Journal of SURGICAL ARTS
CERRAHİ SANATLAR DERGİSİ
"A word can save a life"
jsurgarts.com
1308-0709

Original study

Potential independent risk factors associated with vitamin D deficiency in the post liver transplant patients

Karaciğer nakli sonrası hastalarda D vitamini eksikliği ile ilişkili potansiyel bağımsız risk faktörleri

Arif Atay[1], Deniz Yavuz Başkıran[2], Adil Başkıran[3], Sezai Yılmaz[3]

Izmir Katip Celebi University Atatürk Training and Research Hospital, Department of General Surgery[1], Izmir, Türkiye

Inonu University Turgut Ozal Medical Center, Faculty of Medicine, Institute of Liver Transplantation, Departments of Public Health[2] and General Surgery[3], Malatya, Türkiye.

Corresponding address: Dr. Arif Atay, atayarif@hotmail.com

How to cite: Potential independent risk factors associated with vitamin D deficiency in the post liver transplant patients. J Surg Arts: 2023;16(1):1-5.

Received: 01.01.2023 Accepted: 12.010.2023

ABSTRACT

Background: Deficiency of native vitamin D [cholecalciferol, 25(OH)D3] is a common in patients with end stage liver failure.

Aim: Our study aimed to determine the risk factors and their frequency associated with 25(OH)D3 deficiency after liver transplantation.

Method: This study includes the patients with liver transplantation and carried out at the tertiary care center. Serum 25(OH)D3 levels were measured in those patients.

Results: A total of 148 patients were entered the study. Chronic viral hepatitis was the most common reason for transplantation (66.2%). Post-operative follow-up period was shorter than 1 year in eighty-two patients (55.4 %). Post-transplant 25(OH)D3 levels were below 20 ng/mL in 93 (62.8 %) patients Post-transplant 25(OH)D3 deficiency was greater in patients with follow-up periods shorter than 1 year (p = <0.001), in those receiving immunosupression with mycophenolate mofetil, tacrolimus, steroids and in those with low hematocrit rate and, albumin levels. On multivariate analysis, post-transplant follow-up period shorter than 1 year (OR: 6.18, 95% CI: 2.681-14.255, p<0.001) and steroid use in chronic immunosuppression (OR: 9.47, 95% CI: 1.165-77.009, p=0.035) were detected asindependent accompanying factors with 25(OH)D3 deficiency.

Conclusions: The The risk of 25(OH)D3 deficiency in p atients receiving immunosuppressive treatment with steroids to prevent rejection or those in the first post-transplant year was high. Therefore, serum 25(OH)D3 levels of the patients after liver transplantation should be monitored regularly.

Keywords: 25(OH)D3; liver transplantation; deficiency; post-transplant; risk factors.

ÖZET

Amaç: Doğal D vitamini [kolekalsiferol, 25(OH)D3] eksikliği, son dönem karaciğer yetmezliği olan hastalarda yaygın bir durumdur. Çalışmamızda karaciğer nakli sonrası 25(OH)D3 eksikliği ile ilişkili risk faktörlerini ve sıklığını belirlemeyi amaçladık.

Yöntem: Bu çalışma üçüncü basamak merkezde yürütülen ve karaciğer nakli olan hastaları içermektedir. Bu hastalarda serum 25(OH)D3 düzeyleri ölçüldü.

Bulgular: Çalışmaya toplam 148 hasta dahil edildi. Kronik viral hepatit en sık transplantasyon nedeniydi (%66.2). Ameliyat sonrası takip süresi seksen iki hastada (%55.4) 1 yıldan kısaydı. Nakil sonrası 25(OH)D3 dü-

zeyleri 93 (%62,8) hastada 20 ng/mL'nin altındaydı. , mikofenolat mofetil, takrolimus, steroidler ile immünsüpresyon uygulananlarda ve hematokrit oranı ve albümin düzeyi düşük olanlarda. Çok değişkenli analizde nakil sonrası takip süresinin 1 yıldan kısa olması (OR: 6.18, %95 GA: 2.681-14.255, p<0.001) ve kronik immünsupresyonda steroid kullanımı (OR: 9.47, %95 GA:1.165-77.009) , p=0,035) 25(OH)D3 eksikliğine eşlik eden bağımsız faktörler olarak saptandı.

