Risk Factors for Carpal Tunnel Syndrome in Hemodialysis Patients: A Literature Review

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

Review Paper

ABSTRACT

Background: Carpal tunnel syndrome (CTS) is the most commonly reported complication of dialysis-related amyloidosis in patients on long-term hemodialysis (HD) therapy. The aim of this literature review is to assess and present our current knowledge of the risk factors of CTS in patients on long-term hemodialysis
Materials/Methods: A systematic search to gather the different risk factors of CTS reported in the literature was conducted using PubMed, Cochrane and Google scholar from 2008 to 2018. Key words and their combination were used, including carpal tunnel syndrome, hemodialysis and dialysis related amyloidosis.
Results: This study included 11 articles that met our criteria. Incidence of CTS in hemodialysis patients increased with the duration of dialysis, age of the patient, arteriovenous fistula, and β2-microglobulin deposition.
Conclusion: Several risk factors were identified, but a clear cause was not established. A multifactorial, complex interaction between some or all of the risk factors most likely exists and could explain the incidence of CTS in this population.

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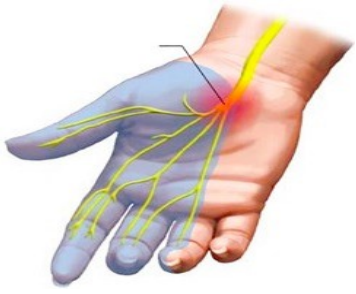
Keywords: Arteriovenous fistula; β2-Microglobulin; carpal tunnel syndrome; dialysis related amyloidosis; ESRD; hemodialysis.

1. INTRODUCTION

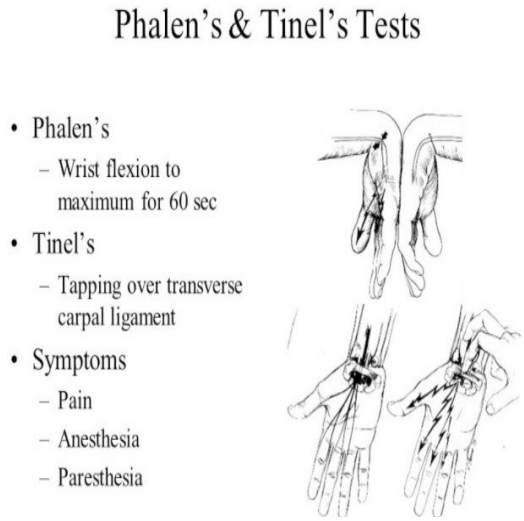
Hemodialysis (HD) is indicated in patients with end-stage renal disease (ESRD) and apart from a kidney transplant, it is currently the treatment of choice for ESRD and the most common treatment used in the USA. Although innovations have been incorporated into the realm of dialysis, it is still far from replacing the physiologic process of filtration of a healthy human kidney. Many complications of long-term (maintenance) HD have been reported, ranging from anemia, depression, and cardiovascular diseases. However, the most commonly reported complication is the manifestation of carpal tunnel syndrome (CTS) due to compression of the median nerve in the carpal tunnel, and which classically presents as a burning sensation affecting the first, second, third, and half of the fourth finger. The diagnosis of carpal tunnel syndrome is based on clinical symptoms (pain, numbness, paresthesia in the distribution of the median nerve) with the two most commonly used tests being Phalen's and Tinel's tests, and eventually confirmed by nerve conduction studies in atypical cases.

Maintenance dialysis is an important procedure to prevent death from uremia in patients with end- stage renal disease (ESRD) and as stated earlier, it is a well-established cause of CTS. It was reported that the incidence of CTS in patients on long-term hemodialysis fluctuates between 2% and 32% [1-2]. Symptoms of CTS are often severe and interfere with independent living.

The aim of this study is to review our current knowledge of the factors influencing the incidence of CTS in patients on HD.



