

THE RELATIONSHIP OF VITAMIN D LEVELS WITH EARLY MORTALITY IN PATIENTS WITH ACUTE CORONARY SYNDROME AND VALUE OF VITAMIN D LEVELS AS A CARDIOVASCULAR RISK FACTOR

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ABSTRACT

Objective: Acute coronary syndrome (ACS) is the main cause of mortality and morbidity worldwide. This study aims to determine the serum vitamin D level in patients with ACS, determine whether the serum 25-hydroxy-vitamin D level is associated with the ACS and to investigate whether serum vitamin D level is effective on early (first 30 days after diagnosis) mortality in patients with ACS, or not.

Material and Method: Sixty five ACS cases (37 males and 28 females) over 18 years old, and 40 controls (20 males and 20 females) with an age and gender distribution similar to the patient group and with no systemic diseases took part in the study. Serum 25-hydroxy-vitamin D level has been clinically described as severe deficiency for <10 ng/ml, deficiency for 10-20 ng/ml, failure for 20-30 ng/ml, and normal for >30 ng/ml based on serum 25-hydroxy-vitamin D levels.

Results: The vitamin D levels of patients in the ACS were found to be significantly lower than the control group. Vitamin D failure distribution differs ($p<0.05$) in the case group and control group. Severe failure and failure rates were higher in the case group. Severe vitamin D failure was found in 27 (41.5%) patients with ACS, vitamin D failure was found in 24 (36%) patients. Three early mortality cases were seen in the ACS patients.

Conclusion: Our data suggest that a low serum 25-hydroxy-vitamin D level predisposes the ACS development. This shows us that serum 25-hydroxy-vitamin D level can be used as a risk factor in the diagnosis of ACS. Serum 25-hydroxy-vitamin D level was also found to be low in early mortality patients with ACS.

Key Words: Vitamin D, acute coronary syndrome, mortality Nobel Med 2014; 10(3): 69-74

AKUT KORONER SENDROMLU HASTALARDA D VİTAMİNİ DÜZEYLERİ İLE ERKEN MORTALİTE İLİŞKİSİ VE KARDİYOVASKÜLER RİSK FAKTÖRÜ OLARAK D VİTAMİNİNİN ÖNEMİ

ÖZET

Amaç: Akut koroner sendromlar tüm dünyada mortalite ve morbiditenin ana sebebidir. Kardiyovasküler olaylar ve D vitamini ilişkisi daha önceki çalışmalarda gösterilmişti. Çalışmamızda akut koroner sendromlu hastalardaki serum D vitamini düzeyinin tespitini, böylece serum D vitamini düzeyinin akut koroner sendromla ilişkili olup olmadığını saptamayı ve yine serum vitamin D düzeyinin akut koroner sendromlu hastalardaki erken dönem (tanı sonrası ilk 30 gün) mortalite üzerine etkisi olup olmadığını araştırmayı amaçladık.

Materyal ve Metod: Öngördüğümüz kriterlere uyan 18 yaş üstü, 65 akut koroner sendrom vakası (37 erkek, 28 kadın) yazılı onamları alındıktan sonra, çalışmamıza dahil edildi. Aynı zamanda yaş ve cinsiyet olarak hasta grubu ile benzer nitelikte, herhangi bir

sistemik hastalığı bulunmayan 40 kişi (20 erkek, 20 kadın) kontrol grubu olarak çalışmaya dahil edildi. Serum 25-hidroksi vitamin D seviyesi <10 ng/ml ise ciddi eksiklik, 10-20 ng/ml arası eksiklik, 20-30 ng/ml ise yeterli olarak tanımlandı.

Bulgular: Akut koroner sendromlu hastalarda D vitamini düzeyi kontrol grubuna göre anlamlı olarak daha düşük bulundu ($p<0,05$). D vitamini yetersizliği ve ağır yetersizliği kontrol grubuna göre belirgin yüksek bulundu. Ciddi vitamin D yetersizliği akut koroner sendromlu 27 (%41,5) hastada; vitamin D yetersizliği ise 24 (%36) hastada görüldü. Akut koroner sendromlu üç hastada izlenen erken mortalite de vitamin D yetersizliği olan grupta izlendi.

