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Original Article / *Özgün Makale*

Atrial fibrillation after cardiac surgery and preoperative vitamin D levels: A systematic review and meta-analysis

Kalp cerrahisi sonrasında atriyal fibrilasyon ve ameliyat öncesi D vitamini düzeyleri: Sistematik derleme ve meta-analiz

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ABSTRACT

Background: In this meta-analysis, we aimed to investigate the possible relationship between atrial fibrillation development after cardiac surgery and preoperative vitamin D levels.

Methods: Literature review was carried out in the PubMed, ScienceDirect and Ovid electronic databases without any limitation of time frame. Published studies which recorded the preoperative levels of vitamin D and atrial fibrillation after cardiac surgery in the English language were included. The results of the studies were evaluated based on either random or fixed effect model according to the presence of heterogeneity (I^2>25%).

Results: A total of 1,865 articles were screened. After the article titles and abstracts were analyzed, six articles involving 769 patients which met the inclusion criteria were included. The results indicated that there was a relationship between preoperative vitamin D levels and postoperative atrial fibrillation (SMD: -0.46, 95% CI: -0.79 to -0.12; p<0.007). Heterogeneity was observed for studies conducted (I^2 =76.1%).

Conclusion: We concluded that low preoperative vitamin D levels were associated with the development of atrial fibrillation after cardiac surgery. However, there is a need for large-scale, randomized-controlled trials for preventing the heterogeneity of the results.

Keywords: Atrial fibrillation, cardiac surgery, meta-analysis, Vitamin D.

ÖZ

Amaç: Bu meta-analizde, kalp cerrahisi sonrasında atriyal fibrilasyon gelişimi ve ameliyat öncesi D vitamini düzeyleri arasındaki muhtemel ilişki araştırıldı.

Çalışma planı: Tarih sınırlaması olmaksızın PubMed, ScienceDirect ve Ovid elektronik veri tabanlarında literatür taraması yapıldı. Ameliyat öncesi D vitamini düzeylerinin ve ameliyat sonrası atriyal fibrilasyonun kaydedildiği İngilizce dilindeki yayımlanmış çalışmalar dahil edildi. Çalışma sonuçları, heterojenite varlığına göre rastgele etki veya sabit etki modeli ile değerlendirildi (I^2>%25).

Bulgular: Toplam 1865 makale tarandı. Makale başlıkları ve özetleri incelendikten sonra, dahil edilme kriterlerini karşılayan 769 hastayı kapsayan altı makale alındı. Bulgular, D vitamini düzeyleri ile ameliyat sonrası atriyal fibrilasyon arasında bir ilişki olduğunu gösterdi (SMD: -0.46, %95 CI: -0.79 ila -0,12; p<0.007). Yürütülen çalışmalarda heterojenite gözlendi (I^2 =%76.1).

Sonuç: Ameliyat öncesi düşük D vitamini düzeylerinin kalp cerrahisinden sonra atriyal fibrilasyon gelişimi ile ilişkili olduğu sonucuna varıldı. Ancak bulgulardaki heterojeniteyi önlemek için daha geniş ölçekli, randomize kontrollü çalışmalara ihtiyaç vardır.

Anahtar sözcükler: Atriyal fibrilasyon, kalp cerrahisi, meta-analiz D vitamini.

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Atrial fibrillation (AF) following cardiac surgery occurs in 20 to 50% of patients.[1] Increased age is the most well-known risk factor for POAF.[2] The increasing number of elderly patients for cardiac surgery also increases the possibility of postoperative AF (POAF) development. Postoperative AF is associated with increased mortality, cost, and stroke.[3-5] In the pathogenesis of POAF, several factors such as local/systemic inflammation and oxidative stress or electrolyte imbalance have been proposed to play a role.[6] There are also several risk factors which contribute to POAF such as age, heart failure, coronary artery disease, prior history of AF, other arrhythmias, hypertension, male gender, chronic obstructive pulmonary disease, kidney disease, diabetes, and obesity.[6]

Vitamin D is a fat-soluble vitamin.[7] It is produced under the skin on exposure to ultraviolet sunlight and metabolized in liver and kidney.[8] Rickets, osteomalacia, osteoporosis, and skin diseases are associated with the low levels of vitamin D. [7] Although vitamin D is associated with calcium metabolism and bone health, vitamin D receptors have been found in cells throughout the body, such as cardiomyocytes, suggesting that it has additional functions.[9] In addition, studies have demonstrated that vitamin D is associated with cardiovascular diseases such as coronary artery disease, myocardial infarction, cardiomyopathy, and heart failure.[10-13] Vitamin D can regulate the renin-angiotensin-aldosterone system activity and inflammatory processes.[14] These processes which implicate in the pathophysiology of AF, suggest a potential role of vitamin D in the etiology of AF.

