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ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
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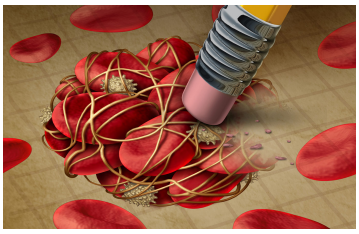

Μεταπτυχιακή Διπλωματική Εργασία

" Θρομβοφιλία-κληρονομική ή επίκτητη - σε ασθενείς που υποβάλλονται σε αιμοκάθαρση και η επίπτωση της στην αποτυχία αρτηριοφλεβικών προσπελάσεων."

υπό

Πετρούλας Νανά

Αγγειοχειρουργός

Υπεβλήθη για την εκπλήρωση μέρους των
απαιτήσεων για την απόκτηση του
Διπλώματος Μεταπτυχιακών Σπουδών
«Θρόμβωση και Αντιθρομβωτική Αγωγή»

Λάρισα, 2024

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Τίτλος εργασίας στα αγγλικά:

Thrombophilia-inherited and acquired-in patients undergoing dialysis and its impact on vascular access failure.

Περίληψη

Εισαγωγή: Παράγοντες θρομβοφιλίας έχουν ανιχνευθεί σε υψηλότερα ποσοστά μεταξύ ασθενών που πάσχουν από νεφρική νόσο, ενώ ανάλογα είναι τα ευρήματα μεταξύ ασθενών που υποβάλλονται σε αιμοκάθαρση. Ο ρόλος της θρομβοφιλίας έχει μελετηθεί στο παρελθόν, καταλήγοντας ωστόσο σε αντικρουόμενα συμπεράσματα. Αυτή η ανασκόπηση της βιβλιογραφίας έχει σαν στόχο να διερευνήσει το αντίκτυπο των παραγόντων θρομβοφιλίας, συγγενούς η επίκτητης, σε ασθενείς που υποβάλλονται σε αιμοκάθαρση και να μελετήσει το αντίκτυπο τους στη βατότητα των αγγειακών προσπελάσεων.

Μεθοδολογία: Οι οδηγίες Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) αποτέλεσαν τη βάση για τη δομή αυτής της μελέτης της βιβλιογραφίας.. Μελέτες παρατήρησης, συγκριτικές ή μη, καθώς και τυχαιοποιημένες μελέτες, που δημοσιεύθηκαν στο διάστημα 2010-2021, στην αγγλική γλώσσα και αναφέρονταν σε διερεύνηση παραγόντων θρομβοφιλίας σε ασθενείς που υποβάλλονται σε αιμοκάθαρση για χρόνια νεφρική νόσο θεωρήθηκαν αποδεκτές για συμπερίληψη. Η αναζήτηση έγινε συστηματικά στις βάσεις MEDLINE, EMBASE και CENTRAL (μέχρι τις 28.02.2022).

Αποτελέσματα: Δεκατρείς μελέτες με 2338 ασθενείς συμπεριλήφθηκαν, μεταξύ αυτών και μια τυχαιοποιημένη μελέτη. Από τους ασθενείς, 2260 υποβάλλονταν σε αιμοκάθαρση. Ένας μεγάλος αριθμός παραγόντων διερευνήθηκε, συμπεριλαμβανομένων των Leiden, prothrombin G20210A, πρωτεΐνες S και C, MTHFR, heme oxygenase-1 (HO-1), ομοκυστεΐνη, D-dimers, αντιγόνο του αναστολέα της ενεργοποίησης του πλασμινογόνου (PAI-1 antigen), το σύμπλεγμα πλασμίνης-α2 αντιπλασμίνης, ο παράγοντας von Willebrand, ιστικός παράγοντας (soluble tissue factor; TF), το σύμπλεγμα θρομβίνης-αντιθρομβίνης III (thrombin/antithrombin III complex; TAT), ο παράγοντας VIII (FVIII), το

