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REVIEW ARTICLE

# Participation of IL-6 in chronic kidney disease

## *Papel de la IL-6 en la enfermedad renal crónica*

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## Abstract

*Chronic kidney disease (CKD) is a kidney condition whereby the structure and function of the kidneys is damaged and compromised for a minimum of three months. The global prevalence of CKD in the general population in 2017 was estimated at 9.1%, which represents approximately 700 million cases. In Mexico, kidney failure related to diabetes mellitus represents 25% of deaths due to diabetes, while kidney failure related to arterial hypertension represents 28% of deaths related to intensive heart disease, and non-specific kidney failure represents 6% of deaths classified as nephritis and nephrosis. CKD is a disease mainly driven by an inflammatory process and in more advanced stages, by fibrosis. These processes go hand in hand with the expression of multiple proinflammatory cytokines, including IL-6. It is widely reported that elevated levels of IL-6 correspond to the progression of CKD, due to its secretion stimulated by oxidative stress and pro-inflammatory factors or accumulation due to decreased renal capacity. The present review aims to know the IL-6 effects on the inflammation in chronic kidney disease process.*

***Keywords:*** *Chronic kidney disease. Inflammation. Interleukin 6. IL-6 Gene.*

## Resumen

*La enfermedad renal crónica (ERC) es una afección renal en la que la estructura y función de los riñones se daña y compromete durante un mínimo de tres meses. La prevalencia global de ERC en la población general en 2017 se estimó en 9,1%, lo que representa aproximadamente 700 millones de casos. En México, la insuficiencia renal relacionada con la diabetes mellitus representa el 25% de las muertes por diabetes, mientras que la insuficiencia renal relacionada con la hipertensión arterial representa el 28% de las muertes relacionadas con enfermedades cardíacas intensivas, y la insuficiencia renal inespecífica representa el 6% de las muertes clasificadas como nefritis. y nefrosis. La ERC es una enfermedad impulsada principalmente por un proceso inflamatorio y en estadios más avanzados, por fibrosis. Estos procesos van de la mano con la expresión de múltiples citoquinas proinflamatorias, incluida la IL-6. Está ampliamente reportado que niveles elevados de IL-6 corresponden a la progresión de la ERC, debido a su secreción estimulada por estrés oxidativo y factores proinflamatorios o acumulación por disminución de la capacidad renal. La presente revisión tiene como objetivo conocer los efectos de la IL-6 sobre la inflamación en el proceso de enfermedad renal crónica.*

***Palabras clave:*** *Enfermedad renal crónica. Inflamación. Interleucina 6. IL-6 Gen.*

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## Introduction

### *Definition of the disease*

Chronic kidney disease (CKD) is defined by the Kidney Disease Improving Global Outcome (KDIGO) guideline as a series of abnormalities in kidney structure and function with health implications that persist for more than three months. In this way, it is a general term for a set of heterogeneous disorders with a clinical presentation that can vary, depending on the cause and severity of the disease[1]. Specifically, the kidney activities that we see generally decreased in most CKD presentations and will be excretory functions, but also endocrine and metabolic functions[2].

The first of the criteria used to delineate CKD from other diseases with implications of decreased kidney function is duration. The KDIGO has explicitly defined a period of 90 days to accept the chronic value of the disease[1]. Moreover, although in most scenarios, the persistent quality of the causal factors of the disease provides it with an irreversible nature, there are cases in which CKD will be partially or completely reversible, so it is important to highlight that irreversibility is not part of the criteria that defines CKD[3].

The second key factor in the delineation of CKD is, of course, the decrease in kidney function as such. The kidney comprises up to one million nephrons. Thus, the glomerular filtration rate (GFR) is calculated by multiplying the filtration capacity of an individual nephron by the total number of nephrons, and is expressed in mL/min/1.73m$^2$. The KDIGO establishes that a GFR of < 60 mL/min/1.73m$^2$ should be considered as decreased GFR, while a GFR of < 15 mL/min/1.73m$^2$ indicates renal failure. In summary, a GFR of < 60 mL/min/1.73m$^2$ that persists for more than ninety days will indicate the presence of CKD[1]. A GFR of < 60 mL/min/1.73m$^2$ can be detected by laboratory analysis. When it comes to an estimate based on serum creatinine, we will talk about an eGFR (estimated Glomerular Filtration Rate). An eGFR can be confirmed using an alternative filtration marker such as cystatin C[4].

