ORIGINAL ARTICLE

Vitamin D reduces TGF-β levels in advanced Fibrosis. (The role of vitamin D in reducing TGF-β levels in advanced Fibrosis)

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ABSTRACT

Every year, a large number of deaths are due to the complications of fibrosis. Fibrosis is an important and unanticipated health problem around the world that has not only medical but also economical costs to the global economy. Pathologically, fibrosis is caused by the proliferation and activation of fibroblasts and myofibroblasts and excessive deposition of extracellular matrix (ECM) components in organs and tissues. In all forms of fibrosis, inflammatory-immunological reactions occur in the early stages, and components of the innate immune have a role in confronting fibrosis. Vitamin D has anti-fibrosis functions, regulates cell proliferation and differentiation, regulates anti-inflammatory elements, and regulates the immune system, therefore, serum levels of 1,25 (OH) 2D3 may be negatively associated with the progression of fibrosis; In fact, Vitamin D causes this by inhibiting TGF-β. In this review study, we intend to investigate the achievements of various studies in this field.

Keywords: Vitamin D, TGF-β, Advanced fibrosis, Vitamin D deficiency, TGF-β cellular receptor

INTRODUCTION

One of the complications of long-term inflammation in the body tissues is fibrosis and inflammation plays an essential role in the progression of fibrosis [1]. During fibrosis, macrophages secrete pro-inflammatory cytokines, and reactive oxygen species play an important role in the collagenization of tissues [2, 3]. During chronic injuries, macrophages secrete factors such as TGF-β to control infection [4]. In this process, fibroblasts are affected by TGF-β and form different structures [5]. During the process of tissue fibrosis, many proteins in the cell interact with TGF-β, the most important of which is the SMAD complex. Cell signaling is an important issue in fibrosis, and the key to many of these mechanisms is phosphorylation, also, the inhibition of continued phosphorylation and reduction of fibrosis has been considered by many biomedical researchers [6-11].

The family of transforming growth factor beta (TGF-β) plays an important role in regulating various cellular processes that are essential for the homeostasis of tissues and organs. TGF-β signaling participates in various stages of disease progression, from primary tissue damage to fibrosis and cancer. In the event of chronic damage, lymphocytes and other inflammatory cells accumulate at the site of inflammation and continue the inflammatory response. TGF-β also mediates the development of epithelial to mesenchymal stem cells (epithelial-mesenchymal transition (EMT)) and the formation of myofibroblasts in cells. Which may, directly or indirectly, help to increase the MFB population. However, vitamin D receptor (VDR) specifically inhibits TGF-β-signal transduction through direct interaction with SMAD3 [12]. Vitamin D, in addition to its important role in regulating bone metabolism and calcium homeostasis, regulating cell proliferation, etc., also has a significant anti-fibrotic effect [13-17]. As mentioned, vitamin D induces the anti-fibrotic effect by inhibiting TGF-β. According to the above, the present review study was performed to investigate the effect of vitamin D on TGFβ in reducing the amount of fibrosis. The required data on the effectiveness of vitamin D in reducing fibrosis were collected through an internet search in Persian and English databases, using the keywords of vitamin D, TGFβ, fibrosis, and fibroblast in the relevant reputable sites. In this study, first the role of vitamin D and TGFβ in cells, and then the efficacy of each in the process of fibrosis was thoroughly investigated.

Fibrosis: The term "tumor" is synonymous with the classic term "neoplasm." In principle, tumors could arise from cells originating in each of the three layers of blastoderm, endoderm, and mesoderm. By definition, mesodermal tumor cells could produce ECM molecules. These types of cells may be transitioned from the epithelial layer to the mesenchymal layer (EMT) under inflammatory conditions. For instance, increased chronic inflammation of the lungs is known to be an important factor for tumors. Thus, inflammation, fibrosis due to profibrotic cytokines produced by inflammatory cells, and tumors are completely intertwined processes [18].