In previous prospective cohort studies, no significant relationship between AF and vitamin D deficiency has been established.[15,16] However, two case-control studies demonstrated that there was a link between low vitamin D levels and non-valvular AF.[17,18] In recent years, the number of studies regarding vitamin D levels and AF has been on a rise. In this systematic review and meta-analysis, we aimed to investigate the possible relationship between AF after cardiac surgery and preoperative vitamin D levels in the light of literature data.

MATERIALS AND METHODS

Database search

We carried out our database search in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA®) statement which was specifically developed for meta-analyses to improve the reporting of reviews by Moher et al.[19] in 2015. An electronic database search in the English language was conducted to identify whether preoperative vitamin D levels might be associated with POAF. The database was screened until the date of March 9, 2019. No time frame limitation was applied. The PubMed, ScienceDirect, and Ovid were utilized as the electronic databases. No searches were conducted other than the electronic database. However, articles found in the references section of articles which may be of interest were analyzed.

The following English keywords or a combination of them were used: “atrial fibrillation”, “cardiac surgery”, “heart surgery”, “valve surgery”, “coronary artery bypass grafting”, and “vitamin D”. Only articles published in English were screened, and those in other languages were excluded.

Selection of studies

All retrospective and prospective studies were included, irrespective of the sample size. *Inclusion criteria were as follows: (i)* clinical study, *(ii)* adult patient population, and *(iii)* articles in English language. *Exclusion criteria were as follows: (i)* experimental studies, *(ii)* case studies or case series, *(iii)* articles in languages other than English, and *(iv)* utilizing non-cardiac surgical interventions. Studies which were relevant to our subject of study, but that did not investigate preoperative vitamin D levels were not included. In addition, articles in which relevant data were presented as figures or graphs were also excluded.

Data collection

Researchers recorded the data in the relevant articles (name of the first author, date of publication, sample number, and research design) independently from each other. Disagreements between the data and articles were resolved on the basis of consensus. Data were entered using the meta-analysis software and expressed in mean and standard deviation (SD), or number and frequency. Data presented in median (min-max) were calculated in mean and SD values according to the formula by Hozo et al.[20]

Statistical analysis

For the statistical analysis, Open Meta-Analyst® software (Brown University, Rhode Island, USA) was used. For funnel plot, we performed analysis with MetaLight® v1.2.0 software (University College London, London, United Kingdom). Data were expressed in standard mean differences (SMD) and 95% confidence interval (CI). Heterogeneity was evaluated by I^2 statistics. If $I^2 \geq 25\%$, heterogeneity was accepted as significant, and analysis of moderators was undertaken to identify the cause of heterogeneity.

