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ORIGINAL

ASSOCIATION BETWEEN FIBROBLAST GROWTH FACTOR-23 AND VASCULAR CALCIFICATION IN ATHLETIC PATIENTS: A META-ANALYSIS

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ABSTRACT

Objective: In the clinic, athletic patients with chronic kidney disease are often complicated with vascular calcification in the process of maintenance hemodialysis (MHD) treatment, and then evolve into cardiovascular events. The increase of FGF-23 is associated with atherosclerosis and abnormal vascular function. We conducted a meta-analysis to examine the association between FGF-23 and vascular calcification in athletic patients. **Methods:** A systematic literature search was conducted in PubMed, EmBae, and the Cochrane library to investigate the relation of FGF-23 and vascular calcification in hemodialysis patients. The heterogeneity was assessed using I-square and Q statistics. Weighted mean difference (WMD) or odds ratio (OR) and 95% confidence interval (CI) in the hemodialysis group and non-hemodialysis group were appropriately pooled. **Results:** Eleven studies (1144 athletic patients) were included. There was no significant difference in FGF-23 between vascular calcification and non-vascular calcification in athletic patients. No evidence of heterogeneity was existent among the included studies. **Conclusion:** FGF-23 showed no effect on the progression of vascular calcification in maintenance hemodialysis.

KEYWORDS: FGF-23; maintenance hemodialysis; Vascular calcification; Meta-analysis

1. INTRODUCTION

Cardiovascular disease is the leading cause of death in athletic patients undergoing maintained hemodialysis (MHD) (Chirakarnjanakorn, Navaneethan, Francis, & Tang, 2017). Vascular calcification in the coronary arteries and aorta has been considered as a bad condition in the MHD athletic patients (Cannata-Andía, Rodríguez-García, Carrillo-López, Naves-Díaz, & Díaz-López, 2006; San Norberto et al., 2021). Although vascular calcification is intrinsically correlated with the aging process, the mechanisms of hyperphosphatemia and elevated calcium phosphate products in vascular calcification remain unclear (Massy, Mentaverri, Mozar, Brazier, & Kamel, 2008; Moe & Chen, 2008).

Moreover, the diffuse medial calcification of arterial vessels is widely prevalent in MHD athletic patients, which induces stiffening of the vessel wall and reduces vascular compliance (Davies & Hruska, 2001; Guérin, London, Marchais, & Metivier, 2000). Currently, the identified risk factors for vascular and valvar calcification in MHD athletic patients include older age, male, longer dialysis duration, diabetes mellitus, hypertension, hyperphosphatemia, hypercalcemia, hyperparathyroidism, hypoalbuminemia, etc. (McCullough, Sandberg, Dumler, & Yanez, 2004; Spasovski, 2007).

Fibroblast growth factor 23 (FGF-23), generated by the bone cells, reduces the activity of 1-hydroxylase as well as the production of 1,25-dihydroxy vitamin D (1,25-OH2 vitamin D) in kidney (Kuro-o, 2010). FGF-23 is a novel bone derived protein with endocrine function, which can regulate calcium and phosphate metabolism (Mirams, Robinson, Mason, & Nelson, 2004). Moreover, elevated phosphate levels could induce the differentiation of human VSMCs into osteoblasts, to accelerate in the progression of calcification (Nishizawa, Jono, Ishimura, & Shioi, 2005).

Furthermore, MHD suffers have markedly elevated FGF-23 contents, which subsequently causes an increased risk of mortality during the first year of MHD (Gutiérrez et al., 2008). However, whether FGF-23 exacerbates vascular calcification remains unclear. Recently, accumulated evidence suggests that FGF-23 can accelerate the progression of vascular calcification in MHD athletic patients with inconsistent results. It is particularly important to clarify whether FGF-23 participates in vascular calcification. Therefore, in this study, a comprehensive analysis of the available studies was performed.

2. Methods

2.1 Data Searches

This meta-analysis was performed with the previous standards (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group*, 2009). We conducted electronic

searches in PubMed, EmBase, and the Cochrane Library electronic databases for studies about FGF-23 and vascular calcification. The studies were considered eligible to include in this meta-analysis from their inception till March 2019. There were no restrictions on publication language and status. The search terms were as follows: ("Fibroblast Growth Factor-23" OR "FGF-23") AND ("vascular calcification" OR "artery calcification" OR "calcification") AND ("haemodialysis" OR "hemodialysis"). The references from relevant reviews and original articles were manually searched for any new eligible study.