Median nerve distribution



2. MATERIALS/METHODS

In order to gather the risk factors of CTS in long-term hemodialysis patients published in literature, a systematic search was conducted using PubMed, Cochrane and Google scholar from 2008 to 2018. The keywords and their combination used for our search were hemodialysis, end stage renal disease, carpal tunnel syndrome, β2-Microglobulin, dialysis related amyloidosis, and arteriovenous fistula Only studies that established a link between a risk factor and the incidence of carpal tunnel syndrome in hemodialysis patients, and published in English (regardless of the country of origin) were selected. A publication was considered relevant for our review if it included risk factors for CTS in hemodialysis patients. Titles and abstracts were reviewed for their pertinence to our study and selected, and full texts, when possible, were obtained.

The quality of each publication was assessed for its design, analysis, and results using the CASP check-list and was included if it met the following inclusion criteria: cohort, cross-sectional and cross-over. We excluded studies that did not have sufficient information, low-quality based on the CASP 10-11 questions or nonrelevant to our research subject. Table 1 shows the data extraction which consisted of first author's name, date of publication, sample size and country of performance.

Table 1. Studies on the risk factors for CTS in hemodialysis patients

First author	Date of publication	Sample size	Country of performance
Ostubo et al. [3]	2009	34	Japan
Mumtaz et al. [6]	2010	50	Pakistan
Hoshino et al. [7]	2010	202 726	Japan
Kopeć et al. [4]	2011	386	Poland
Busch et al. [8]	2012	385	Germany
Kocyigit et al. [11]	2013	12	Turkey
Schiffl [9]	2013	147	Germany
Gargouri-Barrechid et al. [12]	2014	155	Tunisia
Hoshino et al. [10]	2014	166 237	Japan
Huang et al. [13]	2016	866	Taiwan
Haddiya et al. [5]	2018	112	Morocco

3. RESULTS

The search using PubMed, Cochrane and Google scholar databases yielded a total of 64 articles and based on our inclusion criteria, 11 articles were included in our review (Fig. 1).

The 11 studies included 9 cross-sectional and 2 cohort studies with a total sample size of 883 952 patients (Table 1). Different risk factors for carpal tunnel syndrome were assessed in these 11 studies, including duration of hemodialysis, β_2-microglobulin levels, dialysis methods, vascular access, serum albumin levels and loss of residual renal function.

(1) In 4 cross-sectional studies [3,4,5,9], it was shown that duration of the dialysis therapy was a significant risk factor for the incidence of carpal tunnel syndrome in hemodialysis patients.

(2) 2 cohort studies [7,10] as well as 3 cross-sectional studies [6,8,9] showed that β2-microglobulin levels was a good predictor of CTS

(3) In 2 cross-sectional studies [11,12], the authors showed a relationship between the arteriovenous access and the occurrence of CTS.

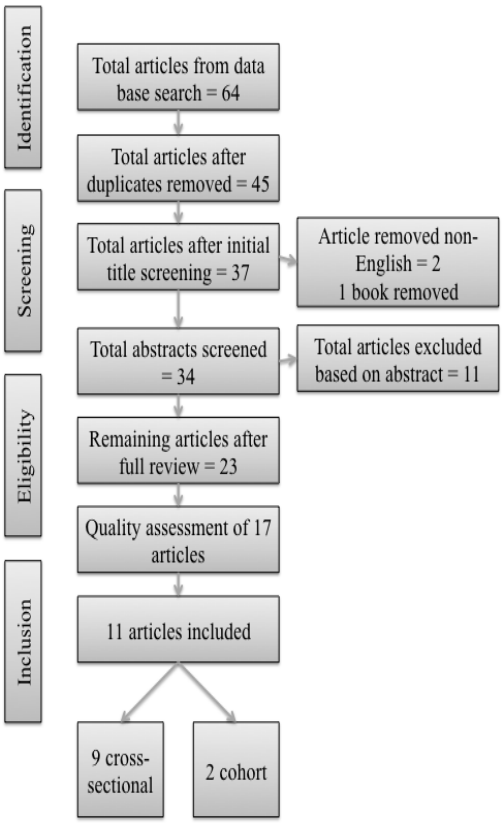


Fig. 1. Flow chart of articles selection

4. DISCUSSION

Carpal tunnel syndrome (CTS) has been recognized as a complication of long-term hemodialysis for more than four decades. The number of patients requiring long-term hemodialysis is increasing in the US population and the incidence of CTS is expected to increase as well. Many studies have shown that the incidence of CTS is 100% after 20 years of treatment.

