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Evaluation of Polymorphisms in Cytokine Genes in Peritoneal Dialysis: Systematic Review

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Abstract

The chronic kidney disease is currently considered a public health problem. End-stage renal disease (ESRD) patients have as an alternative to blood clearance hemodialysis (HD) and peritoneal dialysis (PD). However, the development of local and systemic inflammatory processes in treating long-term PD peritoneal reflects the poor survival rate among patients with PD. In such a situation, polymorphism responsible for the variation of expression of components of immune modulators is relevant since they can increase the permeability of the peritoneal membrane. Therefore, the aim of this systematic review was to evaluate the frequency of interleukin-1 (IL-1), IL-6 and tumor necrosis factor-alpha (TNF-α) gene polymorphisms in patients under PD and their association with peritoneal dysfunction. The search was conducted on Medline, Embase, Lilacs (Scielo) and Web of Science. A total of 76 publications were found and three studies were included according to eligibility criteria. Two polymorphs T15A and -174G/C associated with the transport of solutes through peritoneal membrane, identified on IL-6 gene. In contrast, the polymorphs TNF-α 308 G/A and IL-6 -572 G/C had no correlation with the permeability across the peritoneal membrane. Further studies are necessary in order to unveil the effects of cytokines gene polymorphisms on peritoneal dysfunction.

Keywords: Peritoneal dialysis, Polymorphisms, Cytokines, Peritoneal membrane permeability

Introduction

The chronic kidney disease is considered a public health problem worldwide. Chronic kidney disease is defined as abnormalities of kidney structure or function, present for 3 months, with implications for health [1]. Some risk factors for disease development are described in the literature, such as pre-existing diseases, family history, and demographic variables and behavior [2]. The main causes of chronic kidney disease diabetic nephropathy, hypertension and glomerulopathy [3-6]. Additionally, obstructive uropathy, recurrent urinary infections, renal calculus and reflux nephropathy are also associated with the pathogenesis of chronic kidney disease [7].

In the past two decades, high rates of incidence and mortality of chronic kidney disease have alarmed the international scientific community. A cross-sectional was conducted by the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2004 revealed that approximately 13% of the adult U.S. population has chronic kidney disease [8]. In Brazil there is no conclusive epidemiological studies based on current diagnostic criteria. However, the prevalence and incidence of end-stage renal disease (ESRD) have progressively increased in Brazil and around the world, every year [9]. Whereas, a study of all incident patients enrolled in the National Database on renal replacement therapy starting dialysis between 2000 and 2004, show the increase of prevalence of 354 per million population in 2000 to 431 in 2004 [6].

The treatment for patients diagnosed with ESRD relies on alternative methods able to clearance the blood from toxic metabolites such as haemodialysis (HD) and peritoneal dialysis (PD) or renal transplantation [10-12]. Grassmann et al [13] observed a growing number of patients with ESRD treated with renal replacement therapy of 7% per year, worldwide, exceeding the rate of population growth.

While in HD the blood is dialyzed externally before being re-

introduced back to the patient circulation, the PD makes use of the peritoneum for blood filtration. In this case, a flexible catheter, inserted through an incision into the peritoneal cavity, is used to instill the peritoneal dialysis solution (PDS) and to remove the dialysate [14,15].

Patients submitted to HD are required to be hospitalized about three times a week for at least 4 hours. Despite of the higher mobility offered to the patients, the incidence of PD failure increases over the time of treatment when compared to HD [16]. The main causes of failure are peritonitis and the collapse of the peritoneal ultrafiltration capacity, leading to approximately 16% and 40% of patients death, respectively [17]. In most of the cases, the osmotic effects of glucose present in the PDS are quickly lost because of its absorption [18].

The most of patients with chronic kidney disease under long term of PD therapy develop a chronic inflammatory process. The local and systemic inflammation can be cause or consequence of the PM failure and are considered important prognostic factors for patients under PD. The inflammatory process is related to poor nutritional status, atherogenesis progress and mortality due cardiovascular events [19-21].