2.2 Study Selection

Two independent authors carried out the procedure of choosing the studies. All electronic citations' titles and abstracts were thoroughly examined, and comprehensive publications were retrieved for in-depth analysis and individual re-screening. There were no limitations on the study's period or the number of study population. Any disagreement was resolved by a group discussion until a consensus was reached.

2.3 Eligibility Criteria

Inclusion criteria: (1) Subjects: all subjects undergoing MHD; (2) Groups: athletic patients were divided into vascular calcification and non-vascular calcification groups; and (3) Outcomes: the studies that reported FGF-23 value (mean and standard deviation). Exclusion criteria: (1) Study type was review or case report; (2) Essential data was lack in the study literature; (3) Repeated report for same population".

2.4 Data Collection and Quality Assessment

The data collected from each study included the first author's name, publication year, country, sample size, mean age, percentage male, MHD duration, percentage of athletic patients with diabetes mellitus, body mass index, percentage of the smoker, systolic blood pressure, diastolic blood pressure, and FGF-23 value in vascular calcification and non-vascular calcification groups.

The Newcastle-Ottawa Scale, which was based on selection (4 items: 4 stars), comparability (1 item: 2 stars), and result, was used to rate the quality of the studies (3 items: 3 stars). The "star system" used to rate the caliber of the research that were included varied from 0 to 9 (Moher et al., 2009). Two writers conducted the quality assessment, and a third author resolved any discrepancies by consulting the original research. This comprehensive data collection process ensured that relevant information from each study was systematically recorded and assessed for quality. This approach helps ensure the reliability and validity of the findings synthesized from multiple source.

2.5 Statistical Analysis

The results from each study were considered as continuous data. The weighted mean differences (WMDs) with 95% confidence intervals (CIs) were calculated in each study before data pooling. Although both the fixed-effects and random-effects models yielded similar findings, results from the random-effects model were presented here due to its assumption of the true underlying effects that varied among the included studies (DerSimonian & Laird, 1986; Wells et al., 2000).

Heterogeneity among the included studies was assessed by I-square and Q statistics. Prior to data pooling, the weighted mean differences (WMDs) with 95% confidence intervals (CIs) were computed in each study. Significant heterogeneity was defined as I-square 50.0% or a P-value for the Q statistic of 0.10. (Ades, Lu, & Higgins, 2005; Deeks, 2008).

Sensitivity analysis was performed to evaluate the influence of a single study and the stability of pooled results (Higgins, Thompson, Deeks, & Altman, 2003). P values between subgroups were calculated as well as subgroup analyses by nation, sample size, mean age, percentage of men, MHD duration, body mass index, and study quality (Tobias, 1999).

Results from the Funnel plot, Egger (Egger, Smith, Schneider, & Minder, 1997), and Begg tests were used to evaluate publication bias (Altman & Bland, 2003). All of the published P values were two-sided, and statistical significance was defined as P 0.05. STATA software was used to conduct statistical analysis (version 10.0 StataCorp, Texas, USA).

3. Results

3.1 Literature Search

Our initial electronic search from PubMed, EmBase, and the Cochrane library produced 213 records. 181 articles were initially excluded due to duplications and irrelevant topics. Moreover, 21 studies were excluded from the full-text evaluation of the remaining 32 articles.

The reasons were as follows: no appropriate control (n = 9), athletic patients with other diabetes (n = 7), and no adequate data (n = 5). Finally, 11 studies were included (Figure 1)(Tarek Zakaria El Baz et al., 2017; Berivan Ganidagli et al., 2019; Inaba et al., 2006; Rachana Jasani et al., 2018; Jean et al., 2012; Jean et al., 2008; Ilona Kurnatowska, Grzelak, Kaczmarska, Stefańczyk, & Nowicki, 2011; Moldovan et al., 2014; Ozkok et al., 2013; Noriko Tamei, Tetsuya Ogawa, Hideki Ishida, Yoshitaka Ando, & Kosaku Nitta, 2011; Turan et al., 2016). The manual searches from the reference lists of relevant

studies did not yield any new eligible studies.

