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

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

MATERIAL/METHODS- A systematic search to gather the different risk factors of CTS reported in the literature was conducted using PubMed.

RESULTS- This literature review included 7 articles that met our criteria. Incidence of CTS in hemodialysis patients increased with the duration of dialysis, age of the patient, arteriovenous fistula, and β_2-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.

KEY WORDS: Arteriovenous fistula, β_2-Microglobulin, carpal tunnel syndrome, dialysis related amyloidosis, ESRD, hemodialysis.

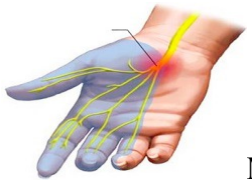
BACKGROUND

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

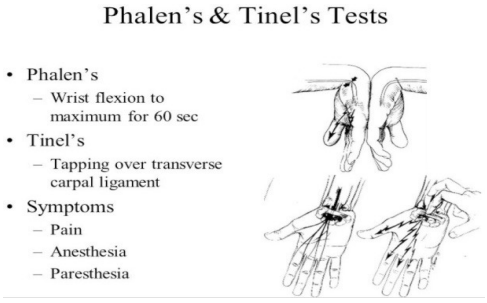
tests being Phalen's and Tinel's tests, and eventually confirmed by nerve conduction studies in atypical cases.

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



MATERIAL/METHODS

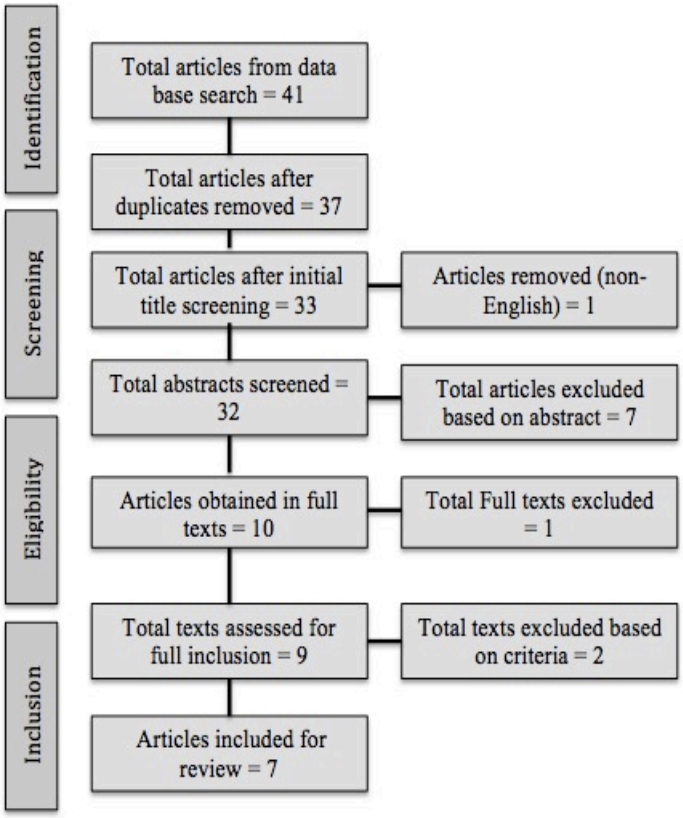
In order to gather the risk factors of CTS in long-term hemodialysis patients published in literature, a systematic search was conducted using PubMed. The keywords used for our search were hemodialysis, end stage renal disease, carpal tunnel syndrome, β_2-Microglobulin, and dialysis related amyloidosis. 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 and was included if it met the following inclusion criteria:

1-The article was published in English
2-The article was published in the last 20 years
3-The article has clearly stated research questions on risk factors of CTS in hemodialysis patients
4-The article has a clear and specified population as well as acceptable diagnostic methods for CST and risk factor evaluation
5-The sampling method is clearly described and appropriate
6-The selection of cases and controls is valid and consistent
7-The cases and controls were matched appropriately
8-The article clearly identified and addressed confounding factors
9-The method of data extraction is described
10. A statistical analysis tool was used

RESULTS

The search using PubMed yielded 41 articles, and based on our inclusion criteria, 7 articles were included in our review.



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Various publications delineated some contributing factors to the development of Carpal Tunnel Syndrome in patients undergoing Hemodialysis procedures, such as the duration of the dialysis, arteriovenous fistula (AVF), and amyloidosis[3,4,5] , increased venous pressure and other factors.