The IL-6, IL-1 and TNF-α released during the inflammatory process contribute to the PM failure by reducing the vascular tonus and increasing the PM permeability. Serum levels of C-reactive protein (CRP) can reflect the generation of these pro-inflammatory cytokines, and thus as CRP also predict mortality [6]. Cytokines are important factors in the structural and functional changes in the peritoneal membrane. In PD, cytokines play a role both in protecting against the development of peritoneal infection as in the course of peritoneal infection. And because of their biological effects, they can affect the permeability of the peritoneal membrane, and consequently the effectiveness of PD. Since not every dialysis patient presents elevated CRP, it has been proposed the involvement of polymorphisms in genes encoding these cytokines [22-25].

Different alleles have been reported for these cytokine genes among the population, which may contribute to the large spectrum observed on the peritoneal dysfunction outcomes [25,26]. According Padyukov *et al.* [27], there is an interest to estimate genotype patterns, which may be typical for certain ethnic groups, since they can contribute to prevalence of certain diseases or clinical changes. The author identified the allele frequencies of the -308 polymorphism of TNF-α in the Caucasian and Chinese populations. The G allele frequency at the first population was 81% and the A allele was 19%.As for the Chinese population the G allele appeared in 88.5%. Although the frequencies of the genotypes were not significantly different, the allele frequencies showed a different distribution among the Caucasians and the Chinese population.

According to Fishman [28] the G/C polymorphism at position -174 of the gene IL-6 has the potential to influence the binding of the glucocorticoid receptor and therefore its ability to repress transcriptional activation. It is significant that the change from a G to a C at position -174 creates a potential binding site for the transcription factor NF-1, a repressor of gene expression. The C allele and further the CC genotype result in lower expression of IL-6 expression after an inflammatory stimulus as compared with the GG genotype.

Although many studies investigating the presence and the frequency of cytokine genes polymorphisms in chronic kidney disease patients have been reported, there is still a lack of information regarding how it can be correlated with the prognostic of PD patients. Therefore, the aim of this systematic review was evaluate IL-1, IL-6 and TNF-α cytokines genes polymorphisms frequency in patients under PD and its association with peritoneal dysfunction.

Materials and Methods

Search strategy and data extraction

An electronic database search was conducted for four databases (Medline, Embase, Lilacs/Scielo and Web of Science) from the earliest record to May 2014.

The search was based on the following question: Do the IL-1, IL-6 and TNF-α cytokines gene polymorphisms affect the peritoneal transportation rate in patients under PD?

A sensitive search strategy using controlled vocabulary and free text terms was developed for each database with a combination of relevant key words such as Renal Dialysis, Peritoneal Dialysis, Polymorphism, Genetic, genetic alteration, genetic mutation, Cytokines, Interleukin-6, Tumor Necrosis Factor-alpha, Interleukin-1, Peritoneum or Peritoneal transport, peritoneal cavity.

The studies included in this review were restricted to English, Spanish and Portuguese languages.

Selection of the studies

The choice of the studies was conducted on independent way, considering the type of the study. The analysis consisted in two phases, conducted by two referees: firstly evaluating the titles and the abstracts of all identified studies and then analyzing the complete text of the manuscripts.

The inclusion criteria was investigations associating polymorphisms of [-174G/C], [-511C/T], [-572G/C], [-597G/A] and [T15A] IL-6 gene, [-308G/A], [-863C/A] and [-1031C/T] TNF-α, [-889 C/T], [-511 C/T] e [+3954C/T] IL-1 gene and the peritoneal transportation rate in patients under PD. The exclusion criteria consisted in studies not related to our main question, review articles, others cytokines and polymorphisms.

The results obtained with this search were evaluated by two referrers, independently, according the inclusion criteria.

Results

Eighty articles were found in different data bases: *Medline* (13.7%), *Embase* (62.5%) and *Web of Science* (23.8%). No results were found on *Lilacs (Scielo)* data base. After exclusion of duplicate articles, 63 articles remain and among them three articles were in agreement with the inclusion criteria (**Figure 1**). The selected studies were published between 2005 and 2011