Although the etiology of CTS has not been determined with certainty yet, many factors have been suggested such hypothyroidism, diabetes or peripheral polyneuropathy. What is known is that CTS in patients on hemodialysis is closely related to accumulation of β2-Microglobulin.

Table 2. Methodology of studies included

First author	Study design	Statistical method	Conclusion
Ostubo et al. [3]	Cross-sectional	Kaplan-Meier Student t-test Chi-Square Fisher exact probability	Hemodialysis-associated amyloidosis was common in extremely long-term survivors
Mumtaz et al. [6]	Cross-sectional	Levene's test	β2-m levels are significantly high in dialysis patients. Use of low-flux dialyzer seems to be the major reason
Hoshino et al. [7]	Cohort	Odd ratios Propensity score	The incidence of first-time CTS as proxy for DRA decreased significantly from 1998 to 2010. Several factors may have contributed to this decrease, including improved dialysis method
Kopeć et al. [4]	Cross-sectional	Mann-Whitney test Chi-square	Duration of dialysis treatment was the statistically significant risk factor for the development of CTS
Busch et al. [8]	Cross-sectional	Chi-square	Prevalence of CTS as a possible manifestation of DRA is still high. Serum concentration of CML may be a predictor of CTS besides β2-m and malnutrition
Kocyigit et al. [11]	Cross-sectional	Kolmogorov-Smirnov Paired t-test Pearson's correlation	Increased venous pressure on the same arm with AVF could be responsible for CTS in hemodialysis patients
Schiffl [9]	Cross-sectional	Chi-square	Duration of dialysis treatment was the only significant risk factor for the development of CTS. CTS occurred significantly earlier in conventional HD patients
Gargouri et al. [12]	Cross-sectional	Chi-square	The positive correlation between CTS and arteriovenous fistula confirms the pathogenic role of the latter. The risk rises in these patients with the duration of hemodialysis and the presence of diabetes
Hoshino et al. [10]	Cohort	Odd ratios	ORs of first-time CTS almost doubled with every 5-year increase in dialysis vintage. ORs of CTS were highest for patients aged 60-70. Other factors associated with CTS were gender, serum albumin and diabetic nephropathy. β2-m clearance > 80% may decrease the incidence of CTS
Huang et al. [13]	Cross-sectional	Kolmogorov-Smirnov Mann-Whitney test Logistic regression Student t-test	High nPCR and low serum albumin level is associated with CTS in HD patients
Haddiya et al. [5]	Cross-sectional	Chi-square Mann-Whitney Fisher test	Long dialysis vintage, positive HCV and loss of residual renal function were associated with CTS in chronic HD patients

β2-Microglobulin is a globular low-molecular-weight protein component of MHC class I molecules, encoded by the B2M gene on chromosome 15 [14], and is present on all nucleated cells. It was postulated by Gejyo et al. [15] that β2- Microglobulin aggregates in the tissues because conventional hemodialysis is unable to remove it from blood and therefore

forms amyloid fibrils accumulating in the carpal tunnel. It remains unclear how the β2-Microglobulin forms amyloid polymers, as it was shown [16] that the β2- Microglobulin circulates as an intact monomer.

Another worth mentioning point is that the different dialysis membranes seem to have an influence in the CTS rate and progression. With a high-flux, high-performance dialyzer like the polyacrylonitrile membrane, there is a better removal of protein-bound uremic toxins, and middle to large molecular-weight solutes, including β2-Microglobulin [17] than conventional hemodialysis membrane.