Sonuç: Elde ettiğimiz veriler düşük serum 25-hidroksi-vitamin D düzeylerinin akut koroner sendrom gelişiminde etkili olduğunu düşündürmektedir. Bu bize düşük serum 25-hidroksi-vitamin D düzeylerinin akut koroner sendrom için bir risk faktörü ve erken dönem mortalite ile ilişkili olduğunu göstermektedir.

Anahtar Kelimeler: D vitamini, akut koroner sendrom, mortalite Nobel Med 2014; 10(3): 69-74

INTRODUCTION

Acute coronary syndrome (ACS) is the main cause of mortality and morbidity worldwide. An improvement in clinical outcome may be achieved by clearly identifying the risk factors and with an optimum treatment following an early and accurate diagnosis. Certain biochemical markers can also be used as well as classical risk factors to be able to make a risk assessment for ACS.¹⁻³

Vitamin D is a hormone which is an effective on many systems in the body. In addition to the known effects of vitamin D on the musculoskeletal system, epidemiological studies associate it with many diseases including carcinomas, autoimmune diseases, hypertension, and cardiovascular diseases possibly due to the anti-inflammatory and immunomodulatory properties of vitamin D and its potential effects on cytokine levels.⁴⁻⁸ Studies have reported that suboptimal vitamin D levels are associated with an increased risk in cardiovascular diseases.¹¹ A lower rate of mortality associated with cardiovascular diseases is reported in patients with higher vitamin D values. A higher rate of coronary diseases is seen in Nordic countries, with heart attacks occurring 53% more in winter time.^{9,10}

This study aims to determine the serum vitamin D level in patients with ACS, determine whether the serum vitamin D level is associated with the ACS and to investigate whether or not serum vitamin D level is effective on early (first 30 days after diagnosis) mortality in patients with ACS.

MATERIAL and METHOD

Sixty-five ACS patients (37 males and 28 females) over 18 years old, who were hospitalized at the Coronary Intensive Care Unit, were included in this study after their written approved consents were obtained. At the same time, 40 controls (20 males and 20 females), who admitted to our hospital with an age and gender distribution similar to the patient group and with no systemic diseases, were included in this study after their written approved consents were obtained. Approval was obtained for the study from the ethical committee (Date: 26.01.2012, Decision number:190).

Patients diagnosed with osteomalacia and osteoporosis, patients using medications containing calcium and vitamin D, and patients with hyperthyroidism, hypoparathyroidism, chronic renal failure, chronic liver disease, and malignities were not included in the study. →

Fasting blood samples were collected from the patients in gel tubes in the first 24 hours after their hospitalization in order to determine serum 25 hydroxy-vitamin D level. Blood samples were transferred to the laboratory in a cool dark container. They were centrifuged at 3000 rpm for 5 minutes. Then their plasma membranes were isolated. They were kept at -20°C until the day of analysis. They were left to melting in room temperature on the analysis date. Then, the collected samples were chromatographically measured in the HPLC device. A Serum 25(OH) vitamin D level <10 ng/ml was described as severe deficiency, 10-20 ng/ml as deficiency, and 20-30 ng/ml as failure.

Patients included in the study were followed for mortality within the first 30 days after the diagnosis of early mortality, ACS.

SPSS 20.0 (Statistical Package for Social Sciences 20) was used for statistical analyses when evaluating the findings of this study. Mean, standard deviation, percentage, and frequency values were used in the descriptive statistics of data. The Kolmogorov Smirnov test was used to analyze the distribution of data. An independent sample t-test was used to analyze quantitative data. Chi-square test was used to analyze qualitative data. Efficacy was analyzed using the ROC curve and logistic regression. $p < 0.05$ was considered statistically meaningful for the results.