The third defining factor of CKD is kidney damage, which can occur in the parenchyma, epithelial tissue, or collection systems[5]. Kidney damage is generally inferred through the use of markers and not necessarily by direct examination of kidney tissue. These markers may even provide information about the location of the damage[6]. A key marker of kidney damage in glomerular diseases is the increase in the amount of protein suspended in the urine, that is, the presence of proteinuria, which may be due to an increase in glomerular permeability to high molecular weight proteins, tubular reabsorption incompleteness of low molecular weight proteins, the loss of constituents of the tubular cells of the kidney or, if applicable, an increase in the concentration of low molecular weight proteins, although in this scenario, unlike the first three; proteinuria will not necessarily reflect a decrease in the ability of the kidneys to filter plasma protein due to the existence of damage[1,6].

### *Disease classification*

The KDIGO proposes and recommends a classification system for CKD based on a two-dimensional matrix where one axis incorporates the level of albuminuria expressed in mg/g, this being an estimator of kidney damage and divided into three categories (A1- A3). The other axis incorporates the GFR, that is, an estimator of kidney function, divided into 6 categories (G1, G2, G3a, G3b, G4 and G5). At the intersection of each of these classifications we find a stage of the disease (for example G3bA2), with a description of the patient's risk of disease progression, manifested as progression to end-stage renal disease (ESRD), the risk of developing cardiovascular disease, suffering from acute kidney injury, hospitalization, and even death[1]. However, this classification system suffers from some weaknesses, for example, stages G2-G4 could underestimate the extent of nephron loss because the decrease in GFR is not only associated with disease progression, but also with natural mechanisms such as physiological aging[7]. Furthermore, serum creatinine could, in the same way, underestimate the degree of kidney damage because protein levels have more notable changes the more advanced the disease is[8].

Likewise, KDIGO insists that the diagnosis of CKD at a certain stage does not constitute a comprehensive diagnosis, but rather it is important to determine the etiology of the disease to issue a prognosis and provide adequate treatment. In general, the etiology of the disease has been classified based on the presence or absence of systemic diseases, as well as the location of the renal abnormalities detected. In primary kidney diseases, the pathological process is restricted to the kidney, while, in systemic diseases, the kidney is only one element in a process that affects other body systems. Localized pathology regarding renal abnormalities is based on what is revealed by imaging techniques, urine sediment analysis, as well as the level of proteinuria. KDIGO also offers a classification of CKD based on the

presence or absence of systemic disease, as well as the location of the identified pathological processes[1].

## Chronic kidney disease and inflammatory processes

As the nephron receives a progressive increase in filtration load during the establishment of kidney disease, the expression of growth factors such as the transforming growth factor alpha (TGF-α)[9] and epidermal growth factor receptor (EGFR)[10], result in an increase in the filtration surface of the nephron that allows it to adapt to filtration overload stress. However, there will come a time when the size of the glomerulus will be such that the podocytes that maintain the glomerular filtration barrier will begin to detach due to mechanical stress, leading to the development of glomerulosclerosis and renal fibrosis[11,12]. Renal fibrosis will be accompanied by persistent inflammation as well as oxidative stress. NF-kB is an inflammatory factor activated by the accumulation of reactive oxygen species that occur in the context of fibrosis processes. This factor will trigger the production of inflammatory cytokines such as interleukin-1α (IL-1α), interleukin-1β (IL-1β), tumor necrosis factor (TNF) and interleukin-6 (IL-6)[13].

The microvascular networks in the kidneys have a unique structure that allows them to maintain an adequate osmotic gradient for the absorption of fluids and the production of concentrated urine. The key region of the kidney for this function is the medulla, which under physiological conditions will remain in a hypoxic environment, so it depends on a large number of locally produced regulators, mainly hormones and a variety of vasoactive molecules to maintain homeostasis[14]. This fine balance that takes place in the kidney medulla, and on which its function depends, is highly vulnerable to any influence from the microenvironment. The inflammatory response within the intrarenal architecture will contribute to the amplification of inappropriate microvascular activity, as well as the production of tubular toxins and even more reactive oxygen species[15]. This will lead to the impairment of the integrity of the endothelial glycocalyx, as well as the expression of cell adhesion proteins. The increase in the concentration of cytokines will also lead to the disruption of the normal metabolism of the extracellular matrix, the proliferation of resident cells, and the procoagulant activity of the renal endothelium[16].