Fibrosis is defined as the deposition of collagenous and non-collagenous extracellular matrix (ECM) components in organs and tissues as a result of the proliferation and activation of fibroblasts and myofibroblasts. In the early pathogenesis of fibrosis, neutrophils (during bacterial infections), eosinophils (during parasitic infections), monocytes/macrophages, mast cells, and lymphocytes including natural killer/natural killer T cells (NK / NKT) are found in affected areas [19].

Neutrophil granules, which have the main effect on acute inflammation, contain numerous enzymes, many of which act in response to fibrosis in two ways: on the one hand, enzymes such as matrix metalloproteinases (MMPs), elastase, and Cathepsins are released that could specifically break down collagen and non-collagen connective tissue components that are involved in the fibrosis process; On the other hand, Neutrophils play an indirect role by activating more cellular components of the innate immune system that promote fibro genesis [20].

Inflammation plays a key role in the progression of fibrosis. After the injury, macrophages, lymphocytes, eosinophils, and plasma cells enter the damaged part of the immune system. Lymphocytes produce cytokines and chemokines that activate macrophages. Activated

macrophages stimulate inflammatory cells; Which in turn causes excessive activation and preservation of the inflammatory environment [1].

During fibrosis, macrophages produce profibrotic factors such as TGF-β and platelet-derived growth factor (PDGF). ECM is controlled by regulating the balance of various matrix metalloproteases and tissue inhibitors of metalloproteinases (TIMPs) and is very close to collagen production. Also, it means that macrophages have been described as potential targets for fibrosis [2, 21, 22].

In the early stages, active macrophages secrete proinflammatory cytokines and produce reactive oxygen species (ROS). In the late early stages, macrophages are associated with the release of anti-inflammatory agents, reducing inflammation, and enhancing tissue regeneration [3]. Macrophages are divided into two groups, M1 and M2. The first group is known as the classical or anti-inflammatory group and the second group, which is M2, are known as alternative or anti-inflammatory macrophages [23].

M1 macrophages predominate at the onset of the injury. By releasing metalloproteinases that degrade ECM, they enable the transition of EMT / endothelial to mesenchymal tissue (EndMT). While, M2 macrophages secrete anti-inflammatory agents such as IL-10, arginase, TGF-β. M2 macrophages stimulate the onset of an anti-inflammatory environment and promote wound healing. However, if the damage is chronic, M2 macrophages secrete pro-fibrotic substances such as TGF-β, PDGF [4].

A set of processes takes place in fibrosis tissue. Myofibroblasts accumulate additional ECM components such as fibronectin, smooth muscle actin (α-SMA), and collagen I. Mechanically, fibroblasts secrete transforming growth factor-1 (TGF-β1) to differentiate myofibroblasts. Apart from fibroblast activation and epithelial to mesenchymal transition (EMT), endothelial to mesenchymal transfer (EndoMT) is also a source of myofibroblasts. Latent TGF-β1 remains inactivated in the ECM to be activated by mechanical signals in the ECM, such as the contractile force of a myofibroblast. Mechanical symptoms can alter ECM sequence, cell adhesion, morphology, intracellular cytoskeletal organization, gene expression, and more [5, 6].

Fibrosis usually occurs in organs and tissues for various reasons. For example, infections are one of the most common causes of fibrosis. Bacterial and viral infections affect intestinal and liver fibrosis, respectively. Studies have shown that damage to functional renal epithelial cells also requires inflammation, which, if left untreated, could lead to interstitial fibrosis similar to liver fibrosis [20].

TGF-β: The TGF-β superfamily is a large group of important cellular proteins that are evolutionarily linked to cytokines. TGF-β regulates a wide range of cellular processes by signaling via high-performance TGF-β receptors [7].

Binding of TGF-β to its receptors causes phosphorylation of SMAD transcription factors, which are the main mediators of TGF-β signal transmission [24]. SMAD2 and SMAD3 are activated receptors, while SMAD4 acts as a common partner for all receptor-activated SMAD proteins. Signaling pathways containing non-SMAD proteins such as MAPK or PI3K are activated directly by ligand-bound TGF-β receptors to amplify, reduce, or otherwise modulate downstream cellular responses [8].

