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Aggravation of chronic kidney disease by inflammatory factors; a narrative review on current concepts

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Abstract

Chronic kidney disease (CKD) is a common disease worldwide with several causal factors such as inflammation, as one of the most important factors. Inflammation is in turn an outcome of many factors associated to renal dysfunctions like immune dysfunction which could act as a catalyst of many other CKD risk factors. Moreover, inflammation seems to be a logical target for preventive and remedial – general and particular anti-inflammatory interventions – in patients with CKD.

Keywords: Chronic kidney disease, Inflammatory markers, Chronic renal failure, Inflammation, Transforming growth factor beta, Interleukin 6, Tumor necrosis factors, chronic inflammation, Renal fibrosis

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Introduction

Chronic kidney disease (CKD) consists of conditions which could damage the kidneys and lead to reduction of renal capability to keep its normal function (1). Equally important, chronic renal failure refers to the progressive and irreversible decrease in kidney function and structure which is described as kidney insufficiency for more than three months based on damages to the structure of renal tissues and is accompanied by glomerular filtration rate reduction (2). Moreover, CKD may be produced by high blood pressure, diabetes and other syndromes (1). It is indeed an universal health problem which its prevalence might be increased with age; furthermore, recent studies showed a middle prevalence of chronic renal failure of 7.2% in patients older than 30 years, and among 35.8% in those patients aged 64 years or more (3).

Inflammation is a fast and serious protective reaction to infection or trauma. The beginning of the complement pathway may motivate the degranulation of mast cells and the elaboration of inflammatory cytokines (4). Chronic inflammation is also related to other comorbidities commonly seen in chronic renal failure such as conditions influencing on the endocrine system (insulin resistance and metabolic disorders) and neurological system (5). Additionally, chronic renal failure itself might result in an intricate multidimensional inflammatory condition (6).

The aim of this paper was the review of the impact of various inflammation factors, including transforming growth factor beta (TGF-β), interleukin 6 (IL-6) and tumor necrosis factors (TNFs) which may influence on the aggravation of chronic kidney insufficiency.

Materials and Methods

In this review, a variety of sources have been used by searching through PubMed/Medline, Scopus, EMBASE, EBSCO and directory of open access journals (DOAJ). The search was conducted, using combination of the following key words: "chronic kidney disease", "inflammatory markers", "chronic renal failure", "inflammation", "transforming growth factor beta", "interleukin 6", "tumor necrosis factors", "chronic inflammation" and "renal fibrosis."

Inflammation and chronic kidney disease

Inflammation has both local (heat production, redness, pain and swelling) and systemic outcomes (fever) due to changes in area blood flow and the corresponding influence of cytokines on the hypothalamus (1-3). Systemic inflammatory cytokines such as interleukin-1 (IL-1), IL-6 and TNF-α could irritate hepatocytes to elaborate the acute-phase protein C-reactive protein (CRP), the most widely used indicator of inflammation (6). Accordingly, when the early insult could not sufficiently be resolved or when responsible anti-inflammatory systems for controlling the inflammation are dysfunctional, then inflammation perseveres. A chronic inflammatory condition is indeed damaging, rather than protecting, as it may tend to ending of the organ and vascular disease (4).

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Implication for health policy/practice/research/ medical education

Systemic inflammation is a situation intrinsically associated to CKD and its other typical sequelae. In fact, inflammation is a key contributor to problems in CKD with some inflammatory markers.

Furthermore, in CKD, chronic inflammatory recreations, as a key role in the disease course, could lead to decrease of renal function (7). Notably, in the pre-dialysis CKD individuals, the proportion of inflammation is also excessive and could be an important marker of patient's condition. Indeed, high levels of CRP may replicate a chronic inflammatory condition connected to decreased serum albumin levels, inadequate answer to erythropoietin substitute, and greater hospitalization (8). Despite this fact, the definite effect of chronic inflammation on renal function is uncertain. While, inflammation is obvious condition in pre-dialysis CKD subjects; however, the association between the level of inflammation (using CRP or other inflammatory cytokines), and estimated glomerular filtration rate has not been found to be associated (8,9). In fact, TGF-β, IL-6, TNFs family, osteoprotegerin and myeloperoxidase were higher among individuals with CKD (10).