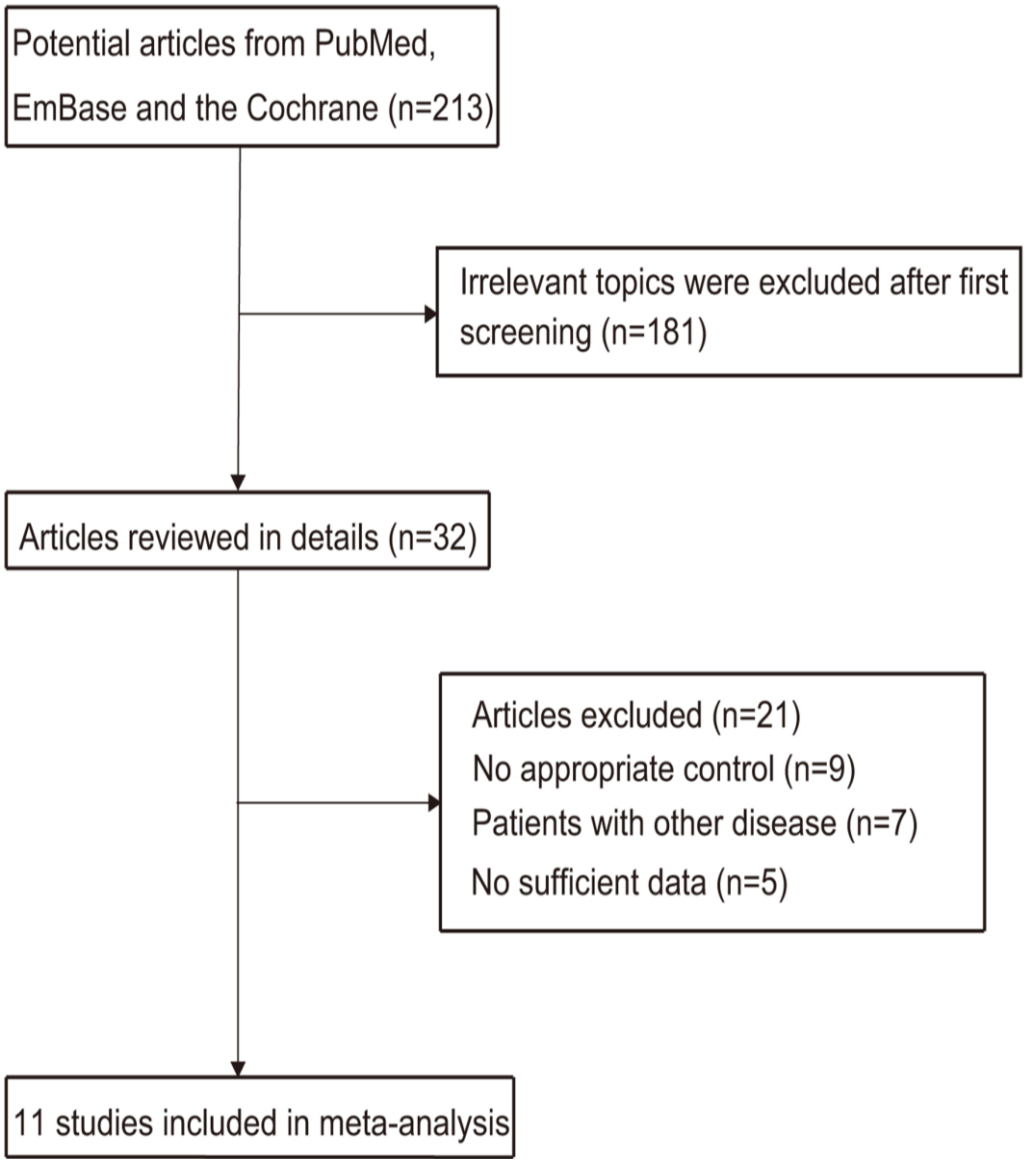

Figure 1: Flow diagram of literature search and selection process of the studies.

3.2 Study Characteristics

The general characteristics of the included studies were presented in Table 1. Eleven studies involving a total of 1,144 MHD athletic patients were included, which were published from 2006 to 2019. Three studies were conducted in Eastern countries (Japan and India), and the remaining eight studies were conducted in Western countries (France, Poland, Turkey, Romania, and Egypt).

The MHD duration ranged from 40.5-210.0 months, and 47-161 patients were included in individual study. The mean age of included athletic patients ranged from 48.5-67.0 years old, and the percentage of males ranged from 46.7%-100%.

