



The Beneficial Role of Vitamin D in Interstitial Cystitis

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Authors' contributions

This work was carried out in collaboration between both authors. Author KL designed the study and wrote the protocol. Author LN managed the literature searches. All authors read and approved the final manuscript

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ABSTRACT

Interstitial cystitis (IC) is a poorly understood chronic bladder disorder that is generally characterized by bladder discomfort and increased urination urgency and frequency. Vitamin D levels are associated with bladder pathology, and both rat and human bladders express receptors for vitamin D₃. Vitamin D significantly reduced edema and bladder wall leukocyte infiltration in a IC animal model. Genetic studies have provided the opportunity to determine which proteins link vitamin D to IC pathology (i.e., the major histocompatibility complex (MHC) class II molecules, the transcription factor nuclear factor kappa B (NF- κ B), RANTES (regulated on activation, normal T cell expressed and secreted), epidermal growth factor (EGF), transforming growth factor beta (TGF- β) family, and vascular endothelial growth factor (VEGF)). Vitamin D also exerts its effect on IC through non-genomic factors, i.e., Bacillus Calmette-Guérin (BCG) vaccination, mast cells and histamine, prostaglandins (PGs), reactive oxygen species (ROS), and inducible nitric oxide synthase (iNOS).

Conclusion: Vitamin D may have a beneficial role in IC. Calcitriol is best used for IC because it is the active form of the vitamin D₃ metabolite, and it modulates inflammatory cytokine expression. Further investigation with calcitriol in IC patients is needed.

Keywords: Calcitriol; interstitial cystitis; neurogenic cystitis; vitamin D.

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1. INTRODUCTION

There are many studies that suggested a relationship between vitamin D and bladder pathology. Lower serum 25-hydroxyvitamin D₃ levels are associated with a significantly increased risk of bladder cancer (Mondul et al., 2010) and incidence rates are higher in countries at higher latitudes compared to those near to the equator (Mohr et al., 2010). For each 10 degrees in latitude from the equator, there is a progressive decrease in ultraviolet B (UVB) radiation exposure (Diffey, 1991), which is the primary source of vitamin D for most people. Calcitriol enhances the anti-tumor activity of gemcitabine and cisplatin in human bladder cancer models (Ma et al., 2010). Rat and human bladders express receptors for vitamin D₃, and chronic exposure to the vitamin D receptor (VDR) ligand elocalcitol prevented starvation-induced cell phenotype modification (Crescioli et al., 2005). Normal and neoplastic human bladder tissues and cell lines expressed VDR and calcitriol inhibits proliferation and induces apoptosis in human bladder tumor cells in vitro (Konety et al., 2001). VDR is also reported to be associated with the nuclear matrices of human and rat bladder cell (Nanglia et al., 1998). There is evidence that vitamin D intake is significantly associated with decreased risk for developing overactive bladder (OAB) (Dallosso et al., 2004). Elocalcitol reduced both the frequency and the amplitude of non-voiding contractions in a rat model of partial bladder outflow obstruction (Schröder et al., 2006). Elocalcitol also increased the mean volume voided and decreased the frequency of incontinence episodes in female patients with OAB (Digesu et al., 2012). The vitamin D-induced anti-microbial peptide cathelicidin was reported in urinary tract infections (UTIs) with *E. coli*, suggesting that vitamin D may be useful in the preventing of UTIs (Hertting et al., 2010). Furthermore, human bladder contraction mainly depends on Ca²⁺ influx via L-type voltage-gated Ca²⁺ channels and on RhoA/Rho kinase contractile signaling, which is up-regulates in OAB (Bing et al., 2003). Elocalcitol inhibits RhoA/Rho kinase signaling and up-regulates L-type calcium channel activity in both human and rat bladders (Morelli et al., 2007; 2008). In addition, elocalcitol treatment significantly reduced edema, bladder wall leukocyte infiltration and levels of interleukin-13 (IL-13) and mast cell-derived protease 1 (MMCP1) in the bladder in a rodent model of interstitial cystitis (IC) (Benigni et al., 2006). Based on the evidence described above, we discuss the role of vitamin D in IC.