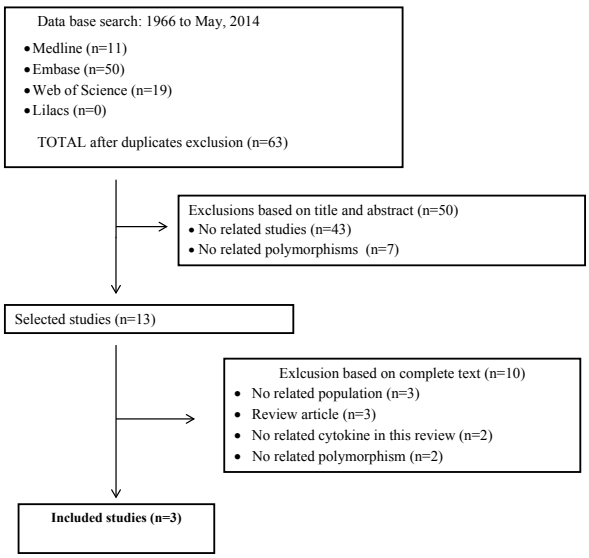

Figure 1 Ilustrative fluxogram of design of the study.

and consisted in case-control, transversal and prospective cohort studies, from Belgium, North of France and Korea and Taiwan, respectively.

Although the selected studies investigated the association of IL-6 polymorphisms and the transportation rate in PD patients, only Hwang *et al.* [25] and Lee *et al.* [26] evaluated the TNF-*α* polymorphisms. No reports about IL-1 polymorphism in patients under PD were found.

Tables 1 and 2 present synopsis and main conclusion of the studies, respectively.

Discussion

This systematic review showed that IL-6 T15A and [-174G/C] gene polymorphisms were associated with peritoneal transportation rate in patients under PD. On the other hand, no association was observed for TNF-α [-308G/A], [-1031 C/T] and [-863C/A] gene polymorphism and IL-6 [-572 G/C] gene polymorphism. No information about IL-1 and PM dysfunction was found.

Although several cytokines regulate the inflammatory response, IL-6 is a particular mediator, with pro- and anti-inflammatory effects. Systemic IL-6 promotes inflammatory events through activation and proliferation of lymphocytes, B cells differentiation, leucocytes recruitment and hepatic proteins induction in acute inflammatory process [29]. The IL-6 is produced by several types of cells as monocytes, mesothelial cells, fibroblasts, adipocytes and lymphocytes, under physiologic *stimuli* such as TNF-α, IL-1β, endotoxins, physical exercise and oxidative stress. The effect of IL-6 is based on a complex receptor system, with IL-6R (or gp 80) subunit and one subunit of signal transduction (gp 130) [29].

The cytokines, such as IL-6 and TNF-α in dialysate regulates the PM permeability and are strongly associated with peritoneal solute transportation rate. Studies show that intraperitoneal levels of IL-6 correlates with the pattern of transport of the peritoneal membrane [30,31]. Higher plasma levels were observed in the study of Pecoits-filho et al [30] with high standard transport for small solutes. It is suggested then that local inflammation and angiogenesis interfere with the transport of solutes by the peritoneum [32,33].

Lee *et al.* [26] evaluated the role of polymorphisms of these cytokines, including IL-6 [-572 G/C] and TNF-α [-308 G/A] on longitudinal evolution of peritoneal function. A total of 141 stable patients under PD, with average of treatment 84.4 months participated of the study. Clinical parameters, such as high comorbidity, older age, diabetes, episodes of peritonitis and exposure to high glucose concentration, were included as factors that affect the longitudinal peritoneal transport, in period of three years of the first therapy. Considerable evidence demonstrated that chronic inflammation exerts apparent effects on uremic patients [29]. It also became clear that the concentrations of pro inflammatory cytokines in dialysate implicated in the regulation of PM permeability are strongly associated with the peritoneal solute transport rate in dialysis patients [33]. Among them 48% were classified as high/average and high and 52% as low/average and low transporters. No significant differences were observed for IL-6 [-572 G/C] and TNF-α [-308 G/A] polymorphisms between these two groups. No significant differences were observed for IL-6 [-572 GG/GC; CC] and TNF-α [-308 AA/AG; GG] polymorphisms for longitudinal peritoneal transportation after 12, 24 and 36 months of observation. In agreement with these findings Hwang *et al.* [25] demonstrated similar results for IL-6 [-572G/C, T15A] and TNF-α [-1031C/T, -863C/A, -308G/A]. Only IL-6 [T15A] was associated with peritoneal transportation and dyalisate IL-6 levels. In this study 132 patients under PD were evaluated for three years and clinical and biochemical tests, including PET and cytokines genotyping were made. Patients were classified as high/average-high and low and average-low transporters based on dyalisate and plasma creatinine concentration after four hours of infusion of dialysis solution (D4/PCr). Among seven polymorphisms, IL-6 [T15A] was significantly correlated with different profiles of peritoneal transportation. Patients with TA genotype had significantly reduced D_4/PCr (0.65 ± 0.087 vs 0.73 ± 0.110, p=0.0046). and high levels of glucose on dyalisate after four hours of infusion (D4/D0) (0,39 ± 0.174 vs 0.31 ± 0.119, p=0.0273) comparing to TT genotype. On the other hand, no significant differences were observed for TNF-α gene polymorphisms. In a multivariate analysis, considering gender, clinical data, age, diabetes, cardiovascular disease, us-CRP, residual renal clearance in to the model, the TA genotype was negatively associated with increased peritoneal transportation rate (high or average-high). Thus, IL-6 [T15A] gene polymorphism, located on exon 5, was considered as a independent predictor of peritoneal transportation rate, in the Korean population evaluated.