In a study published by Kopeć[3] et al. in 2011 and which included 386 patients on long-term hemodialysis, it was shown that 10.4% of those patients (40) developed carpal tunnel syndrome, and confirmed by nerve conduction. It was reported that the duration of the treatment was the most statistically significant risk factor for the development of carpal tunnel syndrome (CTS) and that 100% of patients on maintenance dialysis for over than 20 years required surgical intervention to release the pain. It was also shown that about 33% of patients on chronic hemodialysis presented with CTS after less than 4 years of treatment and the proportion of the affected patients increased significantly after 5 years to reach 100% after 20 years. They also concluded that CTS was diagnosed more often in patients with anti-HCV profile compared to a negative profile (47.5% vs. 6.9%; $p<0.0001$). Patients with CTS had a much longer duration of HD treatment compared to patients without CTS
(Figure 1 & Table 1 Kopeć et al.)[3]

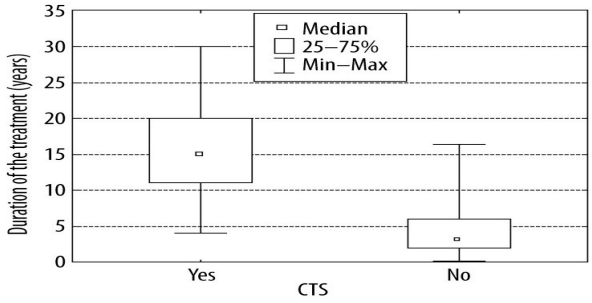

Figure 1: Incidence of CTS and duration of dialysis treatment[3]

Table 1: Duration of dialysis therapy among patients with CTS[3].

Dialysis duration (years)	Patients with CTS	Percentage of population
25–30	5	100.00
20–24	5	100.00
15–19	10	66.66
10–14	16	42.10
<10	4	1.60

Prior to mid-80s, arteriovenous fistula (AVF) was thought to be responsible for CTS with at least some local effect of AVF on CTS demonstrated by a study[5], due to edema, venous hypertension or steal syndrome. Many authors have reported that the side of the AV fistula played a role in the frequency of CTS[6,7]. However, there was a discrepancy between the clinical assessment and the electrodiagnosis that showed significant correlation between the CTS frequency and the AV fistula, rising questionable utility of electrodiagnosis for CTS.

In 2011, Kwon HK[8] et al. conducted a study on 112 patients with ESKD with 64 on HD and 48 on peritoneal dialysis (PD) and concluded that there was no significant association between the frequency of CTS and the A-V fistula (Table 2[8]).

Type	Site of A-V Fistula	Site of CTS			*P* Value
		Right	Left	Bilateral	
A-V Fistula	Right (n=2)	0	0	0	0.816
	Left (n=56)	1	2	16	
Venous Catheter	Right (n=0)	0	0	0	0.816
	Left (n=7)	0	0	1	

Table 2. Frequencies of CTS according to the side of the fistula in patients on hemodialysis[8] (Kwon HK et al.)

A more recent study published in 2014 by Gargouri[4] et al. confirmed the correlation. The authors looked at the relationship between CTS and the arteriovenous fistula (AVF) and concluded that AVF is an additional risk factor for the development of CTS in patients on maintenance hemodialysis with a high

frequency ($p<0.001$) and more severity ($P=0.08$) in the arm where the fistula is located.

Although some studies have demonstrated a strong correlation between AVF and CTS[4,5,16] others have found no clear relationship between AVF and CTS[6,7,8,9,10,11], and since the documentation of amyloidosis in carpal tunnel in late 80s[12,13], β_2-microglobulin deposition is considered to be the major risk factor for the development of CTS and is known as the dialysis related amyloidosis (DRA). Interestingly enough, a study by Robert[14] et al. have concluded that there was no significant difference ($p = 0.7$) in incidence of CTS between HD population vs. the peritoneal dialysis population. The modality of dialysis is not reported to be a risk factor in the development of CTS related amyloidosis (DRA).

PATHOGENESIS

β_2-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 β_2-Microglobulin is filtered through the glomerular membrane and reabsorbed to be degraded in the proximal tubule. Therefore, the clearance of β_2-Microglobulin is dependent on the glomerular filtration rate (GFR). The synthesis of β_2-Microglobulin remains constant in a healthy individual. However, in kidney failure, there is an accumulation of β_2-Microglobulin and serum levels can increase by several folds. This accumulation plays a role in the pathogenesis of dialysis-related amyloidosis (DRA)[19].

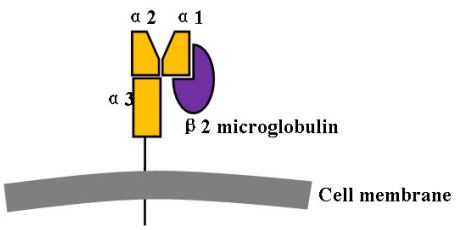

Figure 2: Molecular structure of MHC class I[20]

There are some indications that the dialysis itself, as an inflammatory process, stimulates β_2-Microglobulin synthesis by activating the cytokines production[21] (IL-1, TNF-α, IL-6).

Membranes used in conventional dialysis (Cuprophan and cellulose acetate) are impermeable to β_2-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 β_2-Microglobulin but the rate of β_2-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

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

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 β_2-Microglobulin.

β_2-Microglobulin is a globular low-molecular-weight protein component of MHC class I molecules, encoded by the B2M gene on chromosome 15[15], and is present on all nucleated cells. It was postulated by Gejyo et al.[16] that β_2- 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 β_2-Microglobulin forms amyloid polymers, as it was shown[17] that the β_2- 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 β_2-Microglobulin[18] than conventional hemodialysis membrane.

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.

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