Disturbance in TGF-β signal transmission is involved in the development of various human diseases. For example, the regulation of TGF-β is associated with fibrotic diseases and cancer progression. In addition, activation of SMAD signaling by TGF-β exacerbates tissue fibrosis [9, 25].

The major regulator in the pathogenesis of fibrosis is TGF-β1. In addition to its role in fibrogenesis, this pleiotropic cytokine has essential functions in regulating immunity, angiogenesis, and repairing normal tissue. Thus, it is not surprising that TGF-β1 antibodies in SSC patients increase morbidity and mortality in a placebo-controlled I / II phase. However, no trace of fibrosis has been observed. Unlike TGF-β1, TGF-β2 could act as an anti-fibrous cytokine [26].

The TGF-β signaling pathway in fibrosis as well as in liver and gastrointestinal cancers has a complex and tissue-dependent role that suppresses and stimulates oncogenesis by epithelial-mesenchymal transmission (EMT). TGF-β affects the suppression pathway of fibrosis through serine-threonine receptor kinases Types I and II. TGF-β receptors are activated by phosphorylation and regulate Smads (specifically, Smad2 and Smad3) and activate the receptor; And then form a set with Smad4 and this set becomes the core. The activated set of Smads also modulates transcription receptors and suppressor collaborations, which in turn regulates a large number of genes and produces complex results that include connective tissue deposition, cell cycle arrest in the G1 / S phase, induction of apoptosis, suppression of the immune system, and etc [27].

Limans et al. Showed that TLR2 activation could initiate renal inflammation during progressive kidney injury, but the absence of TLR2 does not affect the development of interstitial fibrosis. In renal fibrosis, TGF-β1 exerts its biological effects primarily through its downstream signaling molecules, which are Smad2 and Smad3. While the induction of Smad7 inhibits inflammation and fibrosis by blocking the activation of Smad2 / 3 and NF-κB. Rearrangement of Smad7 production in glomerular podocytes during various kidney diseases may often be an unsuccessful attempt to prevent fibrosis and, consequently, loss of function [28]. Figure 1 shows an important function of TGF-β on various cells of the body and the inflammation of kidneys.