Sonuçlar: Reddi önlemek için steroidlerle immünsüpresif tedavi alan hastalarda veya nakil sonrası ilk yılda olan hastalarda 25(OH)D3 eksikliği riski yüksekti. Bu nedenle karaciğer nakli sonrası hastaların serum 25(OH)D3 düzeyleri düzenli olarak izlenmelidir.

Anahtar kelimeler: 25(OH)D3; karaciğer nakli; defisit; nakil sonrası; risk faktörleri.

INTRODUCTION

Vitamin D (25(OH)D3) deficiency and hepatic osteodystrophy cause bone pain, fractures and growth retardation in children, which are encountered in patients with end-stage liver failure. Liver transplantation is the only curative treatment of end-stage liver failure. However, 25(OH)D3 deficiency, metabolic bone disease, and growth retardation are seen in children in the first year after liver transplantation [1-5]. Recovery of metabolic bone disease takes approximately one year after liver transplantation. Although the reason cannot be fully explained, immunosuppressant agents such as steroids which are initiated after transplantation to prevent rejection are thought to be the cause of delay in recovery [6]. Corticosteroids lead to an increase in catabolism of 25(OH)D3 and contribute to 25(OH)D3 deficiency and development of metabolic bone disease [7]. There are many studies showing associations between 25(OH)D3 deficiency and cancer, autoimmune diseases (diabetes mellitus, psoriasis, and multiple sclerosis), atopic diseases, hypertension, and obesity [8-11]. Vitamin D deficiency and insufficiency can lead to liver transplantation-related metabolic bone diseases (e.g. rickets, osteomalacia, fractures, and bone pain) as well as immunological (e.g. failure in proliferation and differentiation of immune cells), metabolic (e.g. insulin resistance) and cardiovascular (e.g. hypertension) complications. Therefore, detection and treatment of vitamin D deficiency in the post-transplant patients is important to reduce transplantation-related complications.

Our primary aim is to determine the frequency of 25(OH)D3 deficiency in the post-transplant patients. The secondary aim is to determine the independent risk factors associated with 25(OH)D3 deficiency after liver transplantation.

MATERIAL and METHOD

Study group

The patients who underwent liver transplantation at University Hospital, Transplantation Institute were entered the study. The post-transplant patients have been monitored periodically at transplantation clinic. A previously prepared questionnaire form was completed by the researchers. The form included questions about, the duration of failure prior to transplantation, patient demographics, donor and donor affinity, the age at liver transplantation, the cause of liver failure, the chronic immunosuppressant therapy and concomitant atopic diseases. In the follow-up period, complete blood count parameters, liver function tests and immunosuppressant blood levels were examined regularly. Serum 25(OH)D3 , calcium, alkaline phosphatase, and phosphorus levels were also measured. Blood samples were obtained in summer to prevent seasonal differences in 25(OH)D3 levels,. Patient receiving vitamin D supplements and those with concomitant renal failure or underwent multiple organ transplant and those who were unwilling to participate were excluded from the study. Serum 25(OH)D3 levels below 20 ng / ml were accepted as vitamin D deficiency [12].

Informed consent form was obtained from each patients for both treatment modalities and publication. The study protocol was approved by the institutional Ethics Committee (Number 188/2013).

Statistical Analysis

Statistical Package for Social Sciences (SPSS) 15.0 software were used for statistical analysis. Quantitative data were expressed as median (min-max) and descriptive statistics were expressed as frequency and percentage for categorical variables. Mann-Whitney U test and Pearson chi-square test were used for comparison. The variables used in the multiple logistic regression analysis consisting of statistically significant parameters were as follows: chronic immunosuppressant regiment with tacrolimus, with mycophenolate mofetil, with steroid, the time after liver transplantation ≤ 1 year, serum level of hematocrit and serum level of albumin.