The accumulation of these inflammatory stimuli, in conjunction with high levels of albumin, and the secretion of complement proteins, will lead to the activation of an inflammatory response of tubular cells[17], which promotes the recruitment and activation of immune system cells such as macrophages, as well as the secretion of pro-fibrotic factors including platelet-derived growth factor (PDGF), connective tissue growth factor (CTGF), and transforming growth factor β (TGF-β)[18]. These elements trigger the enrichment and activation of myofibroblasts, which will consequently lead to an increase in interstitial collagen deposition and fibrosis, and contribute to progress in tubulointerstitial tissue remodeling and loss of renal function[19].

Unlike acute inflammation, which is a natural response to kidney damage, chronic inflammation is the result of a negative adaptation resulting from persistent hyperstimulation of pro-inflammatory signals and pathways, leading to disease progression[20]. It is a state of aberrant activation of resident cells of the kidney with a pro-inflammatory phenotype, including mesangial, endothelial, tubular cells, and the podocytes themselves, thus perpetuating the increase in cytokine levels and extracellular matrix secretion[21].

## Interleukin-6 and kidney disease

Interleukin 6 (IL-6) is part of the IL-6 family that includes interleukin 11 (IL-11), interleukin 27 (IL-27), interleukin 31 (IL-31), leukemia inhibitory factor (FIL), oncostatin M (OSM), ciliary neurotrophic factor (CNF), cardiotrophin 1 (CT-1), cardiotrophin-like cytokine (NNT-1), granulocyte colony-stimulating factor (G-CSF) and neuropoietin (NP)[22]. This family is involved in a wide range of signaling pathways, both physiological and pathological[23]. They have a similar four-helix structure and share the glycoprotein gp130 as a receptor, allowing some redundancy among family members. However, although gp130 is found in all cells, by itself it is not capable of binding to cytokines, but rather requires additional receptors that are specific for each member of the family and are expressed only in certain types of cells[24].

## Two pathways for interleukin-6

Specifically, IL-6 was first identified in 1986[25]. Its most important target cells include lymphocytes, myeloid cells, epithelial cells, and hepatocytes. This cytokine has two signaling pathways known as the classical pathway and the trans pathway[26]. Classic signaling occurs when IL-6 affects its target cells by binding to the alpha chain of a membrane-associated IL-6

receptor (mbIL-6R), which is connected to two gp130 molecules, thus beginning a transduction cascade operated by JAK/STAT3 and SHP2/Gab/MAPK that are activated by the TxxQ and Y759 motifs of gp130 respectively[27]. However, cells such as macrophages, neutrophils, CD4+ T cells, podocytes and hepatocytes that express mbIL-6R are rare[28]. It is the trans pathway that allows IL-6 to reach more cell types, this through the expression of a soluble form of the IL-6 receptor (sIL-6R). IL-6 can associate with this receptor with the same affinity as its intermembrane counterpart, and once this happens, the IL-6/sIL-6R complex will be able to activate gp130 in almost any type of cell[29]. In humans, sIL-6R is generated through two pathways. The first consists of the cleavage of mbIL-6R through the activity of Zn2+ zinc-binding catalytic domain metalloproteinases of the ADAM family[30]. It is believed that ADAM10 and ADAM17 could cleave mbIL-6R, with slow and fast activity respectively. ADAM17 is an enzyme that is activated by many damage markers such as: pro-inflammatory cytokines, bacterial toxins, lack of cellular cholesterol, and DNA damage, among others[31]. The second pathway by which sIL-6R is generated is alternative splicing of the receptor mRNA[32]. There is a perception that the classical pathway and the trans pathway of IL-6 have specific activity during inflammation, where the classical pathway is associated with an anti-inflammatory effect, while the trans pathway with a pro-inflammatory effect. However, this pattern is not always constant, since in different scenarios we can find an effect opposite to that attributed to each of the pathways, so it is evident that the effect of IL-6 on the inflammation process will be context dependent[28].

## Interleukin-6 in the immune response

IL-6 is best known for its effects on the immune system's inflammation process. This acts mainly on T lymphocytes and monocytes. In T cells it is able to stimulate the differentiation of Th17 cells by positively regulating the expression of RORγt[33], while blocking the differentiation of Treg cells[34]. These Th17 cells will initiate the inflammatory response by secreting various pro-inflammatory cytokines[28]. Additionally, IL-6 has the ability to promote the proliferation of Th17, as well as provide resistance against their apoptosis through the production of IL-2[35], in addition to the activation of STAT3 and Th2[36]. Furthermore, IL-6 has the ability to direct the differentiation of monocytes, changing their cell fate from dendritic cells to macrophages by upregulating M-CSF receptors[37].