Effect of TGF-β on kidney function

TGF-β is a classical cytokine, which had growth and mutation property (11). In recent years, researchers have found definitive evidences that they are responsible for mesangial deposition in glomeruli and fibrosis in interstitial area (12).

In addition, extensive investigations have demonstrated that, TGF-β could play a key role in the renal fibrosis, characterized by the raised accumulation of extracellular matrix (ECM) within renal tissue, and may show the final usual pathway for the loss of renal function connected with primary disorders like chronic glomerulonephritis, disruptive nephropathy and diabetic kidney disease (13-16). Thus, rises or reductions in the production of TGF-β have been linked to different disease states, consisting atherosclerosis and fibrotic disorders of the kidney, liver, and lung (17). Furthermore, extensive animal surveys as well as human clinical samples have demonstrated the significance of TGF-β in renal fibrosis (18), which is supported by in vitro surveys showing that TGF-β not only persuades the expression of ECM (19,20), but also prevents its degradation by preventing matrix metalloproteases (MMP) and initiating the tissue inhibitor of metalloproteinases (TIMP) (21). Overexpression of TGF-β by the primer of exogenous TGF-β cDNA to the kidney, could direct into glomerulosclerosis and extreme supporting the pro-fibrotic impression of local TGF-β (22).

In addition, TGF-β could overpower the immune system and may persuade extracellular-matrix components, having a critical role during wound healing and tissue mend (23). Even though TGF-β is critical for wound healing, overproduction of TGF-β can result in extreme deposition of mark tissue and fibrosis (24). Likewise, in animals, the overexpression of TGF-β may result in fibrosis of skin, heart and other organs. Hence, the pathologic fibrosis which is arbitrated to TGF-β is confirmed by the following proceedings; tissue injury increases the manufacture of TGF-β before the production of ECM rises. TGF-β is indeed a strong stimulator of extracellular production and deposition; and the level of TGF-β and of TGF-β messenger-RNA (mRNA) are elevated in fibrotic organs. Interestingly, exogenous TGF-β accelerates fibrosis independently of tissue injury (24-26). Notably, inhibitors of TGF-β–receptor binding decrease or abolish the process of fibrosis. Additionally, tissue- particular overexpression of TGF-β1 (one of the isoforms of TGF-β) in transgenic mice resulted in fibrosis of those organs (25,26).

The pathologic consequence of the extreme activity of TGF-β has in fact been identified as the "dark side" of tissue damage (27). As shown in Figure 1, TGF-β is discharged from platelets following tissue harm. TGF-β persuades the local cells to create ECM and more TGF-β, while platelet-derived growth factor (PDGF) appears to excite cell proliferation and perhaps augment TGF-β manufacturing (28).

Effects of interleukin-6 on kidney function and structure

IL-6 is an interleukin which acts as an anti-inflammatory myokine and also as a pro-inflammatory cytokine (29). IL-6 is squirted by macrophages and T cells to incite