Table 1: Baseline characteristics

STUDIES	PUBLICATION YEAR	COUNTRY	SAMPLE SIZE	MEAN AGE (YEARS)	PERCENTAGE MALE (%)	HD DURATION (MONTHS)	PERCENTAGE DM (%)	BMI (KG/M^2)	SMOKER (%)	SBP (MMHG)	DBP (MM HG)	STUDY QUALITY
(INABA ET AL., 2006)	2006	Japan	88	53.8	100.0	57.7	57.1	NA	NA	NA	62.4	6
(JEAN ET AL., 2008)	2008	France	161	66.1	55.3	69.6	35.0	25.1	72.0	123.7	71.7	7
(NORIKO TAMEI ET AL., 2011)	2011	Japan	127	62.1	65.4	210.0	NA	21.3	NA	144.7	76.1	6
(ILONA KURNATOWSKA ET AL., 2011)	2011	Poland	47	55.8	66.0	51.5	NA	26.2	NA	NA	NA	5
(JEAN ET AL., 2012)	2012	France	85	67.0	51.8	79.7	35.3	25.8	63.5	NA	NA	7
(OZKOK ET AL., 2013)	2013	Turkey	74	52.0	48.6	54.0	NA	24.2	NA	125.0	75.0	6
(MOLDOVAN ET AL., 2014)	2013	Romania	88	61.0	51.1	48.0	22.7	NA	NA	NA	NA	5
(TURAN ET AL., 2016)	2016	Turkey	229	60.8	51.0	41.3	24.0	24.3	31.0	NA	NA	6
(TAREK ZAKARIA EL BAZ ET AL., 2017)	2017	Egypt	60	54.1	46.7	52.8	NA	27.5	NA	NA	NA	5
(RACHANA JASANI ET AL., 2018)	2018	India	100	48.5	47.0	40.5	NA	22.4	NA	154.0	90.0	6
(BERIVAN GANIDAGLI ET AL., 2019)	2019	Turkey	85	49.8	54.1	52.5	34.1	NA	NA	134.6	76.1	6

**BMI: body mass index; DBP: diastolic blood pressure; DM: diabetes mellitus; HD: hemodialysis; NA: not available; SBP: systolic blood pressure*

3.3 The relation between FGF-23 and vascular calcification in MHD patients

After pooling all the included studies, there was no significant relation between FGF-23 value (log RU/ml) and vascular calcification in MHD athletic patients (Figure 2). It suggested that FGF-23 was not associated with the risk of vascular calcification in MHD athletic patients. Moreover, no evidence of heterogeneity exists among the included studies (I-square: 0.0%; *P* = 0.951).

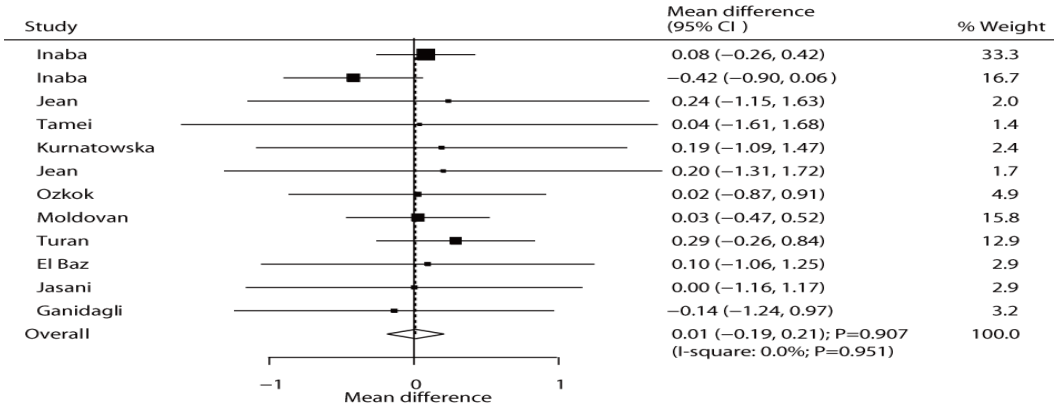

Figure 2: Summary of WMD for FGF-23 value between vascular calcification and non-vascular calcification in hemodialysis patients

3.4 Sensitivity Analysis

The results of sensitivity analysis were calculated (Figure 3). Although the pooled results showed relatively large variations with the exclusion of the two studies (Tarek Zakaria El Baz et al., 2017), the sequential exclusion of the included studies had no effect on the pooled conclusion, which remained constant and unmodified.

