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Review

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The role of interstitial changes in the progression of chronic kidney disease

Rola zmian zachodzących w śródmiąższu w progresji przewlekłej choroby nerek.

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Summary

Interstitium – the renal tubulointerstitial compartment – is located between the renal tubule basement membrane and microcirculation vessels. Interstitial fibroblasts produce the extracellular matrix and constitute the structure's cellular skeleton, regulating spatial relationships between its components (microenvironment).

The tubular epithelium and endothelium cooperate within an integrated microenvironment. Structural or functional impairment of the extracellular matrix, microcirculation vessels or tubular epithelium results in disturbances of tubulointerstitial compartment components.

In the course of glomerular kidney diseases, the intrarenal RAA system becomes activated and inflammatory mediators are released. Interstitial inflammation and microcirculatory disorders develop, inducing adverse consequences, manifested mainly through the process of hypoxia and inflammation.

Inflammation-induced increase in interleukin-1 (TNF-α) expression leads to increased concentrations of VEGF, ICAM-1, angiotensin II, IL-6 and IL-8. Cytokines activate fibroblasts, myofibroblasts and endothelial cells. Fibrosis is also triggered by HIF-1alpha pathway activation, resulting in vascular growth and fibroblast proliferation. This reaction likewise occurs through activation of NF-κβ, EPO, GLUT-1, IGF-1 and INOS.

Interstitial fibrosis is one of the factors determining the clinical course of kidney diseases. Apart from inducing fibrosis, microcirculatory disorders lead to the progression of hypoxia.

Angiogenesis is a part of the repair process accompanying fibrosis. Its determinant is the normal function and structure of endothelial cells manifested by their ability to migrate and proliferate in response to, inter alia, angiopoietins, VEGF and nitric oxide synthase.

Administering a three-drug RAAS-inhibiting therapy to patients with chronic glomerulopathies improves tubular function, measured by the decrease in excretion of NAG and propeptide of type III procollagen fibres, and contributes to the improvement in microcirculation functioning.

Keywords: **angiogenesis • hypoxia • interstitial fibrosis • renal disease progression • therapy**

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The role of interstitial changes in the progression of chronic kidney disease

Interstitium – the renal tubulointerstitial compartment – is the space between the basement membrane of the renal tubular epithelium and the microcirculation vessels. It is filled with an amorphous, hydrated extracellular matrix. In addition to creating the extracellular matrix, fibroblasts present in the interstitium constitute the cellular skeleton of the structure by virtue of which the spatial relationships between the tubular cells and microcirculation are regulated properly [16].

The tubular epithelium and the endothelium create a common, structurally and functionally integrated microenvironment. The vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) as well as hepatocyte growth factor (HGF), secreted by the endothelium into the extracellular matrix, regulate metabolic processes and inhibit the apoptosis of tubular epithelial cells. The said factors exert autocrine and paracrine actions, and on a feedback basis modify, among other things, endothelial cell functions [40] (Fig. 1). Therefore, disturbing the normal structure or function of even one of the aforementioned elements, that is the extracellular matrix, the microcirculation vessels or the tubular epithelium, results in disorders of the remaining two components of the tubulointerstitial compartment [16].

Hypoxia and interstitial fibrosis

Within the interstitium, the oxygen partial pressure in normal conditions is low, approximately fivefold lower than in the renal cortex. On that account, even in physiological conditions, within the interstitium there occurs an oxygen supply insufficiency, namely hypoxia. Even though normal blood flow through the interstitium remains retained, the relative oxygen insufficiency in this part of the kidney results from its high demand due to its utilisation in energy processes pertaining to sodium reabsorption by renal tubular cells. Another process is the diffusion of oxygen between the ascending and descending branches of the interstitial vessels [32]. Such conditions lead to a situation whereby a relatively slight decrease in oxygen pressure caused by, for instance, perfusion disorders, may underlie the development of irreversible changes, for example in the form of excessive connective tissue deposition, that is interstitial fibrosis. As a result of the fibrosis process, there occurs an impairment of the integrity of the tubulointerstitial compartment microenvironment, manifested inter alia by a microcirculatory impairment termed capillary rarefaction.