2. GENETIC FACTORS RELATED TO VITAMIN D IN INTERSTITIAL CYSTITIS

2.1 Human Leukocyte Antigen (HLA)

Studies have suggested that several genes in the major histocompatibility complex (MHC) region promote IC susceptibility. HLA genes are located in the MHC region and have been implicated in IC susceptibility. In normal control bladders, the urothelium was negative for HLA class II molecule expression; in contrast, HLA-DR expression was identified in urothelial cells from IC patients (Christmas and Bottazzo, 1992). IC has been shown to be associated with *HLA-DR6* (Christmas et al., 1990). Biopsied urothelial cells also exhibit increased HLA-DR expression in IC patients (Liebert et al., 1993). HLA-DR staining patterns correlate with symptoms, including bloating, constant urge to void and absence of burning in patients with IC (Erickson et al., 1997). Differential effects on MHC class II molecules were associated with Hunner's ulcer type IC, including HLA-DQB1, HLA-DRB1, HLA-DPA1, HLA-DOA, HLA-DMA and HLA-DRA (Tseng et al., 2010). However, calcitriol is known to stimulate phagocytosis but suppresses MHC class II antigen expression in human mononuclear phagocytes (Tokuda et al., 1992; Tokuda and Levy, 1996). Calcitriol also decreases

interferon-gamma-induced HLA-DR antigen expression on normal and transformed human keratinocytes (Tamaki et al., 1990; Tone et al., 1993).

2.2 The Transcription Factor Nuclear Factor Kappa B (NF- κ B)

NF- κ B is a hetero-dimeric, sequence-specific transcription factor that is found in many cell types. NF- κ B has been implicated in chronic inflammatory diseases and is a key regulator of genes involved in responses to infection, inflammation and stress. NF- κ B is predominantly activated in bladder urothelial cells and cells of the submucosal layer in biopsies from patients with IC compared to controls (Abdel-Mageed and Ghoniem, 1998). The NF- κ B-induced expression of pro-inflammatory cytokines correlates with increased protein levels of NF- κ B-regulated pro-inflammatory factors in the urine of IC patients compared with controls (Abdel-Mageed, 2003). These findings suggested a pivotal role for NF- κ B in IC pathophysiology. Sodium pentosanpolysulfate (SPP) has been promoted as an urothelialcyto protective agent for treating IC. NF- κ B activation by lipopolysaccharide (LPS) and double-stranded RNA were suppressed when the stimulants were incubated with SPP before cell treatment (Sadhukhan et al., 2002). However, VDR negatively regulates bacterial-induced intestinal NF- κ B activation and attenuates the infection response (Wu et al., 2010). Calcitriol impairs NF- κ B activation in human naïve B cells (Geldmeyer-Hilt et al., 2011). There are a significant negative correlation between vitamin D levels and both high-sensitivity C-reactive protein and NF- κ B activity in type 1 diabetic patients (Devaraj et al., 2011). In mice, calcitriol suppresses inflammation-induced expression of plasminogen activator inhibitor-1 by blocking NF- κ B activation (Chen et al., 2011). In addition, vitamin D₃ upregulated protein 1 (VDUP1) suppresses tumor necrosis factor (TNF)- α -induced NF- κ B activation during hepato-carcinogenesis (Kwon et al., 2010). Taken together, the evidence indicates that calcitriol may suppress NF- κ B activation in IC.