RESULTS

This study included 37 males (56.9%) and 28 (43.1%) females, total of 65 patients. The mean age of the group with ACS was found to be 62 ± 11 years. 20 were males (50%) and 20 females (50%) out of the 40 persons in the control group included in the study. The mean age of the control group was found to be 60 ± 7 . The difference between the ages and genders of the group with ACS included in the study and the control group was not statistically significant ($p > 0.05$) (Table 1).

The mean vitamin D level of patients in the ACS group was found to be 14.63 ± 10.94 ng/ml and the mean vitamin D level was found to be 26.38 ± 11.72 ng/ml in the control group. The vitamin D levels of patients in the ACS were found to be significantly lower ($p < 0.001$) than the control group (Figure 1) (Table 2).

The mean serum 25-hydroxy-vitamin D level in the ACS group was found to be 14.3 ± 6.3 ng/ml in male patients and 15.0 ± 15.2 ng/ml in female patients. No significant difference ($p > 0.05$) was found between the vitamin D levels of male and female patients in the ACS group and in the control group (Figure 2).

Table 1: Age and gender distributions of the group with ACS and the control group.

		Case Group	Control Group	p
Age (Mean±S.D)		62±11	60±7	0,381
Gender	Male	37	20	0,489
	Female	28	20	

Chi-square test/ Independent sample t-test

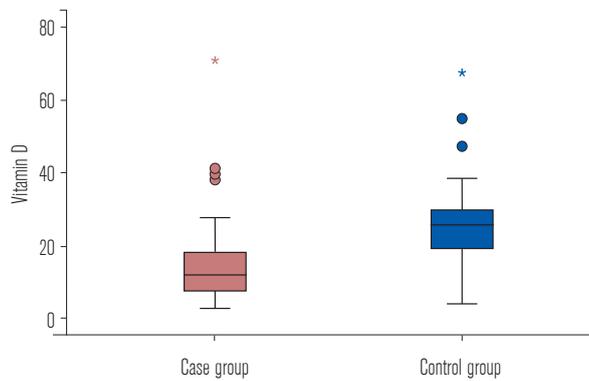


Figure 1: Serum 25-hydroxy-vitamin D levels of the acute coronary syndrome group and the control group.

Vitamin D failure distribution differs ($p < 0.05$) in the case group and control group. Severe failure and failure rates were higher in the case group. Severe vitamin D failure was found in 27 (41.5%) patients with ACS, vitamin D failure was found in 24 (36%) patients, vitamin D deficiency was found in 10 (15.4%) patients and a normal vitamin D level was found and in 4 (6.2%) patients (Table 3)

The cut off value with the highest area under the curve of vitamin D level of patients with ACS was found to be 18 ng/ml (Figure 3).

Sensitivity was 73.8% and specificity was 80% in pointing out the ACS from the vitamin D level 18 ng/ml cut off value. The positive predictive value was 85.7%, and the negative predictive value was 65.3%.

Three early mortality cases were seen in the ACS patients (4.6%). Serum 25-hydroxy-vitamin D levels of these 3 cases were found to be 5.61 ng/ml, 12.74 ng/ml and 17.33 ng/ml, respectively Vitamin D level in all 3 of these cases was below 18 ng/ml (Table 4).

DISCUSSION

Coronary heart disease and ACS are the major causes of mortality and morbidity worldwide. Cardiovascular risk factors should be controlled first in order to be able to reduce the incidence and →

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Table 2: Serum 25-hydroxy-vitamin D levels of the ACS group and the control group.			
	Case Group	Control Group	p
Vitamin D (Mean±S.D.)	14.63±10.94	26.28±11.72	<0,005

Table 3: Clinical classification of case and control groups by 25-hydroxy-vitamin D levels.					
Vitamin D level	Case Group		Control Group		p
	n	%	n	%	
Severe failure	27	41,5	1	2,5	0,005
Failure	24	36,9	10	25	
Deficiency	10	15,4	19	47,5	
Normal	4	6,2	10	25	