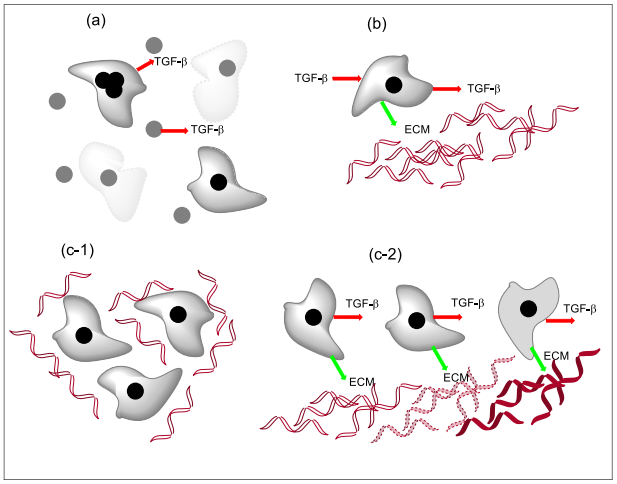

Figure 1. A graphic depiction of the role that TGF-β is supposed to play in the mend of tissue harm through the body, counting the kidney. The capability of TGF-β to persuade the production of TGF-β by aim cells may underly the conversion of the repair procedure into a chronic fibrotic disease. (Data from Border and Ruoslahti) (27). (a): Injury: Platelets and leukocytes release TGF-β in hurt tissue. (b): Repair: TGF-β persuades the surviving cells to create extracellular matrix (ECM) and additional TGF-β. Other cytokines inspire cell proliferation (c-1): Shutdown (Normal): Unknown procedures shut down the TGF-β and ECM production when mend is complete. (c-2): Vicious Circle (Disorder): Failure to shut down TGF-β creation is caused by continuous damage or a defect in TGF-β control resulting in accelerated creation of TGF-β and ECM.

immune reaction, for example during infection or trauma, particularly burns or other tissue harm leading to inflammation. IL-6 also performs a role in fighting infection (30). In the role of an inflammatory cytokine, IL-6 is one of the most highly controlled mediators of inflammation and has an essential role in infection, cancer and autoimmunity (31-34). IL-6 could also attribute to the development of kidney insufficiency and related to its complications (for example vascular calcification, cardiovascular risk, wasting and fatigue) (35). Moreover, IL-6 reactions in vivo are consequently mediated by IL-6 initiation of a membrane-bound IL-6 receptor (IL-6R) (typical IL- 6R signaling) or through its soluble receptor (Figure 2) (36) .

Obviously, it is vital for recent clinical investigations to provide a more personalized method to patient stratification, and improvements in therapy decisions. Findings have emphasized that IL-6 and connected downstream signaling events may denote one such marker (Figure 3). However, to detect the ways contributing to chronic disorder progression in individuals with various grades of kidney disorder, one should realize how cytokines like IL-6 may direct critical resolving inflammation and how their actions could become distorted to drive chronic inflammation (36). In fact, it is extensively acknowledged that cytokines act an integral role in controlling the course of disease and IL-6 is raising viewed as main drug targets for treatment (Figure 3) (36).

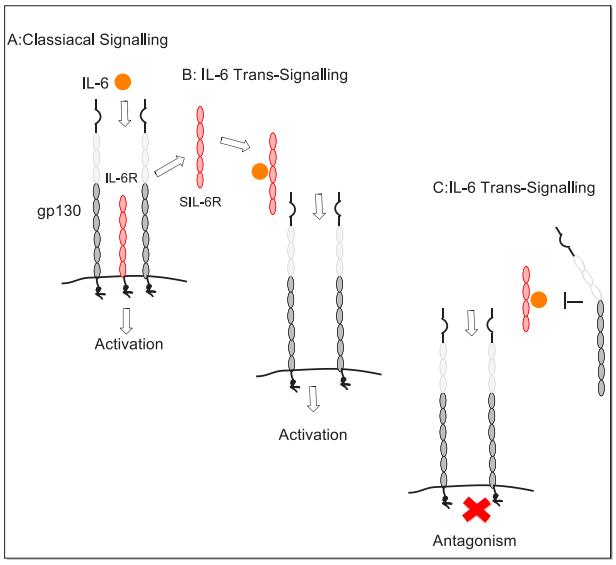

Figure 2. Interleukin 6 and methods for receptor signaling. IL-6 initiates cells through two distinct methods termed typical IL-6R signaling and IL-6 trans-signaling. The receptor complex accountable for regulating IL-6 responses contains a non-signaling cognate receptor (IL-6R, CD126), that binds IL-6 and dimerizes with the signal-transducing receptor subunit gp130. (A) Typical IL-6R signaling happens in cell types that inherently definite both IL-6R and gp130. (B) While, presentation of IL-6R has a controlled cellular expression (hepatocytes, leukocytes and definite epithelial cells), these cells also make a soluble form of the IL-6R (sIL-6R) that keeps cytokine-binding properties and mediates IL-6 reactions in cell types that absence IL-6R, but expression gp130 (IL-6 trans signaling). (C) In several cases, IL-6 trans-signaling controls numerous inflammatory actions and should be closely controlled. At this time, a soluble form of gp130, that circulates at elevated serum concentrations performances as an antagonist of IL-6 trans-signaling and binds IL-6 only what time bound to sIL-6R.