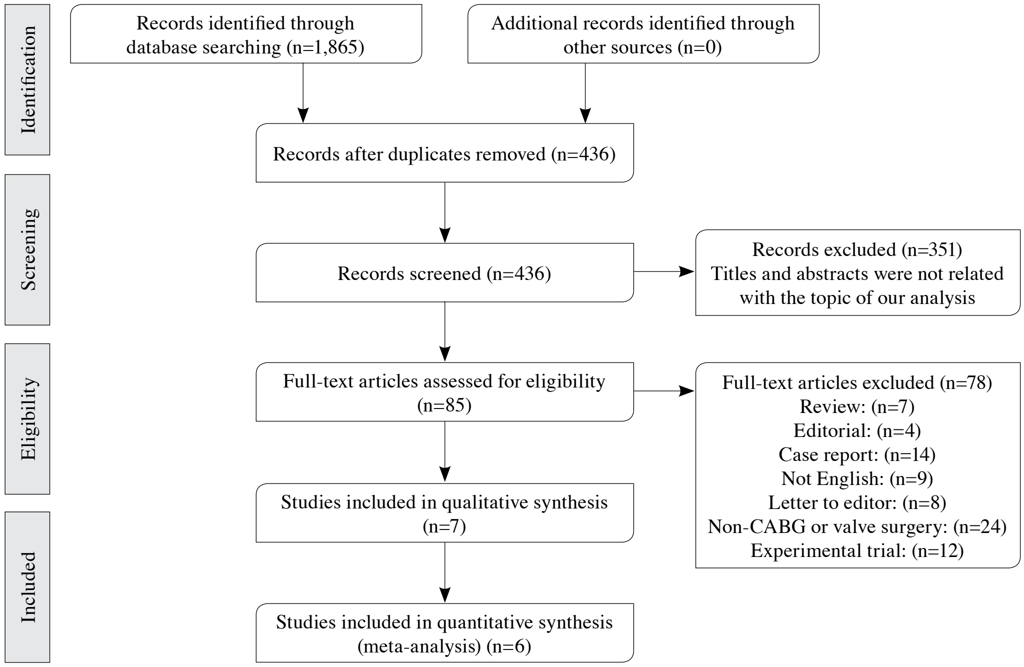

Figure 1. Flow chart of database search.
CABG: Coronary artery bypass grafting

Meta-analysis was carried out using fixed or random models. In the presence of heterogeneity (I^2>25%), random effects model was used, while in its absence (I^2<25%), fixed effect model was used. Publication bias was evaluated with the Begg's test. File drawer analysis was performed using the Jamovi® v0.9 software (retrieved from https://www.jamovi.org). A *p* value of <0.05 was considered statistically significant.

RESULTS

The flow chart of literature search is shown in Figure 1.

A total of 1,865 articles were identified in the electronic databases. After the repeating articles were excluded, 436 articles were left. Upon reviewing the abstracts and titles of the articles, 351 articles which were not relevant with the subject were eliminated. Of the remaining 85 articles, the entire texts of 78 which were analyzed for compliance with the meta-analysis were excluded (review article: 7, editorial: 4, case report: 14, not in English language: 9, letter to editor: 8, non-coronary artery bypass grafting [CABG] or valve surgery population: 24, and experimental trial: 12). Seven of them were evaluated in the qualitative

Table 1. Properties of trials included the analysis

					Binary logistic regression analysis			
	Date	POAF (n)	SR (n)	Comparing the groups	Univariate analysis	Multivariate analysis	Trial design	Time process for data collection
Skuladottir et al.[26]	2016	66	52	+	+	-	Prospective	Non-randomized
Emren et al.[25]	2016	72	211	+	+	+	Prospective	Non-randomized
Shadvar et al.[24]	2016	25	25	-	-	-	Prospective	Randomized
Cerit et al.[23]	2017	41	87	+	+	-	Retrospective	Non-randomized
Gode et al.[22]	2016	15	75	+	+	+	Prospective	Non-randomized
Özsin et al.[21]	2018	50	50	+	+	+	Prospective	Randomized

POAF: Postoperative atrial fibrillation; SR: Sinus rhythm +: Statistically significant; -: Statistically not significant. Only two of studies were randomized (Shadvar et al.[24] and Özsin et al.[21]). Vitamin D levels were related with POAF according to univariate logistic regression analysis in all studies except Shadvar et al.[24] and Cerit et al.[23] and Skuladottir et al.[26] could not show any relation according to multivariate regression analysis. Data of the studies except Cerit et al.[23] were collected prospectively.

Studies	Estimate (95% CI)
Skuladottir et al.[26]	0.265 (-0.100, 0.630)
Emren et al.[25]	-0.398 (-0.668, -0.129)
Shadvar et al.[24]	-0.443 (-1.004, 0.118)
Cerit et al.[23]	-0.798 (-1.182, -0.414)
Gode et al.[22]	-0.748 (-1.313, -0.183)
Özsin et al.[21]	-0.736 (-1.141, -0.331)
Overall (I^2=76.1%, p<0.001) -0.462 (-0.798, -0.125)	

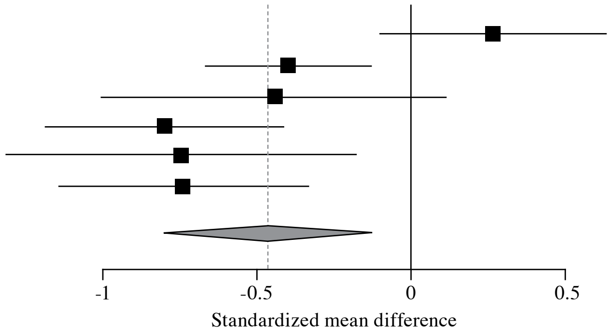

Figure 2. Forest plot of overall analysis.
CI: Confidence interval;

synthesis and finally, a total of six research studies involving 769 patients were included in the quantitative synthesis.[21-26] Demographic data and characteristics of the articles are summarized in Table 1. The overall POAF development rate was 34.98% (269/769).