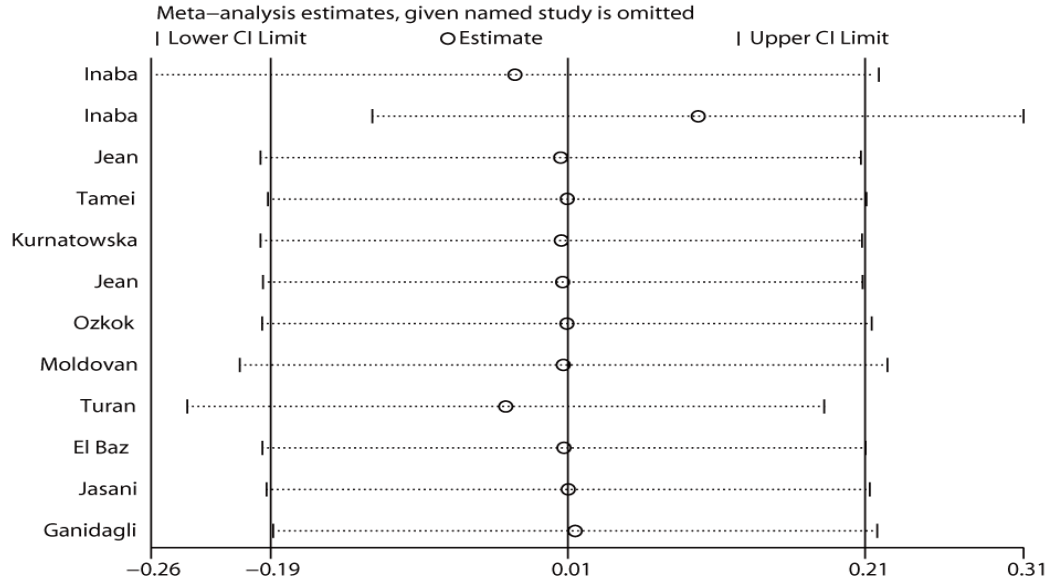

Figure 3: Sensitivity analysis for FGF-23 value between vascular calcification and non-vascular calcification in hemodialysis patients

3.5 Subgroup Analyses

The subgroup analyses were conducted and summarized in Table 2. Although there were no significant differences in FGF-23 between vascular calcification and non-vascular calcification groups, we noted that the vascular calcification athletic patients had similar FGF-23 values in studies conducted in western countries, with sample size ≥ 100, mean age ≥ 60.0 years, percentage male < 60.0%, hemodialysis duration of <50.0 months, irrespective body mass index ≥25.0 kg/m^2, or < 25.0 kg/m^2, and studies with high quality. Similarly, there was not significantly low FGF-23 value in vascular calcification group in studies conducted in eastern countries, sample size < 100, mean age < 60.0 years, percentage male ≥ 60.0 %, and hemodialysis duration ≥ 50.0 months. Moreover, these factors did not yield any significant impact on FGF-23 value.

Table 2: Subgroup analyses for FGF-23 (log pg/ml) between VC and non-VC

FACTORS	SUBSETS	WMD AND 95%CI	P VALUES	I^2 (%)	P VALUE FOR HETEROGENEITY	P VALUES
COUNTRY	Eastern	-0.08 (-0.34 to 0.19)	0.570	0.0	0.423	0.333
	Western	0.12 (-0.17 to 0.41)	0.428	0.0	0.997	
SAMPLE SIZE	≥ 100	0.22 (-0.23 to 0.67)	0.332	0.0	0.970	0.307
	<100	-0.04 (-0.26 to 0.18)	0.732	0.0	0.860	
MEAN AGE (YEARS)	≥ 60	0.15 (-0.19 to 0.49)	0.389	0.0	0.971	0.330
	< 60	-0.06 (-0.30 to 0.18)	0.637	0.0	0.800	
PERCENTAGE MALE (%)	≥ 60	-0.07 (-0.34 to 0.20)	0.610	0.0	0.400	0.380
	< 60	0.11 (-0.18 to 0.40)	0.470	0.0	0.997	
HD DURATION	≥ 50	-0.04 (-0.28 to 0.19)	0.719	0.0	0.911	0.417
	< 50	0.13 (-0.22 to 0.48)	0.461	0.0	0.765	
BMI (KG/M^2)	≥ 25	0.17 (-0.48 to 0.83)	0.608	0.0	0.999	0.550
	< 25	0.18 (-0.24 to 0.60)	0.408	0.0	0.942	
STUDY QUALITY	High	0.22 (-0.80 to 1.24)	0.672	0.0	0.973	0.683
	Low	0.00 (-0.20 to 0.20)	0.971	0.0	0.885	