RESULTS

Demographics

Of the 118 patients, 99 (66.9%) were male and 26 (17.6%) were children. The median age was 42.4 (0.7-66) years, and chronic viral hepatitis was the most common indication for liver transplantation (66.2 %). The donors of eighteen patients (12.2 %) were cadavers. The median pre-transplant liver failure duration was 6 months (1-120) and the median follow-up period in post-transplant patients was 9 months (1-78). The follow-up period in post-transplant patients was shorter than 1 year in eighty-two patients (55.4 %). Distribution of chronic immunosuppressant therapy after liver transplantation was

as follows: 86 patients (58.1 %) were on only tacrolimus, five patients (3.4 %) on only cyclosporine, 45 patients (30.4 %) on mycophenolate mofetil, 32 patients (21.6 %) on steroids, and 14 patients (9.5 %) were on everolimus immunosuppression. Of the patients, 37 (25 %) had concomitant atopic disease [asthma in 16 patients (10.8 %), allergic rhinitis in 15 patients (10.1 %), food allergy in five patients (3.4 %) and atopic eczema in four patients (2.7 %)]. Post-transplant 25(OH)D3 levels were above 20 ng / ml in 93 (62.8%) patients and below 10 ng / ml in 51 (35.5 %) patients.

Risk factors associated with 25(OH)D3 deficiency after liver transplantation

Post-transplant 25(OH)D3 deficiency was greater in patients with a follow-up period shorter than 12 months (p = <0.001), in those receiving immunosupression with mycophenolate mofetil (p <0.001), tacrolimus (p <0.001), steroids (p <0.001) and in those with low hematocrit rate and albumin levels (Table 1). Multiple logistic regression analysis revealed that the post-transplant follow-up period were shorter than 1 year (OR: 6.18, 95% CI: 2.681-14.255, p<0.001) and the use of steroid in chronic immunosuppression (OR: 9.47, 95% CI: 1.165-77.009, p=0.035) were found to be the independent risk factors associated with 25(OH)D3 deficiency (Table 2). There were not statistically significant correlation between post-transplant 25(OH)D3 deficiency and patients' age, transplantation indication, having transplanted organ from living donor, presence of concomitant atopic disease and serum phosphorus, calcium, alkaline phosphatase levels (Table 1).

Table 1: Demographics of patients who underwent liver transplantation (n:148).

Variable	Serum 25-D vitamin level > 20 ng/ml	Serum 25-D vitamin level ≤ 20 ng/ml	p-value
Male	42 (76.4)	57 (61.3)	0.089
Age, years (min-max)	41 (1-65)	44 (1-68)	0.476
Median duration of liver disease, months (min-max), month	6 (1-36)	6 (1-60)	0.3
Median duration of follow up, months (min-max)	9 (1-78)	5 (1-78)	<0.001
The time after liver transplantation ≤ 1 year	13 (24.1)	69 (76.7)	<0.001
Type of transplantation, living organ	48 (87.3)	82(88.2)	1.0
Indication of liver transplantation			
Acute fulminant (viral, drug, toxic)	5 (9.1)	6 (6.5)	0.538
Cholestatic liver disease	3 (5.5)	1 (1.1)	0.145
Chronic viral hepatitis	36 (65.5)	62 (66.7)	1.0
Metabolic*	6 (10.9)	10 (10.8)	1.0
Idiopathic	3 (5.5)	10 (10.8)	0.373
Other†	2 (3.8)	3 (3.4)	1.0
Chronic immunosuppressant regiment			
Tacrolimus	43 (78.2)	43 (46.2)	<0.001
Cyclosporine	4 (7.3)	1 (1.1)	0.064
Everolimus	4 (7.3)	10 (10.8)	0.683
Mycophenolate mofetil	6 (10.9)	39 (41.9)	<0.001
Steroid	1 (1.8)	31 (33.3)	<0.001
Co existing of atopic disease			
Asthma	7 (12.7)	9 (9.7)	0.592
Allergic rhinitis	3 (5.5)	12 (12.9)	0.242
Atopic eczema	1 (1.8)	3 (3.2)	1.0
Food allergy	3 (5.5)	2 (2.2)	0.361
Blood parameters, median (min-max) mg/dL			
Hematocrit	40.4 (33.1-54.1)	37.5 (23.3-54.1)	0.002
Serum calcium level	9.4 (7.9-10.1)	9.4 (8-10.8)	0.912
Serum phosphor level	3.5 (1.7-5.7)	3.3 (1.9-6.8)	0.378
Serum alkaline phosphates level	125 (43-693)	127 (42-602)	0.874
Serum albumin level	4 (1.9-4.7)	3.7 (2.8-4.7)	0.009

***Metabolic:** Wilson's disease;15, Alfa 1 anti trypsin;1
†**Other:** Autoimmune hepatitis;1, Giant cell hepatitis;1, Hepatocellular carsinoma; 2, Budd Chiary;1

Table 2: The multivariate analysis: potential predictors affecting D vitamin deficiency after liver Tx.