As a result of analysis of the articles, heterogeneity was observed (Q: 20.92, df(5), p<0.001, I^2: 76.1%). Therefore, the random effects model was used for the final analysis. Accordingly, there was a statistically significant relationship between the preoperative levels of vitamin D and AF after cardiac surgery (SMD: -0.46, 95% CI: -0.79 to -0.12; p=0.007). The results are given in Figure 2 and Table 2.

When we analyzed heterogeneity among the studies, we reviewed the randomization as a moderator. We also found the main reason of heterogeneity to be non-randomization (I^2>25%). Subgroup analysis for moderator is shown in Figure 3 and Table 2. However,

Table 2. Results of analysis

	Results				Heterogeneity				Publication bias
	SMD	95% CI		*p*	Q	df	*p*	I^2 (%)	Tau²
Retrospective studies	-	-	-	-	-	-	-	-	-
Prospective studies	-0.39	-0.76	-0.01	0.04*	16.53	4	0.002	75.8	0.13
Randomized studies	-0.63	-0.96	-0.3	<0.001*	0.69	1	0.4	0	0.00*
Non-randomized studies	-0.4	-0.86	0.06	0.09	18.15	3	<0.001	83.47	0.18
Overall analysis	-0.46	-0.79	-0.12	0.007*	20.92	5	<0.001	76.1	0.13

CI: Confidence interval; SMD: Standard mean difference; * Statistically significant <0.05.

Studies	Estimate (95% CI)
Skuladottir et al.[26]	0.265 (-0.100, 0.630)
Emren et al.[25]	-0.398 (-0.668, -0.129)
Cerit et al.[23]	-0.798 (-1.182, -0.414)
Gode et al.[22]	-0.748 (-1.313, -0.183)
Subgroup nonrandomized (I^2=83.47%, p=0.000)	-0.402 (-0.867, 0.062)
Shadvar et al.[24]	-0.443 (-1.004, 0.118)
Özsin et al.[21]	-0.736 (-1.141, -0.331)
Subgroup randomized (I^2=0%, p=0.406)	-0.636 (-0.964, -0.307)
Overall (I^2=76.1%, p=0.001)	-0.462 (-0.798, -0.125)

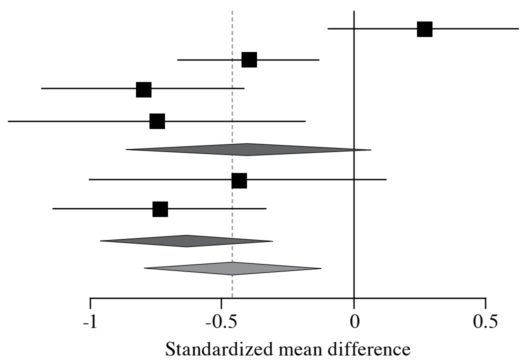

Figure 3. Forest plot of subgroup analysis according to randomization.
CI: Confidence interval.

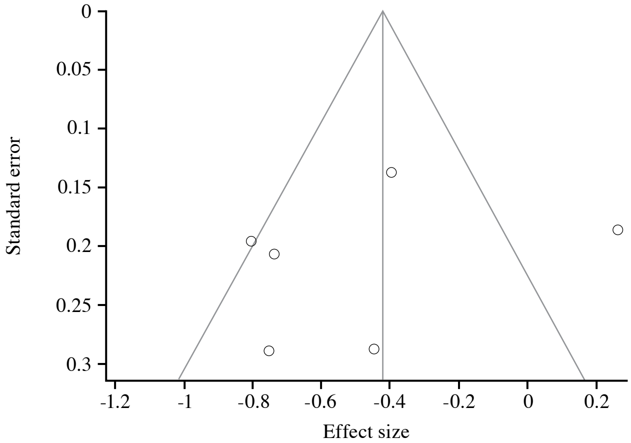

Figure 4. Funnel plot for publication bias.

we were unable to perform the designs of studies according to time process such as prospective or retrospective, as there was only one retrospective study.[23] The results of the heterogeneity analysis are summarized in Table 2.

Model fitting weights were between 19.79% (Emren et al.[25]) and 13.83% (Gode et al.[22]).