Effects of tumor necrosis factor on kidney function and structure

TNF family is a group of cytokines which can produce cell death (apoptosis) (37). The TNF, previously known as TNF-α, is the best-known member of this class. In fact, TNF is a monocyte-derived cytotoxin which has been associated in tumor regression, septic shock, and cachexia (37,38). The protein is made as a prohormone with an abnormally long and atypical signal succession, that is lacking from the mature squirted cytokine (39). A short hydrophobic period of amino acids could provide the situation to anchor the prohormone in lipid bilayers (40). Both the mature protein and a partially treated form of the hormone can be squirted after cleavage of the pro-peptide (40). The second well-known member of this family is lymphotoxin-alpha, previously known as TNF-β, is a cytokine which is inhibited by interleukin 10 (IL-10) (41). The presence of naturally happening inhibition of TNF in a variety of diseases has been confirmed (42). TNF-α had been recommended as a critical causal factor to renal alterations which may occur during the early stage of diabetic nephropathy (DN), counting renal hypertrophy and sodium retention (43).

Moreover, the methods of action of TNF antagonists have been intensively examined, especially for infliximab and

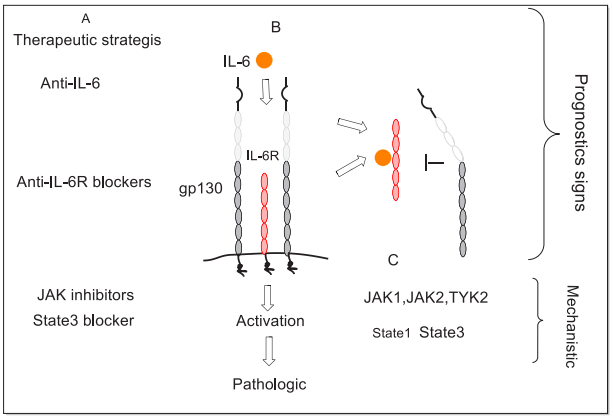

Figure 3. Clinical implications for interleukin 6 investigation. (A) Various therapeutic plans are either in standard clinical studies or emerging through experimental findings and early phase of clinical trials. These include particular cytokine and cytokine receptor blockers and less discerning inhibitors of signal transduction components. (B) Amount of IL-6, sIL-6R and sgp130 are progressively being observed as prognostic indicators and inform clinical choices ranging from the general intensity of inflammation to comorbidities counting heart and vessel risks. (C) An increased understanding of IL-6 signaling is identifying new methods for the participation of IL-6 in disorder, autoimmunity and malignancy. This investigation has also known as a crosstalk between IL-6 signaling and immune sensing methods or other cytokines.