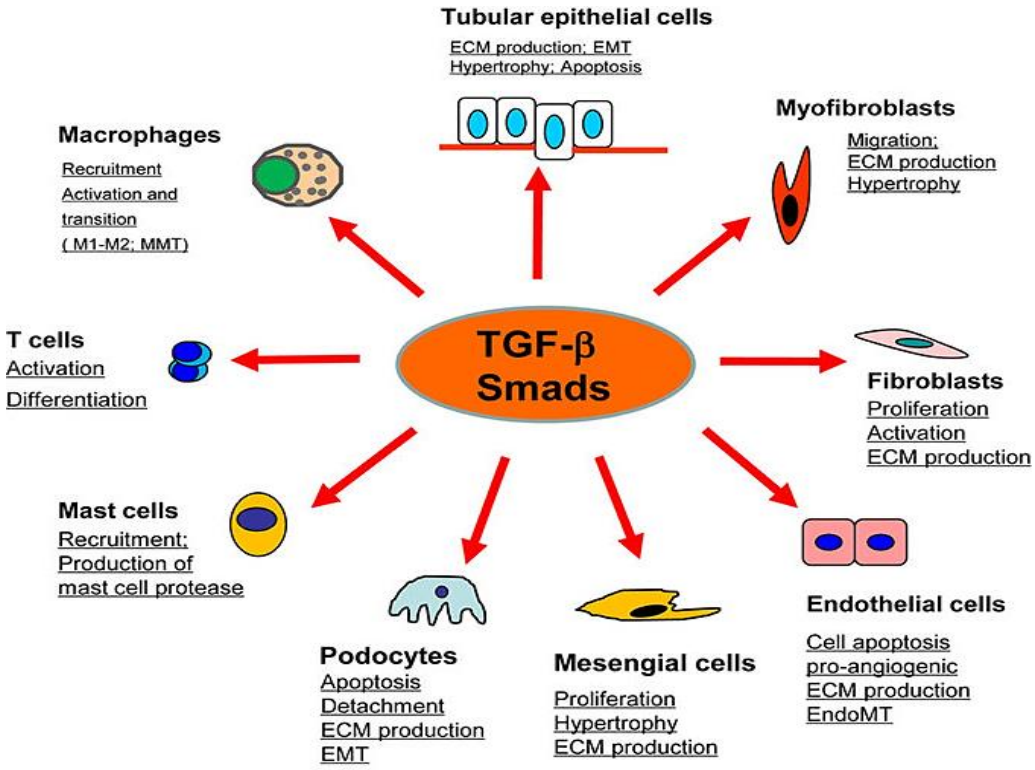

Figure 1. The role of TGF-β/Smad signaling in renal disease. TGF-β affects downstream mediators. Regulation of biological activities is performed on different types of kidney cells during renal inflammation and fibrosis [29].

Vitamin D and TGF-β: Vitamin D is a fat-soluble hormone that is obtained from exposure to sunlight, diet, and some health supplements. Food sources of this substance include oily fish, some mushrooms, and fortified foods such as milk, cereals, and eggs. Sunlight may be responsible for producing up to 90% of vitamin D requirements in most people [13, 30].

Vitamin D is essential for calcium absorption and bone metabolism. Children with vitamin D deficiency struggle with osteoporosis and orthopedic diseases. In recent years, vitamin D has been known for its non-classical actions such as its antioxidant and anti-inflammatory effects and the regulation of cell proliferation [14].

A variety of vitamins D, including VD2 and VD3, are a group of biologically active fat-soluble steroids. 1,25-Dihydroxy D3 is the active form of vitamin 1,25 (OH) 2D3. In addition to its main role in regulating bone metabolism and calcium homeostasis, vitamin D has anti-fibrosis function, regulates cell proliferation and differentiation, regulates anti-inflammatory elements, and regulates the immune system, and etc. Vitamin D also plays an important role in the development of liver fibrosis and has an anti-fibrotic effect on hepatic stellate cells through specific signal transduction mediated by VD receptors [15, 16].

Vitamin D participates in cell cycle regulation and cell differentiation and also has anti-angiogenic properties [31] . In many patients with chronic liver disease (CLD) and animal models of hepatic cirrhosis, 25 (OH) D3 levels are significantly reduced and are negatively associated with liver fibrosis and liver function indices. This suggests that 25 (OH) D3 may be a protective agent for CLD. In the CCl4 model in mice, supplementation of 1,25 (OH) 2D3 could inhibit the proliferation and secretion of collagen HSC-T6 and HSC-T6 activated by the NF-κB and TGF-β1 pathways and reduce lipogenesis and inflammatory gene expression. Finally, improvements in fibrosis and liver function have been observed [32].

The process of vitamin D activation is as follows: Vitamin D is first converted to 25 (OH) D3 by cytochrome P450 (CYP) 2R. It is then converted to 1,25 (OH) 2D3 through CYP27B1, which is the active form of vitamin D3. 1,25 (OH) 2D3 performs its biological function by activating the vitamin D receptor [33, 34].

Vitamin D receptor (VDR) is a member of the nuclear receptor family and acts as a ligand-inducing transcription factor [35]. Binding of 1,25-dihydroxy vitamin D3 from VDR to the ligand-binding domain (LBD) causes the receptor to deform and retinoid X receptors to fade. VDRLBD is highly important for ligand-dependent transcriptional activity [36].

VDR reduces TGF-β-dependent SMAD transcriptional activity by inhibiting SMAD3 uptake into promoter regions of TGF-β target genes in a 1,25 (OH) 2D3-dependent manner. Animal model experiments showed that 1,25 (OH) 2D3 suppresses renal fibrosis by inhibiting TGF-β-SMAD signal transduction [37].