According to the Begg's test, there was no significant publication bias among the studies (tau 2 >0.05). However, due to its asymmetrical nature, this was not completely corrected based on visual analysis with funnel plot. Funnel plot is shown in Figure 4. The number of fail-safe studies according to the file drawer analysis was 7. However, we thought that this figure was not realistic, as only three databases were able to be screened in detail. Furthermore, we were unable to perform meta-regression, due to the small number (<10) of studies included in the meta-analysis.

DISCUSSION

In this meta-analysis, we found that there was a significant relationship between the preoperative levels of vitamin D and AF after cardiac surgery (p<0.05). However, there was heterogeneity among the studies and non-randomization was the main reason for heterogeneity.

Ruiz-Núñez et al.[27] reviewed 55 patients undergoing CABG and found that dietary vitamin D intake was below the recommendations. The percentage was 13%, while the recommended dose was 10 to 20 µg/dL. A recent study also demonstrated that preoperative vitamin D supplementation had a preventive effect for POAF in vitamin D deficiency (serum levels of vitamin D <20 ng/mL).[28]

In the literature, Rienstra et al.[15] and Qayyum et al.[29] found no significant correlation between AF development and 25(OH)D, while more recent studies[9,10] demonstrated that low 25(OH)D was related to non-valvular AF. In addition, hypertension, coronary artery disease, and stroke have been shown to be linked with vitamin D deficiency.[30] On the other hand, the relationship with vitamin D and AF is still controversial. In recent two meta-analyses, this topic was examined.[31,32] Zhang et al.[31] concluded that vitamin D deficiency modestly increased the risk for AF and found that there was a need for further studies to determine the direct causal relationship. In the second and more recent meta-analysis, Huang et al.[32] was unable to show that vitamin D levels might play a major role in the development of new-onset AF. Of note, Zhang et al.[31] did not include the cardiac surgery patients, while Huang et al.[32] included either surgical or non-surgical patients in their study. In our analysis, cardiac surgery population was included.

In an experimental study, Xiang et al.[33] reported that vitamin D regulated cardiac functions through systemic and cardiac renin-angiotensin-aldosterone system. Due to the activation of tissue renin-angiotensin-aldosterone system, vitamin D may lead to new-onset AF.[34] Therefore, the mechanism between vitamin D and AF is associated with apoptosis of cardiomyocytes and changes in the atrial structure due to renin-angiotensin-aldosterone system induction.[35] Also, vitamin D was found to be related with endothelial dysfunction and subclinical atherosclerosis.[36] In the *in vitro* experiments, Canning et al.[37] showed that vitamin D regulated inflammation and up-regulated expression of cytokines (interleukin 10 and 6).

Among the studies included in this meta-analysis, only Shadvar et al.[24] was unable to find a statistically significant difference between the groups. The other studies[21-23,25,26] demonstrated that preoperative vitamin D levels were independent predictors of POAF as assessed by univariate regression analysis. Also, Özsin et al.,[21] Emren et al.,[25] and Gode et al.[22] found vitamin D to be an independent predictor according to the multivariate analysis.

Among the studies, all patients had isolated CABG surgery, except for Skuladottir et al.'s population.[26] They studied both CABG and valve surgery patients, although the type of surgery was not a risk factor for POAF according to the multivariate analysis. In the literature, the incidence of POAF ranges between 25 and 40% for CABG, while it is 62% for combined CABG and valve surgery.[21,38]

Our analysis showed that the main reason for heterogeneity was non-randomized trials. Only two studies were prospective and randomized.[21,24] Among these two studies, only Özsin et al.'s study[21] supported the results of our analysis. The aforementioned authors found the levels of vitamin D as a predictor after univariate and multivariate regression analysis,[21] while Shadvar et al.[24] failed.

There are several limitations of this meta-analysis. First, our analysis includes a small number of studies. Therefore, we were unable to perform meta-regression. Second, studies included have different designs which resulted in heterogeneity. The randomized controlled trials, particularly large-scale trials, may be helpful to eliminate the heterogeneity by standardization of the possible risk factors between the groups. Finally, only articles in the English language were selected, which may have resulted in some useful sources of evidence being missed.

In conclusion, low preoperative vitamin D levels are associated with the development of atrial fibrillation after cardiac surgery. However, there is still a need for large-scale, randomized-controlled trials to prevent the heterogeneity of results and to conduct a meta-regression analysis.

Declaration of conflicting interests

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