## Interleukin-6 in different kidney cells

The podocyte is a key cell in the relationship between IL-6 and the pathophysiology of kidney disease, as it is the only cell in the kidney that expresses mbIL-6R and, therefore, the only one capable of receiving the influx of IL-6 directly through the classical route[38]. IL-6 is secreted by the podocyte when exposed to pro-inflammatory mediators or in the presence of high levels of glucose, promoting its proliferation in an autocrine manner[39]. Furthermore, there is evidence that IL-6 can also act in this cell through the trans pathway in a process that is initiated by Ang II and leads to STAT3 activation[40].

Mesangial cells, although lacking IL-6R expression on their membrane, express gp130 and are capable of secreting IL-6[41]. Furthermore, when exposed to the IL-6/sIL-6R complex, they recruit monocytes through the secretion of chemoattractants, thereby increasing their accumulation of extracellular matrix and their proliferation[42].

Similarly, endothelial cells can receive the IL-6 signal through the trans pathway, which promotes the expression of the Ang II type 1 receptor (ATR1), triggering Ang-induced vasoconstriction II, as well as the production of ROS, which ends in endothelial dysfunction. These cells secrete IL-6 upon exposure to pro-inflammatory mediators such as IL-1 and IL-4 and TNFα[43].

Tubular epithelial cells also receive IL-6 stimulation through the trans pathway, and this promotes the generation of type I collagen[44], thereby accelerating tubulointerstitial fibrosis. These same cells secrete IL-6 under pathological conditions such as hypoxemia and exposure to nephrotoxins, oxidized lipids, advanced glycation by-products, immune complexes, and cytokines[45].

## Interleukin-6 during the development of chronic kidney disease

It is widely reported that elevated levels of IL-6 correspond to the progression of CKD. This is primarily because of its secretion that is stimulated by oxidative stress and pro-inflammatory factors, as well as the decrease in the kidney's ability to remove excess IL-6, which allows for its accumulation[46]. IL-6 will direct the progression of the disease by aggravating kidney damage by inducing overproduction of the extracellular matrix and the proliferation of certain cell lineages, but it will also initiate vascular complications that worsen the patient's health status[28].

## Genetics and cytokine polymorphisms in chronic kidney disease

The development and progression of CKD is strongly influenced by genetic factors. However, unlike Mendelian or monogenic disorders, it is a complex disease driven by a large number of genes and signaling pathways. In diseases of this type, the contribution of each gene is small, confers a relatively low risk, and can be modified by epigenetic and epistatic interactions[47], so that association studies of candidate genes with the development of the disease represent an important tool to unravel its complexity.

When human blood is stimulated by bacterial lipopolysaccharides, great variability is observed in the cytokine production of individuals. This is largely due to the great genetic variability that exists in these soluble factors[48]. It is well documented that variations in cytokine gene sequences have a strong influence on protein transcription and function. Additionally, clinical significance has been reported for many of these variants[47].

## The IL-6 gen

The Interleukin 6 (IL-6) gene encodes the classic cytokine IL-6. This gene was cloned and reported by Hirano and collaborators in 1986[25]. It is composed of five exons and four introns located from 7p15 to 7p21. It encodes the 212 amino acid (aa) IL-6 precursor that includes the 28 aa signal sequence and the mature segment of 184 aa.[49]. As mentioned previously, IL-6 bears structural resemblance to the other cytokines of its family. This protein in its mature state is composed of four alpha helices in a two-up, two-down arrangement. Its molecular mass varies from 21 kDa to 28 kDa depending on the cell that secreted it and N-/O-glycosylations and phosphorylations[50].

## The IL-6 rs1800796 (-634 C/G or -572 C/G), rs1800795 (-174 G/C), and rs1524107 (1400 C/T) polymorphisms

Of the polymorphisms studied in *IL-6* related to the pathophysiology of kidney disease, three have been investigated in detail for this review: rs1800796 (634 C/G or -572 C/G), rs1800795 (-174 G/C), and rs1524107 (1400 C/T) of IL-6.