2.3 RANTES (Regulated on Activation, Normal T Cell Expression and Secretion)

Mast cells secrete several cytokines, including IL-6, TNF- α , IL-8 and RANTES (Castellani et al., 2010). Bladder biopsies from IC patients are characterized by an increased number of activated mast cells in detrusor smooth cells (Sant et al., 2007), which release IL-6, IL-8, and RANTES in response to pro-inflammatory cytokines IL-1 α and TNF- α (Bouchelouche et al., 2006). The intramuscular injection of hrRANTES recruits mast cells and increase histidine decarboxylase transcription in mice (Conti et al., 1998). RANTES also plays a key role in the IC pathogenesis (Bouchelouche et al., 2006). Interestingly, RANTES expression is inhibited by a vitamin D₃ analog in dendritic cells (Griffin et al., 2004). Three active vitamin D₃ compounds, tacalcitol, calcitriol and calcipotriol, inhibited RANTES and IL-8 production in normal human dermal fibroblasts (Fukuoka et al., 1998). In addition, paricalcitol suppressed renal RANTES and TNF- α expression and inhibited renal infiltration of T cells and macrophages (Tan et al., 2008; 2009). Calcitriol also inhibits the synthesis and release of certain cytokines, including RANTES, platelet-derived growth factor and matrix metalloproteinases, from bronchial smooth muscle cells (Sandhu and Casale, 2010). These findings suggest that vitamin D may have a role in IC through its modulatory effect on RANTES expression.

2.4 Epidermal Growth Factor (EGF)

EGF is known to be present in normal human urine and mouse bladder epithelial cells *in vitro* (Jørgensen et al., 1993; Southgate et al., 1994). Urinary EGF levels were significantly elevated in IC patients compared with asymptomatic controls (Keay et al., 1997; Erickson et al., 2002). Serum starved bladder epithelial cells from IC patients also had higher levels of EGF than controls (Keay et al., 2000). However, calcitriol impaired autocrine and EGF-induced nuclear translocation of activated EGF receptors in human epidermoid A431 cells (Cordero et al., 2002), significantly reduced basal and EGF-stimulated cyclin D1 at both the mRNA and protein levels in human colon adenocarcinoma-derived cells (Tong et al., 1999), and suppressed the EGF-induced external signal-regulated kinase activation by EGF in ovarian cancer cells (Shen et al., 2011).

2.5 The Transforming Growth Factor Beta (TGF- β) Family

TGF- β is a group of homologous polypeptides that exert pleiotropic effects on various cell types and stimulate extracellular matrix formation and fibrosis. Urinary tract epithelial cells in the renal pelvis, ureter, bladder and urethra constitutively produce IL-8 and TGF- β (Hang et al., 1998). Antibodies against TGF- β s stain in the sub-mucosal layer beneath the basement membrane in bladder tissues from IC patients with severe rather than mild bladder pain (Ueda et al., 2002). This suggests that TGF- β may be involved in inflammatory processes and painful symptoms in IC patients. However, TGF- β levels negatively correlated with vitamin D levels; increased TGF- β_1 and platelet counts is an early indicator of bone marrow fibrosis in patients with vitamin D deficiency (Isik et al., 2012). There is an association between the *FokI* VDR polymorphism and TGF- β plasma concentrations in type 1 diabetes mellitus (López et al., 2008). Among diabetic children, higher levels of TGF- β_1 were observed compared with healthy children and diabetic carriers of the *ff* genotype exhibit low levels of 25OHD compared with *F* allele carriers. Vitamin D has a significant regulatory effect on levels of bioactive TGF- β_1 and appears to affect aspects of the TGF- β_1 signaling system in renal tissue (Aschenbrenner et al., 2001). Calcitriol reduces TGF- β_3 -induced fibrosis-related gene expression in human leiomyoma cells (Halder et al., 2011). Moreover, vitamin D treatment significantly down-regulates the free fatty acids-induced expression of TGF- β in the HSC line LX-2 (Seydel et al., 2011). These results suggest that vitamin D might participate in reducing inflammation and painful symptoms in IC patients.