Variables	Univariate analysis		Multivarite analysis	
	Odds ratio (95% CI)	p- value	Odds ratio (95% CI)	p- value
Chronic Immunosuppressant regiment				
Tacrolimus	1.5 (1.208-2.1-9)	<0.001		
Mycophenolate mofetil	1.53 (1.261-1.866)	<0.001		
Steroid	1.47 (1.270-1.780)	<0.001	9.47(1.165-77.009)	0.035
The time after liver transplantation ≤ 1 year	3.25 (2.174-4.871)	<0.001	6.18(2.681-14.255)	<0.001
Hematocrit, median (min-max), mg/dL		0.002		
Serum albumin level, median (min-max), mg/dL		0.009		

DISCUSSION

Our study showed that two-thirds of the post-transplant patients had 25(OH)D3 deficiency. The use of steroids as immunosuppressants agents and the first year after transplantation were identified as a risk factors associated with 25(OH)D3 deficiency.

Deficiency of 25(OH)D3 is a major clinical problem for the most of the end-stage liver pathologies. Metabolic bone disease associated with 25(OH)D3 deficiency shows improvement in the long follow-up period after transplantation. However, metabolic bone disease and 25(OH)D3 deficiency remain major clinical problems within the first year after liver transplantation [13-15]. We detected that the frequency of 25(OH)D3 deficiency in the first year after transplantation is 6-fold higher than that of in subsequent years. 25(OH)D3 deficiency in the first year afterliver transplantation can be attributed to the post-transplant use of immunosuppressant agents to prevent rejection and pre-existing metabolic disorder.

A calcineurin inhibitor or an antimetabolite in addition to corticosteroids are used to prevent tissue rejection after liver transplantation. Corticosteroid therapy with antimetabolites (mycophenolate mofetil) or calcineurin inhibitors (tacrolimus) are given in the first 6 months and then the dose of steroid is reduced and ceased. Corticosteroids increase the catabolism of 25(OH)D3 and facilitate calcium deregulation [16]. Therefore, long-term use of steroids causes 25(OH)D3 deficiency and reduction in bone density. We also detected that the ratio of 25(OH)D3 deficiency in patients still receiving corticosteroid therapy to prevent rejection after liver transplantation was 9.5-fold higher than those not receiving corticosteroids. In their study, Eyal et al [6] investigated the risk factors associated 25(OH)D3 deficiency in 103 patients who underwent kidney transplantation. Similarly, they also reported higher rates of 25(OH)D3 deficiency in patients receiving corticosteroids treatment as an immunosuppressant agent.

Whether there is an association with 25(OH)D3 deficiency after solid organ transplantation and transplanted organ dysfunction is a controversial issue. Stein et al [17] reported positive correlation between high albumin level and high 25(OH)D3 levels after liver transplantation. However, Eyal et al [6] reported no relationship between transplanted kidney dysfunction and 25(OH)D3 deficiency. In our study, univariate analysis showed that 25(OH)D3 deficiency is more common in the post-transplant patients with low serum albumin and hematocrit levels. On the other hand, in multivariate analysis, the relation between 25(OH)D3 deficiency and low serum albumin levels and hematocrit rates was statistically insignificant.

In a previous study conducted to determine the associated risk factors with 25(OH)D3 deficiency after liver transplantation, the time of obtaining samples (winter or spring), ethnicity (non-white patients) and first year after transplantation were identified as the independent risk factors [18]. In our study, we obtained blood samples in summer to avoid possible changes in 25(OH)D3 levels. Therefore, we could not evaluate the correlation between seasonal variations and 25(OH)D3 levels. They also found that the first year after transplantation was an independent risk factor for 25(OH)D3 deficiency [18]. In addition, the period in which steroid was used as an immunosuppressant agent was an independent risk factor associated with 25(OH)D3 deficiency.

