Administration of steroids to patients with IGM is a generally accepted treatment method, and different doses of steroid treatment (0.4-0.8 mg/kg) are recommended in various stud-

ies. DeHertogh et al., Norihiro et al., Jorgensen and Nielsen recommend steroid therapy, starting with 60 mg/day (0.8 mg/kg/day) prednisolone treatment and gradually decreasing at different doses, lasting four to six months (7,9,19). Karanlık et al. have recommended starting prednisolone at a dose of 0.5 mg/kg/day for 2-4 weeks and then tapering down slowly for four weeks (20). Jeon et al. have suggested administering the steroid at a dose of 0.4 mg/kg/day and gradually reducing the dose for one to 28 weeks (10). In our study, the average steroid dose we applied to our patients was 0.05-0.1 mg/kg/day and the average recovery time was 8.00 ± 2.68 weeks. We found that there was a similar recovery period with the literature. Current studies show that vitamin D appears to interact with the immune system, with its effects on the regulation and differentiation of lymphocytes, macrophages, natural killer cells

(NK), and its deficiency is associated with several autoimmune diseases, including IBD, RA, SLE, IDDM (12,21). Based on this, we evaluated routine serum 25-hydroxyvitamin D levels from patients with IGM who applied to our clinic and we gave vitamin D replacement in patients with serum vitamin D levels below 30 ng/mL. Although it was not statistically significant, mean recovery time in the group that received replacement therapy was shorter than the group that was not given vitamin D. We think that the limitation of the number of cases should be taken into consideration when the shortening of the recovery period is not statistically significant.

In addition, according to our clinical experience, we think that surgical interventions should be avoided in patients with IGM, except for abscess drainage and excisional biopsy in localized small, non-healing masses. The aim of our study was that in patients diagnosed with IGM, although low-dose steroid treatment is called, could the dose of 0.4-0.8 mg/kg/day steroid given for months until clinical improvement recommended in various publications still be unnecessary? To further reduce the side effect profile, we tried to look if there was a lower steroid dose range that would provide clinical improvement to similar periods. At the same time, we tried to evaluate whether vitamin D level in our patients diagnosed with IGM is a predisposing factor in this disease and contributes to the duration of clinical recovery by replacement.

CONCLUSION

In conclusion, we think that the treatment of patients with the diagnosis of IGM can be planned with steroid doses of 0.05-0.1 mg/kg daily and vitamin D replacement when deficiency is present; in accordance with literature, within acceptable time and with less side effects and cost; while avoiding extensive surgery. Still, we are aware that larger studies with better planned control groups are needed.

Ethics Committee Approval: The approval for this study was obtained from İstanbul Health Science University Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (Decision no: 236, Date: 11.08.2021).

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ORJİNAL ÇALIŞMA-ÖZET

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İdiyopatik granülatöz mastitli hastalarda D vitamini replasmanı ile daha düşük doz steroid tedavisinin rolü

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ÖZET

Giriş ve Amaç: Literatürde çeşitli çalışmalarda idiyopatik granülatöz mastitte (İGM) düşük doz steroid tedavisi önerilmiş ancak terapötik minimum doz henüz belirlenmemiştir. Ayrıca otoimmün hastalıklar üzerinde etkisi kabul edilen D vitamini eksikliği daha önce İGM'de incelenmemiştir. Çalışmamızın amacı, idiyopatik granülatöz mastitisli (İGM) hastalarda daha düşük dozda steroid tedavisi ile birlikte hastaların serum 25-hidroksivitamin D düzeylerini ölçerek vitamin D replasmanının etkinliğini değerlendirmektir.

Gereç ve Yöntem: 2017-2019 yılları arasında kliniğimize başvuran 30 İGM hastasında D vitamini düzeyleri değerlendirildi. Serum 25-hidroksivitamin D düzeyi 30 ng/mL'nin altında olan hastalara vitamin D replasmanı yapıldı ve tüm hastalara 0,05-0,1 mg/kg/gün dozunda prednizolon verildi. Hastaların klinik iyileşme süreleri literatür ile karşılaştırıldı.

Bulgular: Yirmi iki (%73.33) hastaya vitamin D replasmanı yapıldı. D vitamini replasmanı yapılan hastalarda iyileşme süresi daha kısaydı (7,62 ± 2,38; 9,00 ± 3,38; p= 0,680). Ortalama iyileşme süresi 8,00 ± 2,68 hafta idi.

Sonuç: İGM tedavisi daha düşük doz steroid tedavisi ile tedavi edilebilir, bu da daha az komplikasyona ve daha az maliyete neden olur. Serum 25-hidroksivitamin D düzeyinin ölçülmesi ve uygun dozda tedavi edilmesi iyileşme sürecine katkı sağlayabilir.

Anahtar Kelimeler: İdiyopatik granülatöz mastit, daha düşük doz steroid tedavisi, vitamin D

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