Under hypoxia, the cells of the renal tubular epithelium undergo the process of dedifferentiation and assume the phenotype of mesenchymal cells (epithelial to mesenchymal transition). Such dedifferentiated and redifferentiated cells are capable of migration and travel to the interstitium, where they can differentiate into myofibroblasts generating extracellular matrix components, such as collagen. The final effect of this phenomenon is excess connective tissue deposition known as fibrosis [6,23,39].

The myofibroblast phenotype can also be assumed by pericytes pertaining virtually only to the microcirculation [1,35,36]. Before transforming into a myofibroblastic cell, a pericyte is released from the endothelium, which disturbs the structure and function of the microcirculation and consequently results in oxygen deficits affecting a given area. Thus, the pericyte to myofibroblast transition doubly carries adverse consequences: a) the formation of another myofibroblast involved in the process of connective tissue deposition in the interstitium, and b) impairment of the structure of the microcirculation, which contributes to the progression of capillary rarefaction.

Inflammatory response and interstitial fibrosis

Fibrosis can constitute the residual stage of a prior chronic inflammatory process. It is worth noting that the inflammatory process is an umbrella notion and, although often associated with infection, it accompanies various phenomena related to cell or tissue damage. In the process of inflammation, a central role is played by leukocytes, including macrophages and lymphocytes in particular. These cells constitute a source

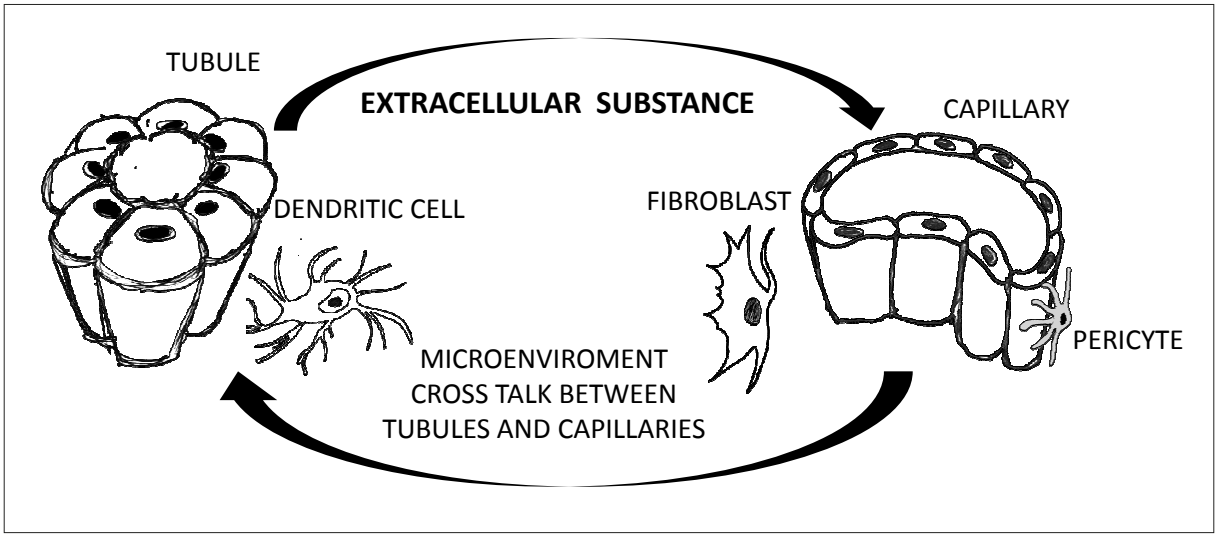

Fig. 1. Schematic view of tubulo-interstitial compartment and physiologic interactions

secreting various mediators which regulate the process of inflammation and additionally influence other cells. In the processes of the so-called chronic inflammation, which primarily involves T cells and macrophages as well as cytokines released by them, exhibiting mainly pro-inflammatory activity, the key role is played by interleukin-1 (TNF-α). Its increased expression secondarily leads to an increase in the levels of, among other things: VEGF, ICAM-1, angiotensin II, IL-6 and IL-8 [9]. A macrophage is treated as the chief administrator of a chronic inflammatory response, and its activation results in the secretion of IL-1/TNF-α, whose "side" effect might be the activation of yet another population of macrophages which become an additional source of cytokines. Secretion of a large amount of cytokines causes the activation of populations of not only leukocytes but also cells present in the microenvironment, such as fibroblasts, myofibroblasts and endothelial cells. Another factor stimulating fibrosis is pathway activation mediated by hypoxia-inducible factor-1-alpha (HIF-1α), which is activated under hypoxia. The result of its excessive activation is acting through the secretion of additional growth factors which induce the survival of cells under hypoxia, promote the growth of vessels in order to increase oxygen supply, and also enhance the proliferation of fibroblasts [28]. This reaction likewise occurs through the activation of NF-kappaBeta [9] or the activation of other pathways involving EPO, GLUT-1, IGF-1 and INOS [22].