In the report by Fishman et al. In 1998, the rs1800795 polymorphism was identified in the United Kingdom population due to the difference in the genotypic frequencies of 383 healthy subjects compared to those found in 92 patients with systemic juvenile idiopathic arthritis. After analyzing the response of HeLa cells to transfection vectors with rs1800795C/rs1800795G, it was determined that the C allele negatively regulates the expression of *IL-6* and reduces the production capacity of the cytokine upon stimulation with lipopolysaccharides and *IL-1*. Finally, the association of the C allele with decreased levels of *IL-6* in healthy patients was confirmed[51].

With the aim of determining whether there is an association of the rs1800796 polymorphism with the risk of diabetic nephropathy progression and *IL-6 sec*retion, Kitamura et al. assembled a panel of Japanese subjects with type II diabetes and microalbuminuria (138 patients), macroalbuminuria (154 patients), or normal albumin levels (162 patients). In this section, the polymorphism was genotyped, and the *IL-6* production capacity was determined upon stimulation by lipopolysaccharides and advanced glycation byproducts, revealing that there is an important association of the G allele and the GG genotype of rs1800796 with the suffering of macroalbuminuria, progression of diabetic nephropathy, and the secretion capacity of *IL-6* by monocytes in peripheral blood[52].

In their 2007 publication, Mittal and Machanda reported that the GG genotype of rs1800795 is associated with the risk of developing end-stage kidney disease in an Indian population of 193 cases and 180 controls without signs of the disease. Additionally, it was reported that the combination of rs1800795GG with the B2B2 genotype of the VNTR polymorphism in intron-3 of *IL-4* confers an even greater risk of disease progression[53].

In the study by Ng et al. carried out in a Caucasian section of patients diagnosed with type II diabetes, the association of *IL-6* polymorphisms with persistent proteinuria or with end-stage renal disease caused by diabetic nephropathy was explored. Initially, 46 single nucleotide polymorphisms (SNPs) were genotyped including rs1524107, rs1800796, and rs1800795. Of these three, only rs1800795 was polymorphic along with 11 other SNPs, and although none demonstrated a significant association with advanced diabetic nephropathy (the combination of proteinuria and chronic kidney failure/end-stage renal disease), a significant association was found for rs1800795 only for end-stage renal disease, but not for albuminuria levels. A similar association was found for a haplotype that includes the G allele of rs1800796 and the G allele of rs1800795 along with four other SNPs[54].

In the 2012 study by Okada et al. conducted in a Japanese cohort of 3,323 subjects, the association of 10 polymorphisms with CKD and eGFR was sought. Each of these polymorphisms belongs to a cytokine involved in pro- and anti-inflammatory signaling. Among these polymorphisms is rs1800796 of *IL-6*, which in its GG genotype was reported to be associated with a lower eGFR and a lower prevalence of CKD. Likewise, it was found that subjects with rs1800796GG and the CC genotype of rs2070874 of *IL-4* have even a lower prevalence of the disease and lower eGFR, while the opposite is reported for subjects with rs1800796CC and rs2070874TT[55].

In their 2014 publication, Zhang and collaborators genotyped the rs1524107 polymorphism for its relationship with biological aging, in a population of 482 Chinese subjects without signs of disease, although no association was found. This study is relevant, since biological aging is strongly associated with CKD progression and nephron loss[56].

Hepatitis induced by anti-tuberculosis drugs is the result of patients' low tolerance to certain drugs administered to combat the disease. There is a strong variation between the tolerance capacity of patients to these drugs. This variation is mainly explained by differences in the ability to metabolize and transport the active substance, as well as in the immune response. This is why Wang and collaborators in 2015 published a study where an association of hepatitis secondary to anti-tuberculosis drugs with three *IL-6* polymorphisms, including rs1524107, was sought; however, no association was found[57].

In the genotyping work of Wang et al. In 2015, performed on liver tissues, it was confirmed that the G allele and the GG genotype rs1800796CC polymorphism promote the transcription of *IL-6*, which confers protection to hepatocytes during hypoxic injuries in the liver[58]. However, in kidney tissue during CKD it may have an adverse effect, resulting in an increase in the progression of the disease as reported by other studies.