5. PATHOGENESIS

β2-Microglobulin is a polypeptide of 11800 Dalton that forms the β-chain of MHC class I, present on the surface of all nucleated cells (Figure 2). In a fully functional kidney, almost 100% of β2-Microglobulin is filtered through the glomerular membrane and reabsorbed to be degraded in the proximal tubule. Therefore, the clearance of β2-Microglobulin is dependent on the glomerular filtration rate (GFR). The synthesis of β2-Microglobulin remains constant in a healthy individual. However, in kidney failure, there is an accumulation of β2-Microglobulin and serum levels can increase by several folds. This accumulation plays a role in the pathogenesis of dialysis-related amyloidosis (DRA) [18].

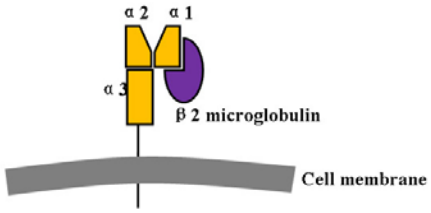


Fig. 2. Molecular structure of MHC class I [20]

There are some indications that the dialysis itself, as an inflammatory process, stimulates β2-Microglobulin synthesis by activating the cytokines production [19] (IL-1, TNF-α, IL-6).

Membranes used in conventional dialysis (Cuprophan and cellulose acetate) are impermeable to β2-Microglobulin because of their small pores size and can only clear substances with molecular weights less than 200 Dalton. The high-performance, high-flux membranes (Table 3) are more efficient in removing β2-Microglobulin but the rate of β2-Microglobulin remains higher. This type of amyloidosis involves predominately the osteoarticular system and evolves over time and is rare in the first few years of hemodialysis and many factors involved in this amyloidogenic protein retention in HD have been implicated:

- Type of dialyzer membrane
- Levels of cytokines
- Decreased diuresis
- Dialysate

Table 3. Please insert a table caption
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Material	Manufacturer	Membrane Type
Cellulose triacetate	**Nipro**	**Hollow fiber**
Polysulfone	**Asahi Kasei** **Kuraray Medical** **Fresenius** **Toray**	**Hollow fiber**
Polyethersulfone	**Nipro** **Membrana**	**Hollow fiber**
Polymethylmethacrylate	**Toray**	**Hollow fiber**
Polyester polymer alloy	**Nikkiso**	**Hollow fiber**
Ethylene vinyl alcohol copolymer	**Asahi Kasei Kuraray**	**Hollow fiber**

Polyacrylonitrile	**Gambro**	**Hollow fiber laminated**

EXAMPLES OF HIGH PERFORMANCE DIALYZERS

MATERIAL	MANUFACTURER	MEMBRANE TYPE
Cellulose triacetate	Nipro	hollow fiber
Polysulfone	Asahi Kasei Kuraray Medical	hollow fiber
	Fresenius	hollow fiber
	Toray	hollow fiber
Polyethersulfone	Nipro	hollow fiber
	Membrana	hollow fiber
Polymethylmethacrylate	Toray	hollow fiber
Polyester polymer alloy	Nikkiso	hollow fiber
Ethylene vinyl alcohol copolymer	Asahi Kasei Kuraray Medical	hollow fiber
Polyacrylonitile	Gambro	hollow fiber laminated

Adapted from Saito A, Kawanishi H, Yamashita AC, Mineshima M, eds. In: High-Performance Membrane Dialyzers. Contributions to Nephrology. Vol 173. Basel: Karger:2011

6. CONCLUSION

We conducted this literature review to get an overview of the different risk factors influencing the incidence for carpal tunnel syndrome in patients on long-term hemodialysis. Several risk factors were identified, but a clear cause was not established. A multifactorial, complex interaction between some or all of the risk factors most likely exists and could explain the incidence of CTS in this population. It is worth mentioning that the duration of treatment is an established risk factor especially after 5 years of treatment. Therefore, physicians should suspect CTS with any signs or symptoms after 5 years of treatment and offer screening to improve the outcome.

7. LIMITATIONS

The limitations of a review of this nature are:

- Complete reliance on previously published studies
- Limitation to studies published in English only
- Determining and integrating the complex interactions between the risk factors

COMPETING INTERESTS

Author has declared that no competing interests exist.

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