The role of vitamin D in reducing fibrosis: Studies have shown that vitamin D affects lung fibrosis through its direct effects on fibroblasts. Vitamin D works in the opposite direction of fibrogenic intracellular signals; In these cells, vitamin D acts as a pro-fibrotic factor by affecting transforming growth factor β1 (TGFβ1). Interestingly,

vitamin D has similar anti-TGFβ1 effects on lung epithelial cells, thereby extending its protective functions to several lung cells [28].

The function of vitamin D in mesenchymal cells is to reduce collagen expression and progressive factors, and vitamin D supplementation is recommended as a preventive and supportive treatment in LC [38].

In addition, vitamin D directly inhibits the proliferation and profibrotic phenotype of hepatic stellate cells and reduces thioacetamide-induced liver fibrosis in an animal model. There is some evidence to support the negative association of vitamin D levels with liver fibrosis caused by chronic viral hepatitis [39, 40].

In particular, high expression of hepatic Toll-like receptors TLR2 and TLR4 could lead to the production of tumor necrosis factor-alpha (TNFα) in chronic hepatitis C. This cytokine has been shown to modulate fibrosis. In this context, vitamin D could select the anti-inflammatory mechanism by down-regulating the expression of TLR2 and TLR4 molecules. Recent in vivo studies have been documented to reduce TNFα production by monocytes, macrophages, and myeloid dendritic cells treated with vitamin D [41, 42].

Previous studies have demonstrated that vitamin D supplementation suppresses renal fibrosis. Also, these studies have shown that vitamin D metabolites and their synthetic analogs may be involved in the therapeutic stimulation of renal fibrosis through VDR-mediated transcriptional stimulation, however, there is little agreement on the underlying mechanism [26, 43].

Numerous animal experiments have indicated that vitamin D3 supplementation reduces BLM-induced interstitial pulmonary fibrosis [44]. On the other hand, vitamin D deficiency is very common, especially in children and the elderly. Several epidemiological reports have shown that vitamin D deficiency is associated with an increased risk of lung infection. According to a new study, vitamin D deficiency was positively associated with mortality in patients with IPF [45, 46]. Studies by Rahmanian et al. in Iran have shown that the treatment of vitamin D deficiency in patients with uterine leiomyoma has been effective in reducing the size of leiomyoma [47, 48].

Studies have demonstrated that the VDD diet leads to vitamin D deficiency, which in turn exacerbates BLM-induced pulmonary fibrosis. In addition, vitamin D deficiency exacerbates TGF-β / Smad2 / 3 activation and subsequent EMT during BLM-induced pulmonary fibrosis [49].

As a result, numerous data show that serum 25 (OH) D is closely associated with the progression of fibrosis, and serum levels of 1,25 (OH) 2D3 may be negatively associated with the progression of fibrosis. But there is still no medication that could confirm the effectiveness of VD supplement on CLD. However, further research is needed to elucidate its regulatory role in inhibiting fibrosis and to evaluate the safety and efficacy of VD supplementation as a relatively inexpensive treatment for fibrosis in patients with CLD. Meanwhile, based on the myriad properties of VD, there is a scientific relationship between VD and CLD. It is speculated that VD supplementation is certainly beneficial for CLD patients with HF [38].

CONCLUSION

TGF-β is a major key to fibrotic disorders. TGFβ stimulates cell proliferation and many important processes. In fact, in many cases, TGF-β regulates cellular messaging and reduces damage, but by increasing the inflammation, it increases the process of cell damage and inhibition of this protein is beneficial to cells. However, 1,25 (OH) 2D3 has a significant inhibitory effect on TGF-β1 in fibrosis tissues. TGF-β plays an important role in the process of fibrosis in human cells, especially benign fibroids, therefore the use of vitamin D could be an appropriate treatment to reduce and inhibit the development of fibrosis in various tissues. In general, although TGF-β1 and TGF-β2 receptor blockers have been developed for clinical use, current understanding of the pathological roles of SMAD proteins suggests that specifically targeting SMAD signaling may lead to better therapeutic efficacy.

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