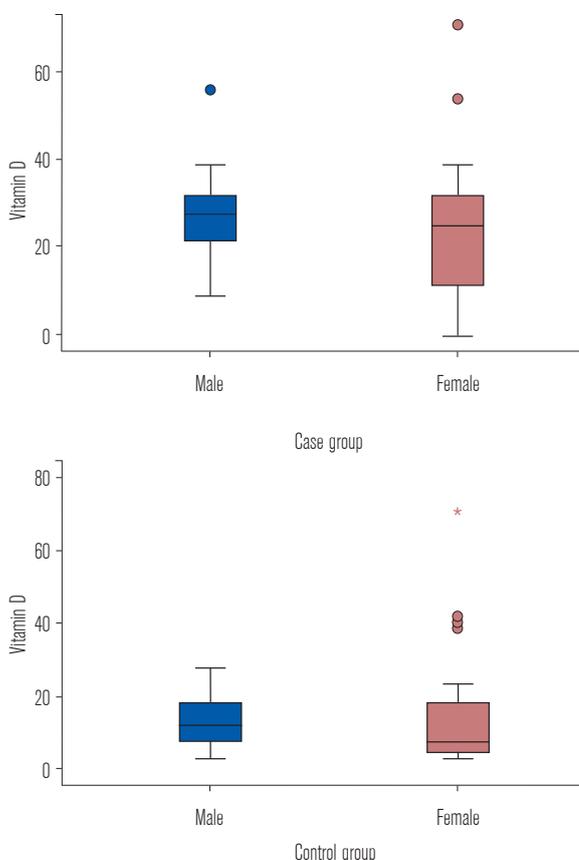


Figure 2: Serum 25-hydroxy-vitamin D level by gender in the case and control groups

mortality rates of coronary heart diseases and other cardiovascular diseases. It is a common knowledge that there are significant risk factors for ACS, with remediable (diabetes mellitus, metabolic syndrome, hyperlipidemia) and non-remediable (age, gender, family history) properties.

Vitamin D level is an important marker in cardiovascular area. Previous studies have revealed that vitamin D has very important biological

effects including cellular differentiation, inhibition of proliferation and immune modulation.^{11,12} Vitamin D deficiency is today described as one of the most common medical conditions in the world. Vitamin D deficiency is associated with risk for a first cardiovascular event in the general population, possibly because of inflammation, insulin resistance and neurohumoral activation.¹³ Serum 25-hydroxy-vitamin D is the major portion of the vitamin D in circulation and is the best parameter giving information about the entire vitamin D pool of the body. Serum 25-hydroxy-vitamin D measurement is the most reliable method in determining vitamin D level.^{7,14} There is no consensus on the optimal level of serum 25-hydroxy-vitamin D in healthy population. Most specialists consider a serum vitamin D level below 20 ng/ml as a deficiency.¹⁵

Many studies have demonstrated that vitamin D is vital in preventing many types of cancer, and autoimmune, cardiovascular and infectious diseases as well as healthy bone development.^{4-6,8} Recent epidemiological studies associate low vitamin D levels with increased risk of many diseases including cancers, autoimmune diseases, hypertension and infectious diseases due to the anti-inflammatory, immunomodulator properties of vitamin D and its effects on cytokine levels.^{7,16} Moreover, many epidemiological and clinical studies note that there exists a strong relationship between vitamin D deficiency and cardiovascular diseases.^{13,17-19} Observational studies have shown that there exists a relationship between low vitamin D levels and blood pressure, coronary-artery calcification and presence of cardiovascular disease.^{20,21}

Correia et al. demonstrated severe vitamin D deficiency is independently associated with in-hospital cardiovascular mortality in patients with acute coronary syndromes.¹³ In their study, they accepted that severe vitamin D deficiency was defined as value ≤ 10 ng/ml. They reported that the average concentration of vitamin D was 20 ± 8.2 ng/ml and 10% of patients were severely deficient. Cardiovascular mortality during hospitalization took place in 14 patients, an incidence of 6.8%. Patients with severe vitamin D deficiency had in hospital cardiovascular mortality of 24%, significantly higher than the remaining patients that observed cardiovascular mortality of 4.9%.