Our study has some limitations. First, not determining pre-transplant 25(OH)D3 deficiency in our patient group might have affected the relationship between 25(OH)D3 deficiency. Second, although samples were taken in summer, we did not examine the patient's daily exposure to sunlight. This might have affected the independent risk factors associated with 25(OH)D3 deficiency after transplantation.

Conclusion

25(OH)D3 deficiency is likely in more than half of the post-transplant patients. Especially, the period in which immunosuppression therapy with corticosteroids is used to prevent tissue rejection and the first year after transplantation are the risk factors for 25(OH)D3 deficiency. Therefore, serum

25(OH)D3 levels should be monitored in the post-transplant patients and supplementary therapy should be given to the patients having deficient levels of vitamin D.

REFERENCES

1. Sylvester FA. Bone abnormalities in gastrointestinal and hepatic disease. Curr Opin Pediatr 1999;11:402-407.
2. Southerland JC, Valentine JF. Osteopenia and osteoporosis in gastrointestinal diseases: Diagnosis and treatment. Curr Gastroenterol Rep 2001;3:399-407.
3. Ginde AA, Liu MC, Camargo CA Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988–2004. Arch Intern Med 2009;23:626-632.
4. Maalouf NM, Shane E. Osteoporosis after solid organ transplantation. J Clin Endocrinol Metab 2005;90:2456-2465.
5. D'antiga L, Moniz C, Buxton-Thomas M, Cheeseman P, Gray B, Abraha H, et al. Bone mineral density and height gain in children with chronic cholestatic liver disease undergoing transplantation. Transplantation 2002;73:1788-1793.
6. Eyal O, Aharon M, Safadi R, Elhalel MD. Serum vitamin D levels in kidney transplant recipients: the importance of an immunosuppression regimen and sun exposure. Isr Med Assoc J 2013; 15:628-633.
7. Pascussi JM, Robert A, Nguyen M, Walrant-Debray O, Garabedian M, Martin P, et al. Possible involvement of pregnane X receptor-enhanced CYP24 expression in drug-induced osteomalacia. J Clin Invest 2005;115:177-186.
8. Morris HA. Vitamin D: A hormone for all seasons–how much is enough? Clin Biochem Rev 2005;26:21-32.
9. Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001–2004. Pediatrics 2009;124:371-379.
10. Reis JP, von Mühlen D, Miller ER 3rd, Michos ED, Appel LJ. Vitamin D status and cardiometabolic risk factors in the United States adolescent population. Pediatrics 2009;124:371-379.
11. Zittermann A, Schleithoff SS, Koerfer R. Putting cardiovascular disease and vitamin D insufficiency into perspective. Br J Nutr 2005;94:483-492.
12. Branch AD, Barin B, Rahman A, Stock P, Schiano TD. Vitamin D status of human immunodeficiency virus-positive patients with advanced liver disease enrolled in the solid organ transplantation in HIV: Multi-site study. Liver Transpl 2014;20:156-164.
13. Valta H, Jalanko H, Holmberg C, Helenius I, Mäkitie O. Impaired bone health in adolescents after liver transplantation. Am J Transplant 2008; 8:150-157.
14. D'antıga L, Ballan D, Luisetto G, Cillo U, Guariso G, Zancan L. Long-term outcome of bone mineral density in children who underwent a successful liver transplantation. Transplantation 2004;78:899-903.
15. American Diabetes Association. Standards of Medical Care in Diabetes-2011. Diabetes Care 2011;34:11-61.
16. Zhou C, Assem M, Tay JC, Watkins PB, Blumberg B, Schuetz EG, et al. Steroid and xenobiotic receptor and vitamin D receptor crosstalk mediates CYP24 expression and drug-induced osteomalacia. J Clin Invest 2006;116:1703-1712.
17. Stein EM, Cohen A, Freeby M, Rogers H, Kokolus S, Scott V, et al. Severe vitamin D deficiency among heart and liver transplant recipients. Clin Transplant 2009;23:861-865.
18. Legarda M, Gordon G, Lloyd C, Baumann U, Kelly DA, Shaw N, et al. Vitamin D deficiency and insufficiency after pediatric liver transplantation. Pediatr Transplant 2013;17:631-637.