αντιπηκτικό του λύκου, τα αντιφωσφολιπιδικά αντισώματα και ο ενδοθηλιακός αυξητικός παράγοντας (VEGF-a). Οι παράγοντες TAT, η μετάλλαξη της προθρομβίνης G20210A και ο παράγοντας V Leiden αποδείχθηκε πως σχετίζονταν με αυξημένη πιθανότητα απώλειας της αγγειακής προσπέλασης. Επιπλέον, η παρουσία συνθετικού μοσχεύματος, σε αντίθεση με αυτόλογη αρτηριοφλεβική επικοινωνία σχετίστηκε με κίνδυνο απώλειας της φλεβικής προσπέλασης. Η ασπιρίνη αντίθετα έπαιζε προστατευτικό ρόλο. Η μετάλλαξη της προθρομβίνη G20210 και ο παράγοντας TAT ανιχνεύθηκαν ως ανεξάρτητοι παράγοντες θρόμβωσης της αγγειακής προσπέλασης.

Συμπέρασμα: Η υψηλή ετερογένεια μεταξύ των πληθυσμών των μελετών δεν επιτρέπει την εξαγωγή ασφαλών συμπερασμάτων. Τόσο παράγοντες θρομβοφιλίας, όπως το σύμπλεγμα TAT όσο και τεχνικά χαρακτηριστικά, όπως η χρήση συνθετικών μοσχευμάτων, μπορεί να επηρεάσουν την βατότητα της αγγειακής προσπέλασης.

Λέξεις-Κλειδιά: θρομβοφιλία, αιμοκάθαρση, αγγειακή προσπέλαση, θρόμβωση

Abstract

Introduction: Thrombophilia risk factors have been more frequently detected among patients suffering with kidney disease and patients managed with hemodialysis. The role of thrombophilia has been investigated providing contradictory findings, regarding its impact on vascular access. This review of the literature aimed to investigate the impact of thrombophilia factors, hereditary or acquired in patients undergoing dialysis and their impact on vascular access patency.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were followed. Observational studies (2010-2021), of the English medical literature, reporting on thrombophilia factors in patients undergoing dialysis for chronic kidney disease were eligible. A systematic search of MEDLINE, EMBASE and CENTRAL databases, was conducted (February 28th, 2022). The risk of bias was assessed using the Newcastle-Ottawa Scale.

Results: Thirteen studies with 2338 patients; one randomized controlled trial were included. Among them, 2260 patients were under dialysis. A variety of factors were controlled, including antiphospholipid antibodies (APAs), factor Leiden, prothrombin G20210A, protein S and C, MTHFR, heme oxygenase-1 (HO-1), homocysteine, D-dimers, PAI-1 antigen, plasmin-a2antiplasmin, von Willebrand factor, soluble tissue factor (TF), thrombin/antithrombin III complex (TAT), Factor VIII (FVIII) and lupus anticoagulant (LA). TAT, prothrombin G20210A, Factor V Leiden were showed to be related to higher failure access rates. In addition, the presence of graft instead of homogenous fistula was related to higher failure rates while aspirin was protective against thrombosis. Among studies that provide a multivariate regression analysis, prothrombin G20210 mutation and TAT were detected as independent predictors for failure.

Conclusion: The high heterogeneity among studies' populations does not permit safe conclusion. Both thrombophilia factors, as TAT and technical factors, as the use of graft, may affect vascular access patency.

Keywords: thrombophilia, hemodialysis, vascular access, thrombosis

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ΕΙΔΙΚΟ ΜΕΡΟΣ

ΓΕΝΙΚΟ ΜΕΡΟΣ

Introduction

Chronic kidney disease (CKD) is a significant health problem affecting around 750 million people worldwide.[1] The prevalence of CKD is not equal between countries or nations and despite that the impact of CKD is well-defined in western world, current data show that developing countries present similar or higher CKD rates within their population.[2,3] Factors, as socioeconomic status and culture may affect CKD rates and the provision of management and may drive to important disparities in disease burden.[2,3]