The variation [T15A] on exon 5 promotes the substitution of aspartate for glutamate on the coding sequence. The exactly mechanism of this polymorphism on the IL-6 levels on dialysate is still unkown. It seems that there is no direct effect of the polymorphism on the cellular effect of IL-6 because the position of the residual amino acid [34,35]. Similar study was reported by Gillerot *et al.* [36], that evaluated IL-6 [-174G/C] and [-597G/A] gene polymorphisms. Significant differences were observed

Table 1 Descriptive synopsis of the investigated studies.

Source	Study design	Sample size and location	Patients characteristics
Gillerot et al., [36]	Case-Control	Cases: n=152 PD patients. Control: n=103 healthy subjects. Five hospitals from Belgium and North of France.	87 men and 65 women Caucasians patients with age average of 57 ± 1.4 years under PD treatment (4-24 weeks) before the initial peritoneal equilibrium test (PET).
Hwang et al., [25]	Transversal	Cases: n=132 PD patients. Four hospitals from Korea.	74 men and 58 women with average of age of 51 ± 14 years submitted to initial PET between one to three months after the dialysis has started. Those patients with active peritonite and/or renal transplantation failure history were not included.
Lee et al., [26]	Prospective cohort	Cases: n=141 PD patients. Patients from Chang Gung Memorial Hospital (CGMH) of Taiwan.	49 men and 92 women between 49.8 ± 13.5 years under PD treatment of 84.4 ± 34.2 months. Patients diagnosed with chronic inflammatory disease, malignance or acute peritonite two months before PET were excluded.

Table 2 Synopsis of results of the investigated studies.

Source	Cytokines and polymorphisms	Effect of polymorphism
Gillerot et al., [36]	IL-6 -174 G/C -597 G/A	(i) Patients with [-174G/C] IL-6 gene polymorphism with GC and CC genotypes presented: a) Increased peritoneal transportation rate (p=0.006). b) Increased plasma and dialysate levels of IL-6 (p=0.002).
Hwang et al., [25]	IL-6: -572 G/C T15A	(i) T15A polymorphism in exon 5 of IL-6 gene found as independent predictor of peritoneal solutes transport rate (PSTR): a) TA genotype was negatively associated to increased peritoneal transportation rate (p=0.025). b) TA genotype was associated with low dialysate levels of IL-6 (p=0.0358).
	TNF-α: -1031 C/T -863C/A -308G/A	(ii) TNF-α gene polymorphisms and [-572 G/C] IL-6 gene polymorphism have not influence over PSTR (p=NS).
Lee et al., [26]	IL-6 -572 G/C TNF-α -308 G/A	(i) No association was found among IL-6 [-572 G/C] and TNF-α [-308 G/A] gene polymorphism and longitudinal alteration of peritoneal function (p=NS).

among high/ average-high and low and average-low transporters.