**BMI: body mass index; CI: confidence interval; HD: hemodialysis; WMD: weighted mean difference*

3.6 Assessment of Publication Bias

A review of the funnel plots could not rule out the potential for publication bias, and the results of Egger (P = 0.693) and Begg (P = 0.837) tests indicated no significant publication bias (Figure 4).

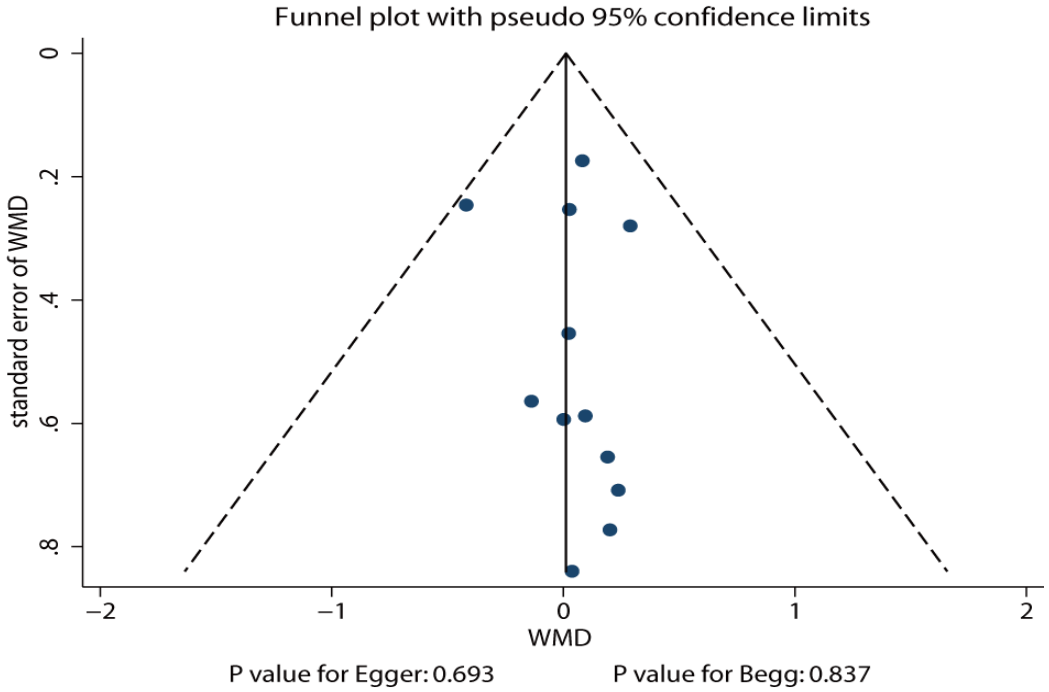

Figure 4: Publication bias for the FGF-23 values

4. Discussion

Numerous studies have already suggested that FGF-23 accelerates the vascular calcification in MHD athletic patients (Inaba et al., 2006; Jean et al., 2008), whereas this association has not been confirmed to date. The current study included all available published articles and explored any potential difference in FGF-23 value between vascular calcification and non-vascular calcification groups. Our comprehensive quantitative study recruited 1,144 hemodialysis athletic patients from 11 studies with a wide range of baseline characteristics. Our results indicated no significant difference in FGF-23 value between vascular calcification and non-vascular calcification in MHD athletic patients. The subgroup analyses confirmed this conclusion to be stable and consistent.