2.6 Vascular Endothelial Growth Factor (VEGF)

Angiogenesis is a complex process involving the coordinated steps of endothelial cell activation, proliferation, migration, tube formation and capillary sprouting and requires the participation of many intracellular signaling pathways. VEGF is a key mediator of angiogenesis. Vascular changes associated with angiogenesis usually occur in cancer, but they have also been reported in inflammatory diseases. VEGF signaling in bladder urothelium is supported by the expression of VEGF receptors and co-receptors neuropilins (Saban et al., 2008a). VEGF overexpression was reported in bladder biopsies from IC patients (Lee and Lee, 2011). Specifically, IC bladder tissue expressed VEGF receptors and co-receptors throughout the urothelium, whereas they were predominantly co-localized to apical cells in control bladders (Saban et al., 2008b). The VEGF expression in the lamina propria was significantly higher in IC tissue compared to control samples. Among IC patients, VEGF expression was significantly higher in those with severe pain than in those with mild pain (Kiuchi et al., 2009). In contrast, calcitriol was reported to inhibit angiogenesis

in vitro and *in vivo* (Mantell et al., 2000). Calcitriol significantly inhibits VEGF-induced endothelial cell spouting and elongation in a dose-dependent manner and decreases VEGF production (Gruber et al., 2008). Calcitriol potently inhibits of retinal neovascularization in a mouse model of oxygen-induced ischemic retinopathy (Albert et al., 2007). Vitamin D and its analog also reduce VEGF expression in various cancer cell lines (Nakagawa et al., 2005; Ben-Shoshan et al., 2007). Moreover, Vitamin D-binding protein-macrophage activating factor(DBP-maf) was reported to inhibit angiogenesis and tumor growth in mice (Krisker et al., 2003) and inhibited VEGF signaling by decreasing the VEGF-mediated phosphorylation of VEGF-2 and ERK1/2, a downstream target of the VEGF signaling cascade (Kalkunte et al., 2005). Table 1 summarizes the genetic factors related to vitamin D and interstitial cystitis.

Table 1. Genetic Factors Related to Vitamin D and Interstitial Cystitis (IC)

Interstitial Cystitis	Vitamin D
<p>Human Leukocyte Antigen (HLA)</p> <p>*Urothelial cells biopsied from IC patients exhibit increased HLA-DR expression (Christmas and Bottazzo, 1992).</p> <p>*HLA-DR staining correlates with IC patient symptoms, including bloating, constant urge to void, and absence of burning (Erickson et al., 1997).</p> <p>*Differential effects on MHC class II molecules were associated with Hunner’s ulcer type IC, including <i>HLA-DQB1</i>, <i>HLA-DRB1</i>, <i>HLA-DPA1</i>, <i>HLA-DOA</i>, <i>HLA-DMA</i>, and <i>HLA-DRA</i> (Tseng et al., 2010).</p>	<p>*Calcitriol suppresses MHC class II antigen expression in human mononuclear phagocytes and decreases interferon-γ-induced HLA-DR antigen expression in normal and transformed human keratinocytes (Tamaki et al., 1990; Tone et al., 1993).</p>
<p>Nuclear Factor kappaB (NF-κB)</p> <p>*NF-κB was predominantly activated in bladder urothelial cells and submucosal layer cells in biopsies from IC patients compared to controls (Abdel-Maggeed and Gohniem, 1998).</p> <p>*NF-κB activation by lipopolysaccharide (LPS) and double-stranded RNA (dsRNA) was suppressed when the stimulants were incubated with SPP prior to treatment (Sadhukhan et al., 2002).</p>	<p>*VDR negatively regulates bacterial-induced intestinal NF-κB activation and attenuates infection response (Wu et al., 2010).</p> <p>*Calcitriol impairs NF-κB activation in human naïve B cells (Geldmeyer-Hilt et al., 2011).</p> <p>*Vitamin D₃-upregulated protein 1 (VDUP1) suppresses tumor necrosis factor (TNF)-α-induced NF-κB activation in hepato-carcinogenesis (Kwon et al., 2010).</p>
<p>RANTES (regulated on activation, normal T cell expressed and secreted)</p> <p>*Bladder biopsies from IC patients are characterized by an increased number of activated mast cells in the detrusor smooth cells (Sant et al., 2007).</p> <p>*RANTES plays a key role in the IC pathogenesis. Intramuscular injection of hrRANTES recruits mast cells and increases histidine decarboxylase transcription in mice (Bouchelouche et al., 2006).</p>	<p>*RANTES expression is inhibited by a vitamin D₃ analog in dendritic cells (Griffin et al., 2004).</p> <p>*Three active vitamin D₃ compounds, tacalcitol, calcitriol, and calcipotriol, inhibited the production of RANTES and IL-8 in normal human dermal fibroblasts (Fukuoka et al., 1998).</p>