Hemodialysis (HD) is the commonest kidney replacement therapy worldwide, representing 70% of any kidney replacement management.[4] Over the last 50 years, HD technology and subsequent, vascular access (VA) have significantly improved, especially in western countries.[4] HD accessibility and outcomes vary across countries and affect patients' quality of life as well as the associated morbidity and mortality.[4] In addition, despite evolution in HD and VA technology, poor outcomes among patients under dialysis still represent a major concern.[4]

The preservation of patent and functional VA is of major importance for patients' survival.[5] Most patients in USA undergo HD using a native arteriovenous fistula (AVF) or a synthetic graft while VA complications are associated to 20-25% of hospitalizations in HD patients and the economic impact exceeds 1 billion dollars per year.[5,6] Among these complications, AV thrombosis is one of the leading causes of failure and for the moment, the mechanisms affecting VA patency are still not well defined.[7] Although most thrombotic episodes are attributed to anatomic abnormalities,

as stenosis due to fibromuscular and intimal hyperplasia, VA thrombosis could occur without them.[8]

Thrombophilia, inherited or acquired, is a state predisposing to AV thrombosis. Previous studies showed conflicting outcomes, with a few suggesting an important relationship while others do not confirm these findings.[9] Small sample size, heterogeneity bias among patients, lacking control groups, inadequate management of confounders did not permit providing robust conclusions.[9]

This systematic review aimed to investigate the impact of thrombophilia factors, hereditary or acquired in patients undergoing dialysis and their impact on vascular access patency.

ΕΙΔΙΚΟ ΜΕΡΟΣ

Materials & Methods

Eligible Studies

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[10] Randomized control trials, retrospective and prospective observational cohort studies and case series (>20 patients), published from 2010-2022, in English and reporting on potential correlation between vascular access thrombosis and thrombophilia of any type; inherited or acquired were eligible.

Studies investigating the correlation of thrombophilia and chronic kidney disease of any type in patients, non-candidates or not under hemodialysis, were omitted. In studies, reporting on mixed cohorts, only patients having vascular access

and under HD were included. Studies on children population were ineligible. Among studies with overlap, the most recent was selected.

Search Strategy

A systematic search of the English medical literature using MEDLINE, EMBASE (via Ovid) and CENTRAL databases was performed following the PICO model [Patient; Intervention; Comparison; Outcome] model (**Table 1**).[11]

P	Population	Patients under hemodialysis
I	Prognostic factor	Thrombophilia impact on vascular access failure
C	Comparison of intervention	Non-applicable
O	Outcome you would like to measure or achieve	Association between inherited or acquired thrombophilia factors to vascular access failure
	What type of question are you asking?	Is thrombophilia related to vascular access failure in patients under hemodialysis?
	Type of study you want to find	Randomized Controlled Trials, Observational studies, prospective or retrospective, case series >20 patients

Table 1. The PICO model.

The endpoint was the 28th February 2022. Various search items, including Expanding Medical Subject Heading (MeSH terms), were applied with or without combinations: (vascular access), (arteriovenous fistula) (hemodialysis), (thrombophilia), (thrombosis).

Data Extraction

A standardized Microsoft Excel file was created by two investigators and included studies' characteristics (authors, journal, year of publication, study design, timespan), general baseline information [age, sex, time of hemodialysis, access type (AVF, graft, catheter)], factors investigated (inherited or acquired), relationship between factor and

access thrombosis and additional factors investigated with potential impact on access patency.

Quality Assessment

The quality assessment was performed using the Newcastle Ottawa Scale (NOS), which evaluates three methodological domains, including selection, comparability and assessment of outcomes, using a star system (maximum nine stars). Studies should achieve seven stars to be considered of higher quality.[12]

Outcomes

The primary outcomes were positive relationship of any thrombotic factor to vascular access dialysis. Secondary outcomes included additional factors affecting access patency.

Statistical analysis

No statistical analysis was performed, as this is a descriptive systematic review of the literature.

Ethical Considerations & Approval

This systematic review of the literature does not need scientific Council approval or patients' consent.