Low and average-low transporters present low prevalence of CC and GC genotype (49% *vs* 69%, respectively) and high prevalence of GG genotype (51% *vs* 31%, respectively) of IL-6 [-174G/C] polymorphism, by comparing to high and average-high group. This polymorphism was identified as an independent predictor of peritoneal permeability. This study show also high expression of IL-6 mRNA in peritoneal membrane of patients with CC genotype. Hwang *et al.* [25] show high levels of IL-6 on plasma and dialysate in patients with CC and GC genotypes. Together, these data suggest that the C allele elevate the IL-6 production, which could reflect on a selective production of CRP.

The correlation of IL-6 and TNF-α with PM dysfunction is presented on **Figure 2.**

The IL-1 (IL-1α e IL-1β) is a multifunctional cytokine acting in almost all cell types and synergistically with others cytokines and mediators. Its production and activity are strictly regulated. The regulation involves gene expression, secretion, surface receptors, soluble receptors and one antagonist receptor [37].

The membrane-associated IL-1α of is biologically active and signalizes through paracrine mechanisms, stimulating the IFN-γ activity [37,38].

Several polymorphisms of IL-1 family gene, such as IL-1α [-889 C/T] and IL-1β [-511 C/T] e [+3954 C/T], have been described

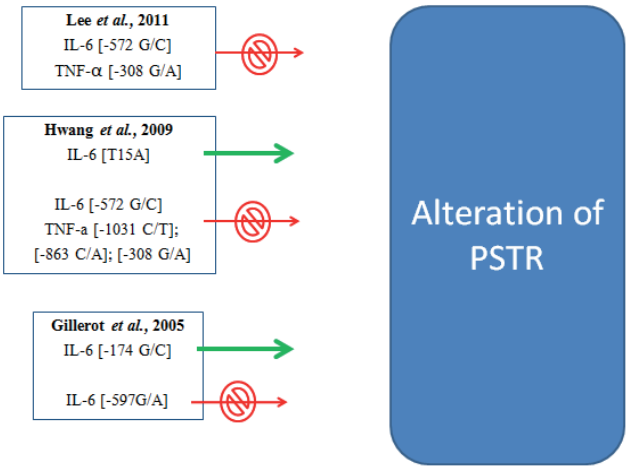

Figure 2 Impact of polymorphisms on peritoneal solute transportation rate (PSTR).
→ associated with PSTR,
⊘→ not associated with PSTR.

among different pathologies. Located at position -889, the IL-1α is characterized by C to T substitution, with allele T related to increased levels IL-1α [39,40]. The allele T of IL-1β [-511 C/T] polymorphism has been associated with high production of this cytokine, while CC and CT genotype have been associated with peritonitis [40-43]. No further information was found about IL-1 polymorphisms and PD.

It is worth of note that the number of polymorphisms in a gene target and its allelic frequency in determined population are critical factors in genetic association studies. On the other hand, negative results could reflect in absence of biological effect of specific variant as well as in no clinical significance [23].

This review suggests that genetic variants, together with clinical factors, could contribute to the variability to peritoneal transport observed at baseline. New approaches well-designed, adequately powered studies, in different populations and different settings will require to confirm the strength of the association and to decipher the influence of genetic determinants on peritoneal transport. These studies of genetic variations, using molecular genetics, epidemiology, and bioinformatics will provide more and robust data about the association between the genotype profile and diseases.

Limitations observed in this study include patient of different demographics regions, since the populations from difference ethnicity can vary the frequency of alleles, different design of the studies, small sample size for this type of analysis and few number of the manuscripts included according to the established criteria.

Conclusion

Data analyses indicated a possible association between IL-6 [T15A] and [-174G/C] gene polimorphisms and peritoneal transport rate of PD patients. On the other hand, IL-6 [-572 G/C] and [-597G/A] gene polymorphisms had no significant association with peritoneal transport rate. None of the gene polymorphism of TNF-α from the selected studies showed a significant association with peritoneal transport rate. This systematic work revealed a lack of studies investigating the role of polymorphism of IL-1 genes on the peritoneal transport. Therefore, this is promising area of research since this cytokine is truly related with MP. Moreover it is necessary more studies focused on IL-6 to define which polymorphisms of this cytokine could best related to the functioning of the peritoneal membrane and its mechanisms. Overall, given the few selected articles more studies are needed with a large number of patients to confirm the mechanisms between polymorphisms and peritoneal function.

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