Epidermal Growth Factor (EGF)

*Urinary EGF levels were significantly elevated in IC patients compared with asymptomatic controls (Keay et al., 1997; Erickson et al., 2002).

*Serum starved bladder epithelial cells from IC patients also revealed higher levels of EGF than controls (Keay et al., 2000).

*Calcitriol impairs autocrine and EGF-induced nuclear translocation of activated EGF receptors in human epidermoid A431 cells, significantly reduces basal and EGF-stimulated expression of cyclin D1 at the mRNA and protein levels in human colon adenocarcinoma-derived cells, and suppresses activation of the external signal-regulated kinase by EGF in ovarian cancer cells (Cordero et al., 2002; Tong et al., 1999; Shen et al., 2011).

Transforming Growth Factor betas (TGF-) family

*TGF- s were stained in the sub-mucosal layer beneath the basement membrane in bladder tissues of IC patients with severe rather than mild bladder pain (Hang et al., 1998; Ueda et al., 2002).

*TGF- levels negatively correlated with vitamin D levels; namely, increased TGF- ₁ and platelet counts are an early indicator of bone marrow fibrosis in patients with vitamin D deficiency (Isik et al., 2012).

*The *FokI* VDR polymorphism is associated with TGF- plasma concentrations in type 1 diabetes mellitus. Among diabetic children, higher levels of TGF- ₁ were observed compared with healthy children and diabetic carriers of the *ff* genotype exhibited low levels of 25OHD compared with *F* allele carriers (López et al., 2008).

*Vitamin D has significantly regulatory levels of bioactive TGF- ₁ and appears to affect aspects of the TGF- ₁ signaling system in renal tissue (Aschenbrenner et al., 2001).

*Calcitriol reduces TGF- ₃-induced fibrosis-related gene expression in human leiomyoma cells (Halder et al., 2011).

*Vitamin D treatment significantly down-regulated the free fatty acids-induced expression of TGF- in the HSC line LX (Seydel et al., 2011).

*Calcitriol significantly inhibits VEGF-induced endothelial cell spouting and elongation in a dose-dependent manner and decreases

Vascular Endothelial Growth Factor (VEGF)

*VEGF overexpression was identified in bladder biopsies from IC patients (Lee and Lee, 2011).

*The VEGF expression in the lamina propria was

significantly higher in IC compared with control samples. Among IC patients, VEGF expression was significantly higher in those with severe pain than in those with mild pain (Kiuchi et al., 2009). the VEGF production (Gruber et al., 2008).

3. THE NON-GENOMIC ROLES OF VITAMIN D IN INTERSTITIAL CYSTITIS

3.1 Bacillus Calmette-Guérin (BCG) Vaccination

BCG was initially developed to provide protection against tuberculosis. However, intravesical BCG treatment has also been used in IC patients, and most studies have demonstrated some benefits (Irani et al., 2004; Probert et al., 2008; Sairanen et al., 2009).