Results

Patient cohort

Initial search, led to 488 studies (**Table 2**). Deduplication was performed automatically using Ovid. After application of the inclusion and exclusion criteria, 13

studies with 2338 patients, published between 2010-2022, were included (**Figure 1**).[13-25] Studies' characteristics are presented in **Table 3**.

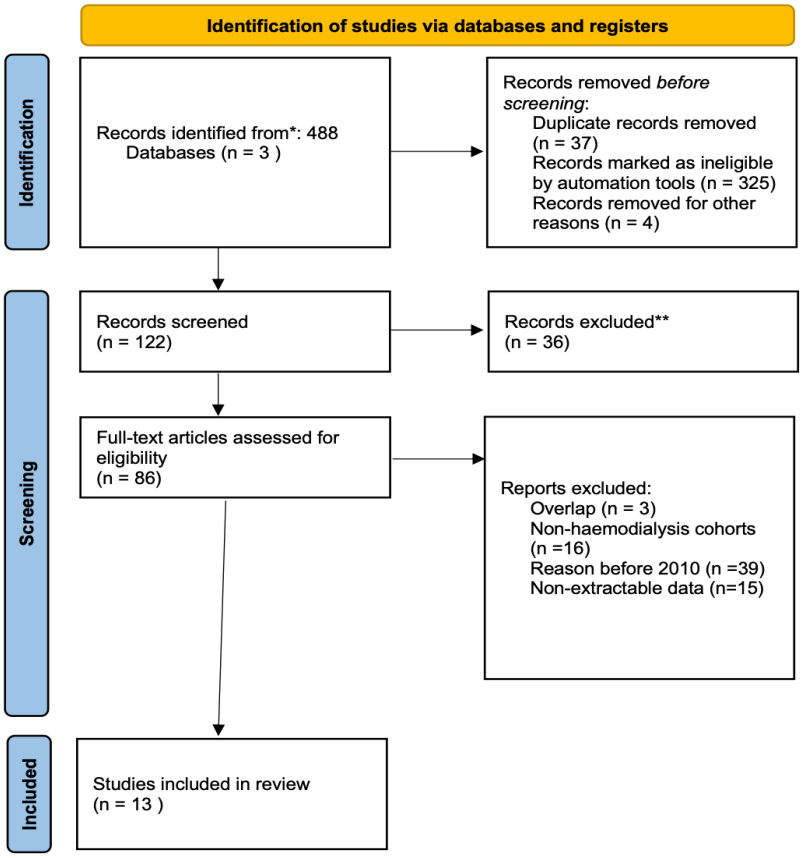

Figure 1. The flow chart of the selection process according to PRISMA statement. Thirteen studies were finally included in the systematic review and meta-analysis.

Frame	Mesh Terms	Search	Inclusion criteria	Exclusion criteria	Sources
P (patients, participants, population)	# 1. # 2. "Thrombophilia" AND "Vascular access"	#1 AND #2 AND #3 AND #4 OR #5 OR#6	Randomized Controlled Trials, Observational cohort studies, Case series > 20 cases reporting on the association of thrombophilia and vascular access failure Peer-review journals English	Irrelevant title or text, Editorial, reviews, meta-analyses, technical notes, images, case series <20 patients, case reports	Databases (Medline, EMBASE via OVID and Cochrane library)
I (intervention)	#3. "Hemodialysis"				
C (reference test)	NA				
O (outcome)	#4. #5. #6. "Thrombosis" OR "Patency" OR "Occlusion"				
Time	Search period: 2010- 2022 Last search:28.02.22				

Table 2. Search strategy.