In their 2016 study, Chang et al. genotyped the rs1524107, rs1800796, and rs1800795 polymorphisms in a sample of 143 Chinese type 2 diabetes patients with ACR ≥30 mg/g. These were compared with a group of 567 diabetic patients with no symptoms of kidney disease, and the association with the progression of nephropathy was analyzed. In this study, a significant association of rs1524107 with disease progression was reported, specifically, a higher risk rate was found with the recessive CC genotype. Additionally, this was found to be strongly correlated with rs1800796. The rs1800796 polymorphism in turn was also reported to be associated with disease progression, specifically in the recessive model for the GG genotype. At the same time, the study could not explore any type of association for the rs1800795 polymorphism because a high homogeneity was found in the population, and only 2 heterozygotes were found in the 568 subjects included with no recessive homozygotes. Furthermore, the study failed to find a significant association of *IL-6* levels with any of the polymorphisms studied or with any of the haplotypes they constructed[59].

In 2017, Zhang et al. gathered a panel of 880 Chinese subjects from the Han region, where 417 IgA nephropathy patients and 463 disease-free controls were included. The association of 7 *IL-1B* polymorphisms and 3 *IL-6* polymorphisms, including rs1800796, was searched. In this study, it was reported that the G allele of this polymorphism is significantly associated with the risk of developing IgA nephropathy, and this allele is even part of two haplotypes with the other two genotyped polymorphisms of IL-6 that confer risk of developing the disease[60].

Alkharasan et al. conducted a study in a court of 149 patients who received an allograph kidney transplant, where the association of an *IL-28B* SNP and two *IL-6* SNPs (one of them the rs1800795 polymorphism) with hepatitis C virus viremia were sought. Although alone, rs1800795 was not associated with the disease, its GG genotype, in combination with other genotypes of the remaining SNPs, were associated with the disease[61].

Tacrolimus is an immunosuppressive drug that is widely used during kidney transplantation to reduce the risk of acute rejection; however, its optimal concentrations vary strongly at the ethnic and individual level. This variation can be explained by genetic differences in the immune response. In 2018, Oetting et al. conducted a study with 1,923 kidney transplant recipients, whereby the association of 44 SNPs belonging to various genes, including rs1524107 of *IL-6,* with variations in the optimal concentrations of Tacrolimus, was sought. However, no significant association was found for this polymorphism[62].

- In the report published by Azeez et al. in 2019, an Iraqi population of 108 patients with CKD divided into two subgroups was gathered, 54 with hemodialysis and 54 with a kidney transplant, as well as 54 controls without signs of kidney disease. In these groups, the *IL-6* SNP rs1800795 was genotyped and serum IL-6 levels were quantified, revealing a

significant association of the GG and GC genotypes with high levels of IL-6 in both subgroups of patients and similarly, associated the GC genotype with the risk of developing CKD[63].

In 2019 Oetting et al. conducted a study in an American population with two subpopulations, one European-American and the other African-American. The association of 75 polymorphisms belonging to 58 genes, including rs1524107 and rs1800795 of *IL-6*, with acute rejection syndrome during allograph kidney transplantation, one of the major risk factors for tubular atrophy and progression of fibrosis of the kidney, was sought. However, with the transplanted kidney, no association was found with this phenomenon[64].

Rocha et al. in 2021 gathered a Portuguese population that included 289 patients with end-stage renal disease. The association of the rs1800795 polymorphism with the inflammatory response and clinical outcome of end-stage renal disease was explored. In the first instance, no significant association of the polymorphism with the disease was reported when comparing the allelic and genotypic frequencies of the cases with the controls. However, the CC genotype was significantly associated with high serum levels of the high-sensitivity inflammatory marker CRP (hsCRP) and lower leukocyte count, but no association was found with other inflammatory markers such as the C-reactive protein. protein, CRP, growth differentiating factor 15 (GCF15), pentraxin-3 (PTX3) or with *IL-6* itself. Additionally, when comparing allelic and genotypic frequencies among patients with end-stage renal disease, it was found that the CC genotype is associated with high mortality, and that the CG genotype is associated with the highest survival rate. Lastly, an association of the GG genotype with higher levels of IL-6 in deceased patients is reported. Similarly, the association of the CC genotype with hsCRP levels was reported again in this same comparison[65].

## Conclusion

IL-6 is strongly related to the pathophysiological process of chronic kidney disease, mainly through podocytes, mesangial cells, endothelial cells, and tubular cells due to the expression of mbIL-6R and the secretion of IL-6 upon receiving the IL-6 signal through the trans pathway. Furthermore, it has been reported that elevated levels of IL-6 correspond to the progression of CKD. This relationship could be reinforced by the correlations that have been identified between the polymorphisms present in the gene and the disease.

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## Conflicts of interest

None.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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