A systemic review and meta-analysis of BCG treatment evidenced improvement for symptoms measured by the Wisconsin Interstitial Cystitis Inventory but not in 24-hour urinary frequency in patients with IC (Matsuoka et al., 2012). Interestingly, BCG-vaccinated infants are almost 6 times more likely to have sufficient vitamin D concentrations than unvaccinated infants 3 months after BCG vaccination; this association remains strong even after adjusting for season, ethnic group and sex (Lalor et al., 2011). Among the vaccinated group, there was also a strong inverse correlation between the IFN- γ response to *M. tuberculosis* PPD and vitamin D concentration; infants with higher vitamin D concentrations had lower IFN- γ responses. Similarly, tuberculosis in cattle usually presents with a rapid transient increase in serum calcitriol within the first two weeks following infection (Rhodes et al., 2003). Calcitriol-positive mononuclear cells were later identified in all of the tuberculous granulomas. During tuberculosis infection, alveolar macrophage-produced calcitriol plays a beneficial role by limiting inflammation-mediated tissue injury, potentiating nitric oxide (NO) production by stimulated monocytes/macrophages, inhibiting INF- γ production by stimulated CD4⁺ cells, and suppressing *M. tuberculosis* growth (Ametaj et al., 1966; Rockett et al., 1988). These findings suggest that BCG treatment may benefit to IC patients by increasing calcitriol levels.

3.2 Mast Cells and Histamine

Clinical studies demonstrated elevated numbers of mast cell in the lamina propria of IC bladder biopsies. Mast cells trigger inflammation that is associated with local pain. Activated mast cells were found to be increased in IC patients compared with controls (Theoharides et al., 1995). A relationship between mast cells and inflammatory processes was demonstrated in IC patients (Lynes et al., 1987). The histamine contents of bladder washings strongly correlate with the number of mast cells in patients with classic IC compared with non-ulcerative IC (Enerbäck et al., 1989). Urinary histamine and methyl-histamine levels were increased in spot and 24-hour urine samples in IC patients compared with normal volunteers (el-Mansoury et al., 1994). Hydrodistension-stimulated release of urinary histamine was highly significant in patients with IC compared with controls (Yun et al., 1992). Histamine receptors were found in situ and in vitro in human detrusor smooth muscle cells (Neuhaus et al., 2006). In a pseudorabies virus (PRV)-induced IC model, both genetic and pharmacologic data suggested that mast cells mediate cystitis pain via histamine receptors (Rudick et al., 2008). SPP inhibits mast cell histamine secretion and is used to treated IC patients (Chiang et al., 2000). However, rats fed a vitamin D-deficient had an increased hypotensive response to histamine (De Novellis et al., 1994). VDR expression was identified in all samples containing reactive mast cells in canine cutaneous mast cell tumors (Russell et al., 2010). The mast cell density in peripheral tissues revealed a moderate increase in the number of

mast cells in the skin of VDR-deficient mice compared with wild-type animals (Baroni et al., 2007). Furthermore, calcitriol can induce mast cells to up-regulate IL-10 mRNA and IL-10 protein secretion (Yu et al., 2011), which can contribute to mast cells' capacity to suppress inflammation and skin pathology at sites of chronic UV-B irradiation (Biggs et al., 2010). In addition, calcitriol selectively inhibits stem cell factor-dependent mast cell proliferation and colony formation and reduced histamine release induced by calcium ionophore A23187 (Toyota et al., 1996).