In our study, vitamin D levels of patients in the ACS group were found to be significantly lower than the patients in the control group. The distribution of vitamin D failure showed a meaningful difference →

in the case group and control group. Vitamin D failure and the severe D vitamin failure in the case group were found to be meaningfully higher than the control group. Dror et al., in their study, found 20 to 36 ng/mL to be the safe D vitamin limit for cardiovascular diseases.²² In this study, ACS patients, the highest cut off value of the area under the curve was 18 ng/ml in separating the vitamin D level and the control group. The possibility of vitamin D being 18 ng/ml or below in ACS patients was 11.3 times more than its being over 18 ng/ml (4,4-29,2) ($p < 0,05$). Three early mortality cases (4.6%) were seen in the ACS patients. Vitamin D level was below 18 ng/ml in all of the 3 cases. One of them (33.3%) had severe vitamin D deficiency.

To summarize, serum 25-hydroxy-vitamin D level was found to be significantly low in patients with ACS in this patient. This shows us that serum 25-hydroxy-vitamin D level can be used as a risk factor in the diagnosis of ACS. Serum 25-hydroxy-vitamin D level was also found to be low in early mortality patients with ACS. However, it is not possible to conclude that low vitamin D causes mortality based on this data. Low number of cases has been the most important restrictive factor. Larger future studies can shed light on this subject.

Study Limitations

A major limitation of our study is the ability to detect sample size in different groups without doing a power analysis. Thus, this study should be considered a pilot study and additional studies should be conducted in future.

CONCLUSION

A significant relationship was found between vitamin D deficiency and cardiovascular diseases. We consider that the anti-inflammatory, immunomodulator, and

Table 4: A comparison of the vitamin D level of patients with and without mortality in the early period in the ACS by an 18 ng/ml cut off value of the vitamin D level

	Early Mortality			
	Yes		No	
Vitamin D	n	%	n	%
<18	3	100	45	72.60
18<	0	0	17	27.40

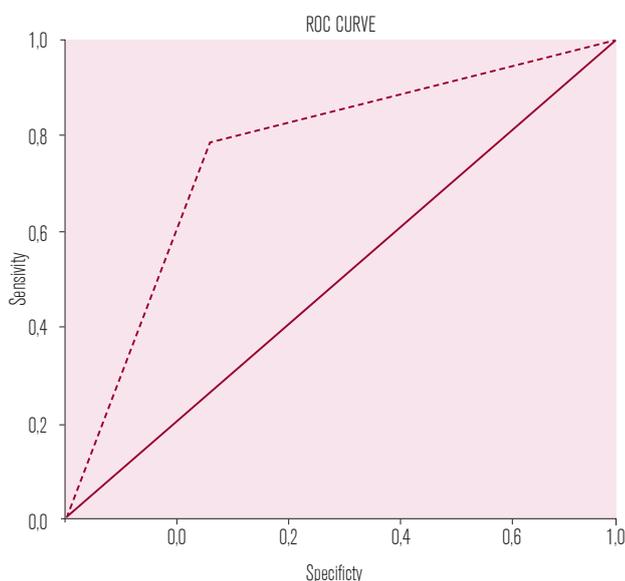


Figure 3: ROC curve comparing the acute coronary syndrome group with the control group by serum 25 hydroxy-vitamin D level

anti-proliferative effects of vitamin D could be the underlying cause. A low serum 25-hydroxy-vitamin D level predisposes the ACS development. Future studies with wider patient population will give better results in showing the effects of 25-hydroxy-vitamin D level on early mortality in patients with ACS.

* The authors declare that there are no conflicts of interest.

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