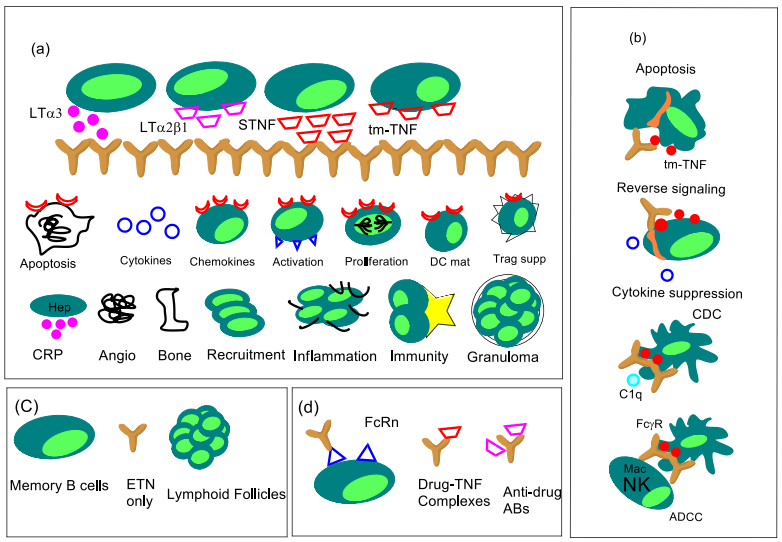

Figure 4. Two classes of putative methods of act of Tumor necrosis factors (TNF) antagonists are shown. The first panel (a: Blocked of TNF-R-mediated procedures) demonstrates the primary methods of action, subsequent from direct blocking of TNFR-mediated biologic actions. In these cases, the TNF antagonists bind to the cognate ligands transmembrane TNF (tm-TNF) or soluble TNF (s-TNF) for all five TNF antagonists and moreover lymphotoxinα3 (LTα3) and lymphotoxin α2β1 (LTα2β1) for etanercept), there by blocking their capabilities to bind TNFR2 or TNFR1. The second panel (b: tm-TNF-mediated procedures) explains several methods induced by the binding of TNF antagonists to tm-TNF that can comprise reverse signaling through tm-TNF or cytotoxicity of the tm-TNF-bearing cell by antibody-dependent cellular cytotoxicity (ADCC) or complement–dependent cytotoxicity (CDC). The third board (C: Blocked of LTαβ) explains 2 LTαβ-mediated methods thought to be blocked by etanercept, the only TNF antagonist which binds LT family members. The forth board (d:PK) shows pharmacokinetic-related methods that contain TNF antagonist binding to FcRn or forming multiplexes with s-TNF or antidrug antibodies. Denotes a TNF antagonist (certolizumab, golimumab, infliximab, adalimumab, etanercept). Mean TNFR2 and TNFR1. ETN = etanercept.

etanercept, but many problems remain uncertain. Possible procedures of TNF–antagonist act in patients are shown in Figure 4. They usually fall into 2 classes; blockade of tumor necrosis factor receptor (TNFR)-mediated methods and induction of transmembrane TNF (tm-TNF)-mediated methods (Figure 4) (44).

The contribution of various methods to drug effectiveness remains an open issue. For instance, the relation roles of apoptosis and reversal of inflammation for decreasing cellularity in rheumatoid synovial tissue during TNF-antagonist treatment are still unclear. Their strong clinical efficiency in rheumatoid arthritis and the strong neutralization of soluble TNF (s-TNF) and tm-TNF suggest that they attain efficacy by preventing TNF from persuading TNFR interceded cellular functions (Figure 4). These functions contain cell proliferation, cell activation, and cytokine and chemokine making, as well as the sequelae of these functions such as inflammation, cell recruitment, immune control, ECM degradation, and angiogenesis. Supportive information for all of these methods and for all of the TNF antagonists are imperfect, but the emerging picture is one in that TNF has a vital role in a network of molecular and cellular events in the pathogenesis of rheumatoid arthritis (44).

Discussion

Generally, a quantity of conditions can produce permanent harm to the kidneys and/or affect the task of the kidneys and cause CKD. Studies have shown three common reasons worldwide, which undoubtedly account for about three in four items of CKD in adults, including diabetes, high blood pressure and ageing kidneys.

Other less usual conditions which can produce CKD may consist of glomeruli (disorders of the tiny filters), for instance glomerulonephritis (inflammation of the glomeruli in the kidneys), renal artery stenosis (tapering of the artery taking blood to the kidney), polycystic kidney disease, stumbling block to the flow of urine and repetitive kidney infections (45). In addition, previous studies have been demonstrated the relationships between impacts of inflammation, counting CRP (46-48), IL-6 (47,49), tumor necrosis factor receptor 2 (TNFR2) and fibrinogen (48,50), with diminished renal function (46,48,50)

Conclusion

As a conclusion, CKD is a common disease worldwide and there are several factors causing CKD. One of the elements is inflammation. It is an outcome of many factors associated to renal dysfunction such as a state of immune dysfunction and doings as a catalyst of many other risk factors in CKD. Inflammation seems to be a logical aim for preventive and remedial —general and particular anti-inflammatory interventions in patients with CKD.

Authors' contribution

MA is the single author of the manuscript.

Conflicts of interest

The author declared no conflicts of interest.

Ethical consideration

Ethical issues (including plagiarism, data fabrication, double

publication) have been completely observed by the author.

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