Author	Year	Journal	Timespan	Type	N of patients
Rios et al	2010	Clinica Chimica Acta	2007-2009	Case control	195
Fekih-Mrissa, et	2011	Ther Apher Dial	2007-2009	Case control	78

al.					
Allon et al	2012	Am J Kidney Dis		Randomized control trial	354
Saifan et al	2013	Vasc Health Risk Man		Retrospective	125
Milburn, et al	2013	PlosOne		Prospective, observational	70
Nweke et al	2014	Hemod Inter		Case control	20
Candan, et al	2014	Int Urol Nephrol		Retrospective	80
Androulakis et al	2015	Nephron		Comparative retrospective	133
Fekih-Mrissa et al	2016	Ther Apher Dial		Case control	121
Chen, et al	2018	Cardiovasc Interv Radiol		Case control	462
Hasuike, et al	2019	J Vasc Surg	2014-2015	Observational	462
Kakaei et al	2021	J Cardiovasc Thorac Surg	2012 (3 months)	Case control	60
Anapalli, et al	2022	Ren Fail	2017-2018	Case control	100

Table 2. Included studies main characteristics.

From the total cohort, 2260 patients were dialysis, while the remaining represented either control groups of healthy individuals or patients suffering with CKD, without need for hemodialysis. The mean age was 63±11.9 years and 51.7% were males. The estimated time under dialysis was reported in four studies and was 57 months (range 16-202).

Inherited thrombophilia and VA failure

Ten studies reported on factors related to inherited thrombophilia and VA failure. Factors as prothrombin G20210A gene, antithrombin III deficiency, proteins N and S, factor Leiden, MTHFR, von Willebrand, and VEGF-A were searched.[13-15,17,19-22,25,26] Two studies confirmed a relationship between prothrombin G20210A gene and VA failure while two reported on the impact of factor Leiden and MTHFR with VA thrombosis.[13,14,20] A study investigating the effect of protein C and S deficiency, as well as antithrombin III deficiency; without finding any significance for each one of them showed, that patients with any thrombophilia factor and graft were at higher risk for thrombosis. The study by Rios, et al. showed an independent relationship between

G20210A mutation and VA thrombosis (OR = 12.0; CI 95% = 1.8–83.5; p = 0.012). No other factor was identified as independent predictor for access failure.[13]

Acquired thrombophilia and VA failure.

Ten studies investigated the corelation of acquired thrombophilia and VA failure.[14-18,20,22-25] Homocysteine was the most investigated factor, followed by thrombin/antithrombin III complex (TAT), D-dimmers, plasmin-antiplasmin complex, tissue factor, lupus anticoagulant, antiphospholipid antibodies (APAs), anticardiolipin IgM and IgG antibodies, lipoprotein (a), high-sensitivity C reactive protein (hs-CRP) and fibrinogen. Among them TAT and hs-CRP were found to affect VA patency.[17] However, only TAT was independently related to VA failure.[17,23]

Other factors related to VA failure.

Aspirin and erythropoietin intake were related to VA fate; the first related to VA patency and the second with VA thrombosis when administrated in higher doses.[16,18] Synthetic grafts were related to lower patency rates in three studies.[15,22,23] Weight and weight gain among HD patients also seemed to affect patency rates.[13,18] The use of synthetic graft was independently related predictor of vascular access failure while aspirin intake showed to be a protective factor.

Risk of bias

Twelve studies were retrospective, except one, which was a randomized controlled trial. The NOS evaluation is depicted in **Table 4**. None of the studies were considered of high quality. All were of low quality, due to small sample size, limited follow-up and missing information.

Studies	Year of publication	Selection	Comparability	Outcome	Total
Rios, et al	2010	**	**	**	6

Fekih-Mrissa, et al.	2011	**	**	**	6
Allon, et al	2012	**	**	**	6
Saifan, et al	2013	**	**	**	6
Milburn, et al	2013	**	*	**	6
Nweke, et al	2014	**	**	**	6
Candan, et al	2014	**	**	**	6
Androulakis, et al	2015	**	**	**	6
Fekih-Mrissa, et al	2016	**	**	**	6
Chen, et al	2018	**	**	**	6
Hasuike, et al	2019	**	**	**	6
Kakaei, et al	2021	**	**	*	6
Anapalli, et al	2022	**	**	**	6

Table 4. The risk of Bias Assessment was performed using the Newcastle-Ottawa Scale.