Renal interstitial circulatory disorders of short duration and affecting a relatively small area lead to chaotic and excessive deposition of connective tissue, thus disturbing the normal architecture of the microcirculation. This, in consequence, results in the aggravation of microcirculatory disorders, as well as further progression of hypoxia and an increase in the area of fibrosis [15,44].

Defence and repair mechanisms

One of the repair processes accompanying fibrosis is angiogenesis. Both hypoxia and the concomitant inflammatory state form a microenvironment creating favourable conditions for angiogenesis, which is found to be the outcome of two opposing processes: stimulation and inhibition of vessel growth [7,24,31].

A necessary condition for the process of angiogenesis is retaining the normal function and structure of endothelial cells manifested by their ability to migrate and proliferate in response to suitable stimuli [7]. Two cell populations participate in the process of endothelial repair: vessel-residing cells and BM-derived circulating endothelial progenitor cells [7].

The proliferation and migration potential of renal vascular endothelial cells in situ is relatively low [2], on which account the process of normal repair of the renal microcirculatory vessels greatly depends on efficient factors regulating the influx of progenitor cells into organs. Progenitor cells derived from the bone marrow reach the site of angiogenesis under the influence of stimuli comprising cytokines and biologically active compounds released from a damaged organ (produced, among other things, by inflammatory response cells).

Angiopoietins, apart from belonging to VEGF, appertain to specific vascular growth factors and serve as ligands of the Tie-1 and Tie-2 receptors present on endothelial cells. Through binding with the vascular endothelial receptor Tie-2 belonging to the tyrosine kinase group, angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2) have an antagonistic impact on the process of angiogenesis. Ang-1 stabilises mature vessels, whereas Ang-2 exerts an opposite effect [14, 34]. Factors determining the affinity of Ang-1 and Ang-2 to the Tie-2 receptor will have