There is no previous meta-analysis that focuses on the association of FGF-23 with vascular calcification in MHD suffers. Although the FGF-23 value between vascular calcification and non-vascular calcification athletic patients showed no statistically significant association in all the included studies, several of the analyzed research presented contradictory findings. According to Inaba et al., regardless of the presence or absence of diabetes mellitus, the plasma

FGF-23 level is strongly linked to peripheral vascular calcification in the hand arteries but not in the aorta. Jean et al.(Jean et al., 2012) have recruited 161 MHD athletic patients and suggested that serum FGF-23 level could aggregate some non-traditional risk factor, affecting the progression of vascular calcification. Tamei et al. (Noriko Tamei et al., 2011) have found that the serum FGF-23 accumulation could inhibit calcification in vessel walls based on 127 MHD athletic patients (N. Tamei, T. Ogawa, H. Ishida, Y. Ando, & K. Nitta, 2011). Kurnatowska has involved 47 hemodialysis athletic patients and finds that the non-vascular calcification athletic patients group have lower FGF-23 values than those in vascular calcification athletic patients after 30.0 months of hemodialysis, whereas similar effect is observed at baseline (I. Kurnatowska, Grzelak, Kaczmarska, Stefanczyk, & Nowicki, 2011).

Jean et al. (Jean et al., 2012) have indicated that the progression of vascular calcification is associated with high FGF-23 levels. Ozkok et al.(Ozkok et al., 2013) have included 74 hemodialysis athletic patients and suggest that particularly in the early phases of the calcification process in hemodialysis athletic patients, FGF-23 may be crucial to the advancement of vascular calcification. Moldovan et al.(Moldovan et al., 2014) have recruited 88 athletic patients and report a significant association between FGF-23 and cardiovascular disease, whereas there is no significant association between FGF-23 and vascular calcification in chronic hemodialysis patients. Turan et al.(Turan et al., 2016) have indicated that the plasma FGF-23 value shows no association with carotid artery atherosclerosis, while there is no significant correlation with coronary artery calcification in athletic patients. El Baz et al.(Tarek Zakaria El Baz et al., 2017) have indicated that increased FGF-23 level indicates a harmful effect on aortic and coronary calcifications after adjusting for lipid profile, left ventricular mass index, and inflammatory markers (T. Z. El Baz et al., 2017). Jasani et al. have indicated that FGF-23 shows no association with the risk of coronary artery calcification in athletic patients (R. Jasani et al., 2018). Ganidagli et al. have reported that FGF-23 is not associated with heart valve calcification in athletic patients (B. Ganidagli et al., 2019). This inconsistency may be due to the adjustment of additional risk factors, and the current study is based on crude data.

According to the results conducted by Inaba et al.(Inaba et al., 2006), diabetes mellitus status might affect the association of FGF-23 with vascular calcification in hemodialysis suffers. Moreover, the subgroup analyses are consistent with the overall analysis. We noted a non-significant increase in the trend of FGF-23 in western countries, sample size ≥ 100, mean age ≥ 60.0 years, percentage male < 60.0%, hemodialysis duration < 50.0 months, irrespective body mass index ≥ 25.0 kg/m^2, or < 25.0 kg/m^2, and study with high quality. The potential reason could be that these factors could accumulate in the progression of vascular calcification and affect the power to detect the difference of FGF-23 between vascular calcification and non-vascular

calcification patients. However, several limitations of this study should be highlighted. Firstly, different comorbidities exist among the included studies, which play an important role in the progression of vascular calcification. Secondly, the current study is based on crude data, and the adjusted results are unavailable. Thirdly, most of the included studies are low quality, which in turn could bias the pooled results. Fourthly, this analysis is based on published articles, and the publication bias is inevitable. Finally, the analysis includes pooled data and the individual data that are not available, restricting us to conduct a more detailed analysis.

In conclusion, our results indicate that FGF-23 shows no association with the progression of vascular calcification in hemodialysis patients, and this conclusion is unaltered through sensitivity and subgroup analyses. Further meta-analysis of individual patient data should be conducted to determine the relation of FGF-23 with vascular calcification in hemodialysis suffers.

4.1 Future Perspective

The current study includes all available published articles and explores any potential difference between vascular calcification and non-vascular calcification for FGF-23 value. Our results indicate no significant difference in FGF-23 value between vascular calcification and non-vascular calcification in hemodialysis patients. The subgroup analyses confirm this conclusion to be stable and consistent.

4.2 Executive Summary

Although this relationship has not yet been proven, numerous studies have already shown the significance of FGF-23 in the development of vascular calcification in hemodialysis patients. In this study, we set out to comprehensively investigate how FGF-23 affects how vascular calcification develops in hemodialysis patients. Through sensitivity and subgroup analysis, our study's findings showing FGF-23 does not appear to be related to the development of vascular calcification in hemodialysis patients remain unchanged. The evolution of vascular calcification in hemodialysis patients should be investigated further using meta-analysis of individual athletic patient data.

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