Discussion

This systematic review of 13 studies showed that despite the high number of studies reporting on the association of thrombophilia and VA failure, no robust evidence exists in the literature supporting any direct relation between them. This highlights further the fact that VA thrombosis is rather a multifactorial phenomenon, related to anatomic, hematologic and demographic factors. Despite that a variety of factors were investigated, only G20210A mutation and TAT were independently related to VA failure.[13,17,23] In addition, the presence of graft was related to higher failure rates while aspirin showed to provide benefit for VA patency.

Despite that some studies supported the association between thrombophilia factors and VA failure, this is not a consistent finding in the published literature.[26-36] This inconsistency in findings may be related to the size of the studies, as many of them included underpowered cohorts and potential type II errors should be acknowledged. Larger prospective, case-control studies as well as randomized control trials need to be conducted to confirm any potential association between thrombophilia and VA failure.

As known from fundamental physiology, thrombosis is a phenomenon evolving when stasis, endothelial injury, and hypercoagulability are present.[37] As stasis and injury have been associated to VA failure in the previously published literature, hypercoagulability state should also be somehow related to thrombosis in these cases.[38] Thrombophilia has been related to arterial and venous thrombosis and as VA, involves both components, thrombophilia may also play a role.[37] However, the non-direct strong association between thrombophilia factors and VA failure, rather signifies that VA thrombosis is multifactorial and thrombophilia factors may be contributors to other underlying pathologies.[9] A biologic gradient may be able to strengthen the association between thrombophilia and VA failure, as for each additional factor, a two-fold odd's increase of VA thrombosis has been shown.[9]

Thrombophilia associated with venous thrombotic events is mainly treated with anticoagulants. However, the combination of aspirin plus clopidogrel has been shown to prevent VA thrombosis, despite that in this analysis thrombophilia was not assessed.[38] In the current review, aspirin showed to be a protective factor for thrombosis. The selective use of antiplatelets or warfarin in HD patients with thrombophilia could be beneficial. However, further studies are needed.

Limitations

The retrospective design of most included studies introduced certain bias due to confounders. Only patients under haemodialysis were included: excluding CKD with potential thrombophilia factors that may affect future VA fate. The time under dialysis varied between studies and was reported only in four. This affected the findings of the current review. Various factors were evaluated, including inflammatory factors and baseline characteristics while statistical corrections for potential errors were not reported in the included studies. Significant heterogeneity was present among studies, regarding definitions. Case reports and case series with less than 20 cases were excluded and the findings may have been affected.

Conclusion

High heterogeneity among studies' populations does not permit safe conclusion. Both thrombophilia factors, as TAT and technical factors, as the use of graft, may affect vascular access patency.

Σύνοψη διατριβής

As thrombophilia risk factors have been more frequently detected among patients with chronic kidney disease under hemodialysis and the role of thrombophilia has been investigated providing conflicting findings, regarding its impact on vascular access patency, this systematic review of the literature aimed to investigate the impact of thrombophilia factors, hereditary or acquired in patients undergoing dialysis and their impact on vascular access patency. Using The Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines, the English medical literature was search (2010-2021), through MEDLINE, EMBASE and CENTRAL databases. After applying the exclusion criteria, thirteen studies (2338 patients). A variety of factors were controlled, including Leiden factor, prothrombin G20210A, protein S and C, MTHFR, heme oxygenase-1 (HO-1), homocysteine, D-dimers, PAI-1 antigen, plasmin-a2antiplasmin, von Willebrand factor, soluble tissue factor (TF), thrombin/antithrombin III complex (TAT), Factor VIII (FVIII), lupus anticoagulant (LA), antiphospholipid antibodies (APAs). TAT, prothrombin G20210A and Leiden Factor V were showed to be related to higher failure access rates. In addition, the presence of graft instead of homogenous fistula was related to higher failure rates while aspirin was protective against thrombosis. Among studies that provide a multivariate regression analysis, prothrombin G20210 mutation and TAT were detected as independent predictors for failure. The high heterogeneity among studies' populations does not permit safe conclusion. Both thrombophilia factors, as TAT and technical factors, as the use of graft, may affect vascular access patency.

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