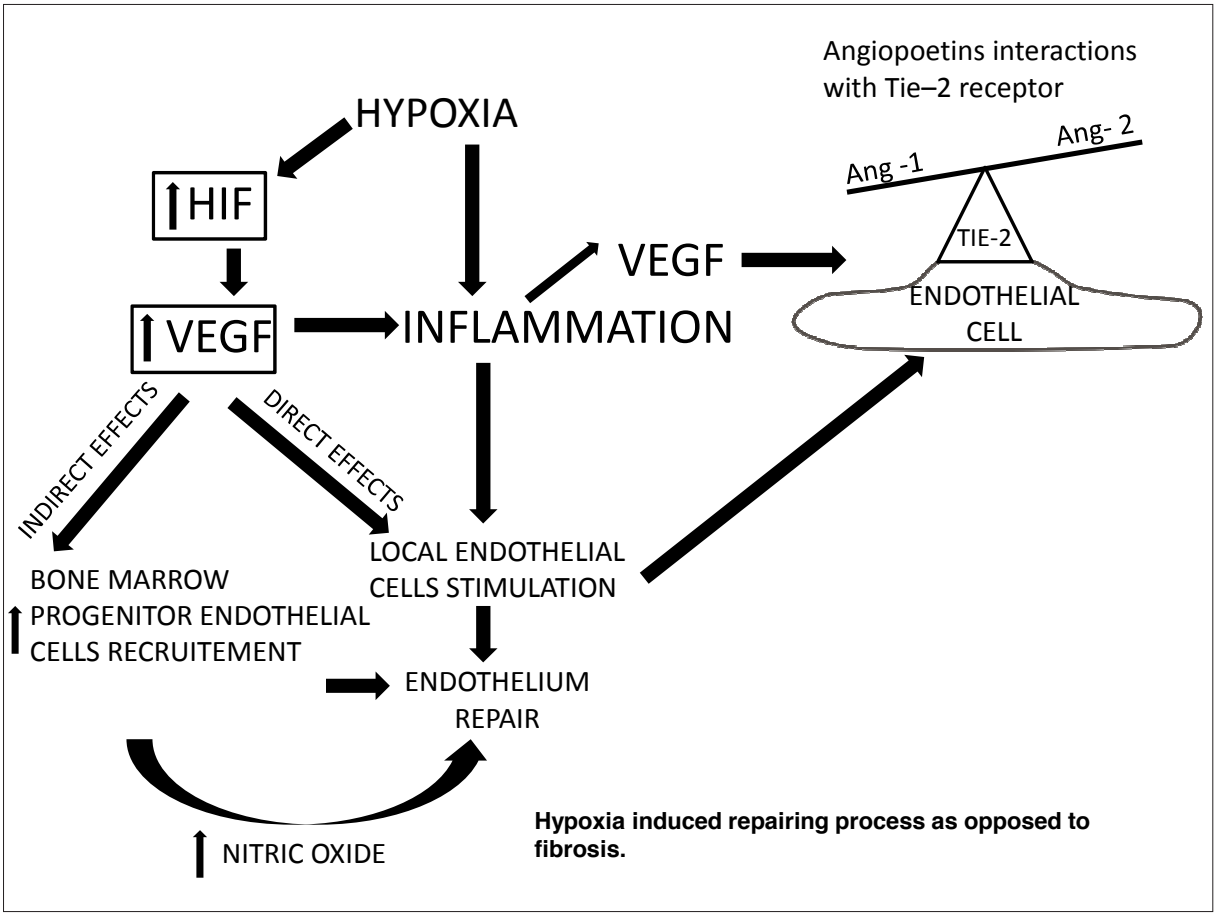

Fig. 2. Hypoxia induced repairing process as opposed to fibrosis

a significant impact on the process of vessel formation [30] (Fig. 2).

The production of both angiopoietins in the kidney is mediated via both receptor-1 and receptor-2 for angiotensin II, and the sites of production of Ang-1, a factor stimulating and stabilising the structure of the microcirculation, are pericytes [5,20,21]. That is why the importance of those cells for maintaining the normal structure and function of microcirculatory vessels is not to be overestimated.

Data concerning the course of angiogenesis in chronic kidney diseases are mainly obtained from research experiments on animals subjected to a resection of 5/6 of the organ. The angiogenesis process in the aforementioned model is alternating in time and is of a two-step nature. After the initial stage characterised by a highly intensive process of endothelial cell proliferation, the process decelerates, verging on suppression. This mechanism entails an increase in VEGF expression in renal tubules. Nonetheless, despite remaining at the same, virtually unchanged level, the aforesaid decrease in the intensity of the angiogenesis process occurs. This is caused by the antagonistic activity of thrombospondin-1 against VEGF [18]. The antagonistic impact of thrombospondin on VEGF arises, among other things, due to its inhibitory activity against endothelial cell migration [31]. On the other hand, however, there exists compelling evidence indicating that repression of thrombospondin-1 activity in renal tubules not only increases VEGF activity within them, but also positively affects the reconstruction of the microcirculation [38].

The advantages of administering VEGF to animals lacking 5/6 of renal parenchyma, manifested in increased vessel density, have only been observed in those parts of the organ where the process of fibrosis and tubular damage was insignificant [17]. The positive influence of VEGF on the process of microcirculatory repair takes place at the time when a certain specific amount of vessels being relatively normal in terms of function and morphology is found in the kidney. This might be the result of a different level of receptor expression for VEGF or the normal course of transcription [27]. An array of data indicates that a positive vascular repair response to VEGF is retained if nitric oxide synthase activity in endothelial cells, determined at a certain minimum level, is concurrently observed. It has been demonstrated that inhibiting the production of nitric oxide by the

endothelium reduces the mitogenic response to VEGF, the unfavourable effect being additionally magnified by hypoxia [19]. Further evidence suggesting the participation of nitric oxide in the process of angiogenesis in the kidney comes from research studies which indicate the existence of a relationship between ADMA, an inhibitor of NO synthase, and capillary rarefaction [25]. The expression of VEGF in the kidney crucially depends on the activity of the hypoxia-inducible factor (HIF). Recent research studies conducted on animals with experimentally induced chronic kidney disease revealed that VEGF expression in the kidney may occur via an alternative route, namely with the participation of the renin-angiotensin-aldosterone (RAA) system [10].

The clinical course of chronic kidney disease, assessed by measuring the decrease in glomerular filtration rates, correlates with the extent and action of the interstitial fibrosis process [3]. The process of renal interstitial fibrosis should thereby be perceived to be not only irreversible, but also progressive with time. Interstitial fibrosis is recognised as one of the factors determining the clinical course of kidney diseases. Moreover, this assumption is so versatile that it explains the correspondence between the extent of the fibrosis process and the progression of kidney diseases, and it equally concerns glomerular and tubulointerstitial kidney diseases [3,13,33].

There is no doubt that far fewer significant results have been obtained through clinical research. Nevertheless, several of them are worth mentioning as evidence validating some of the experimental data.

In the course of glomerular kidney diseases, there occurs activation of the intrarenal renin-angiotensin-aldosterone system and the release of inflammatory mediators from glomeruli into the surrounding vessels and interstitium [11,26,29]. As a result, a local inflammatory state in the interstitium and microcirculatory disorders develop, inducing a range of previously described consequences. In clinical observations, it manifests itself in, among other things, intrarenal circulation disorders associated with renal tubular damage [37]. Administering a three-drug therapy inhibiting the renin-angiotensin-aldosterone system to patients with chronic glomerulopathies improves the function of tubules, assessed by measuring the decrease in the excretion of N-acetyl-beta-glucosaminidase (NAG) and propeptide of type III procollagen fibres. An improvement in renal tubular function ought to be interpreted as an expression of decreased RAA system activity in the kidney and

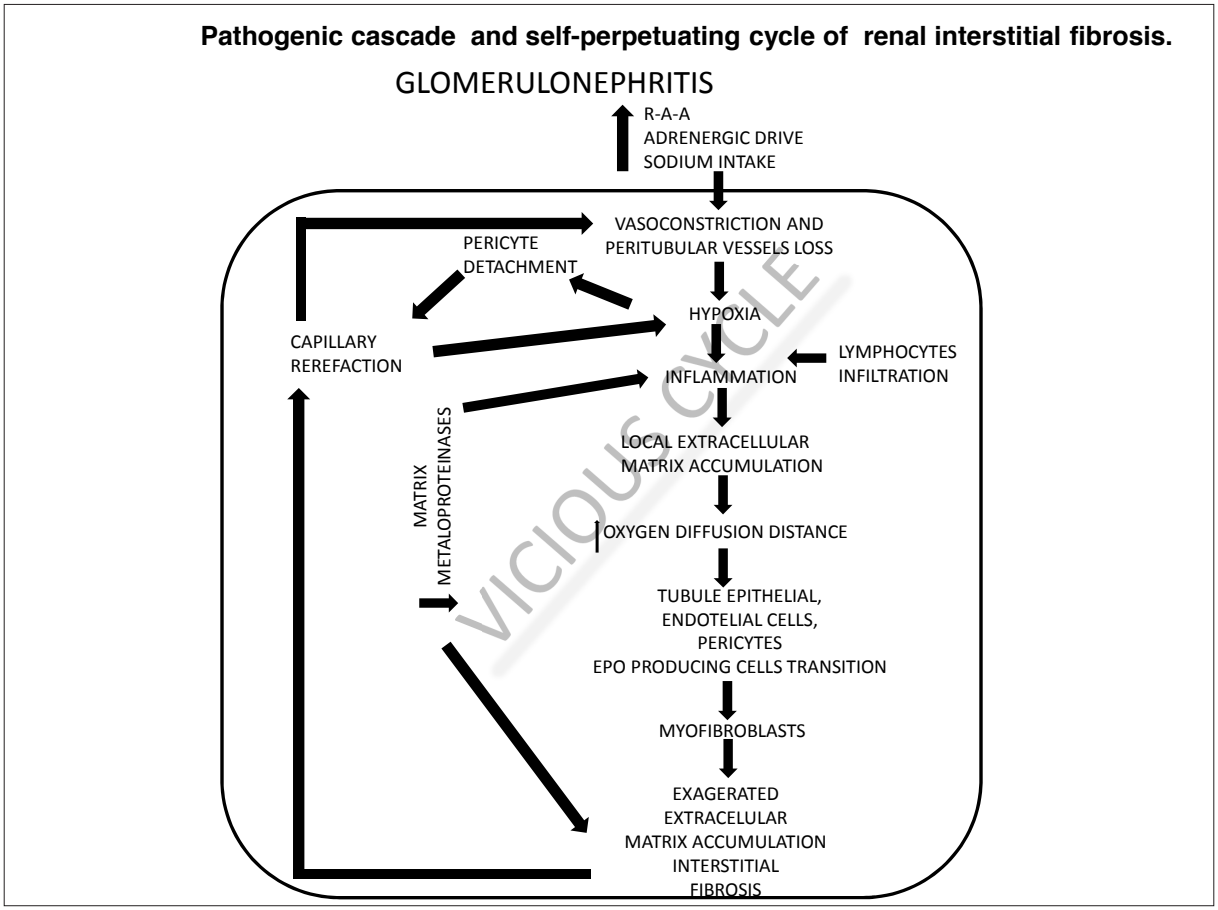

Fig. 3. Pathogenic cascade and self-perpetuating cycle of renal interstitial fibrosis

an enhancement of, inter alia, the functionality of interstitial microcirculatory vessels [42,43]. Referring to the previously discussed relationships between the participation of endothelial progenitor cells, nitric oxide and the angiogenesis process, research studies on the latter indicate that administration of endothelial progenitor cells to the renal artery increases the activity of nitric oxide synthase within the organ and also considerably reduces the extent of fibrosis [12].

Conclusions

To summarise, with respect to mechanisms triggering fibrosis, invariably there occurs signal "switching" to the fibroblast activation pathway. The primary response is usually elicited by inflammation, eventually leading to the activation of macrophages. The second most common mechanism is hypoxia. Attempts to break the vicious cycle consist in searching for mechanisms which would eliminate its causal factors. One method is an attempt at eradicating inflammation or suppressing macrophage activation [8]. Another potential mechanism relies on gradually terminating hypoxia and increasing blood flow into the organ [41]. The above considerations are devoted to presenting pathogenetic factors leading to the progression of chronic kidney disease via impairments in the structure and function of microcirculation in the kidneys. The phenomena are primarily of stabilising and remedial nature, although, as has long been recognised by the trade-off hypothesis, the principle that nothing is for free applies to biology as well [4]. Hence, the likelihood of a simultaneous interaction of numerous factors and the interplay between them lies at the basis of the "vicious cycle". It is this mechanism which makes chronic kidney disease a distinctive, self-driven perpetual motion phenomenon (Fig. 3).

A separate issue, which is extremely important from the practical perspective, is a certain inevitability of the process, resulting in progressive damage or even destruction of the kidneys, consequently leading to their terminal failure. Table 1 presents a range of treatment options substantiated by the above discussion of pathophysiological character, as well as clinical trials conducted in this regard. A subsequent enquiry should investigate potential combinations of specific therapy elements, particularly allowing for the fact that some of them produce contradictory effects.

Table 1. Some therapeutic possibilities for renal fibrosis treatment

Treatment	Mechanism of action
Sleep apnoea treatment*	Reduction of renal adrenergic drive
Blockade of RAA**	Inhibition of intrarenal RAA activity and improvement of microcirculation function Vasodilation of post-glomerular vessels Anti-inflammatory effect Modulation of relationships among angiopoietin-1 and angiopoietin-2 PPAR gamma receptor activation Epithelial-mesenchymal-transition inhibition Inhibition of dendritic cell accumulation in interstitium
Hepatic growth factor administration**	Epithelial-mesenchymal-transition inhibition through counteracting TGF-beta production
Prostacyclin administration**	Increase of hepatic growth factor production
Endothelin receptor antagonist administration**	Vasodilatory and anti-inflammatory effect
Anti-mast cell drug administration**	Anti-inflammatory and antifibrotic effect due to mast cell stabilization
Anti-hyperuricaemic drug administration **	Decrease of extracellular matrix synthesis
Vitamin D_3 administration**	Epithelial-mesenchymal transition inhibition
Propyl hydroxylase inhibitor administration**	Increase of hypoxia inducible factor activation
Vascular endothelial growth factor administration **&*	Increase of endothelial progenitor cell recruitment and local endothelial cell growth stimulation

*Systemic effect; ** Local effect.

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