3.3 Prostaglandins (PGs)

PGs play a role in inflammatory processes (Ricciotti et al., 2011). Cyclooxygenase (COX) participates in the conversion of arachidonic acid into PGs. Human urinary bladder tissue can synthesize several types of PGE series (Abrams et al., 1979). The rat bladder also produces prostacyclin as well in addition to other PGs (Jeremy et al., 1984). Chronic urothelial injury leads to increased urinary frequency and decreased voided volume and is associated with increased PGE₂ levels in the bladder (Shioyama et al., 2008). Urinary PGE₂ excretion is increased in IC patients (Lynes et al., 1987). Intra-vesical instillation of PGE₂ in rats causes detrusor over-activity and stimulates reflex micturition (Ishizuka et al., 1995). PGE₂ has been reported to play a critical role in the generation and maintenance of hyperalgesia that develops at sites of inflammation (Portanova et al., 1996). PGE₂ also induced bladder pressure and had a direct contraction effect on the detrusor smooth muscle (Ishizuka et al., 1995). Furthermore, water avoidance stress increases voiding frequency through COX-2 expression at both their RNA and protein levels in a rat model; however, voiding frequency and high COX-2 expression were reduced by pretreatment with the COX-2 inhibitor etodolac (Yamamoto et al., 2012). COX-2 was up-regulated in epithelial cells explanted from IC bladder biopsies compared with control tissues (Yang et al., 2011). Miki et al. (2011) demonstrated that PGE₂ and its receptor participated in processing cystitis-related bladder pain in mice. ONO-8130, a selective PGE₂ receptor antagonist, relieves bladder pain in mice with cyclophosphamide (CP)-induced cystitis (Miki et al., 2011). However, calcitriol has been reported to regulate the expression of several key genes involved in PG pathways, causing a decrease in PG synthesis (Moreno et al., 2005). Calcitriol and its analogs have also been shown to selectively inhibit COX-2 activity (Aparna et al., 2008). Elocalcitol decreased COX-2 expression and PGE₂ production in benign prostatic hyperplasia cells (Penna et al., 2009).

3.4 Reactive Oxygen Species (ROS)

ROS have been suggested to play a role in IC (Furuta et al., 2012). CP has been known to cause hemorrhagic cystitis mainly via oxidative stress induction. In CP-treated animals, oxidative stress parameters were altered; protein carbonyl content, protein thiol, malondialdehyde (MDA), conjugated dienes and lipid peroxidation were elevated; but thioredoxinreductase and glutathione peroxidase were decreased (Abraham et al., 2009; Rezvanfar et al., 2010; Zhang et al., 2006). However, aminoguanidine and Saturejakhuzestanica protect rats from CP-induced hemorrhagic cystitis by reducing of free radical-induced toxic stress and bladder damage (Abraham et al., 2009; Rezvanfar et al., 2010). Calcitriol has been reported to exert a receptor-mediated effect on human monocyte hydrogen peroxide secretion (Cohen et al., 1986). Human monocytes in culture gradually lose their capability to produce superoxide when stimulated, but the addition of calcitriol, lipopolysaccharide, or lipoteichoic acid (LTA) restores this and increases their oxidative capacity compared with unstimulated monocytes (Levy et al., 1991). Calcitriol may also

protect non-malignant prostate cells from oxidative stress-induced cell death by eliminating ROS-induced cellular injuries (Bao et al., 2008). Vitamin D metabolites and analogs were reported to induce lipoxigenase mRNA expression and activity and ROS production in a human bone cell line (Somjen et al., 2011). Vitamin D could reduce the extent of lipid peroxidation and induce superoxide dismutase (SOD) activity in the hepatic antioxidant system in rats (Sardar et al., 1996; George et al., 2012). In addition, calcitriol also enhances intracellular glutathione (GSH) pools and significantly reduces LPS-induced nitrite production (Garcion et al., 1999).

3.5 Nitric Oxide (NO)

NO is involved in host defense reactions and plays a key role in vascular disorder pathophysiology. Urinary NO concentration was markedly elevated in patients with IC compared with control subjects (Jansson et al., 1998; Ehrén et al., 1999; Logadottir et al., 2004). Hosseini et al. (2004) reported a statistically significant correlation between changes in symptom/problem score and changes in luminal bladder NO in patients with IC. Inducible nitric oxide synthase (iNOS) expression and NO production were increased in incubated primary cell cultures with plasma from CP-treated rats (Xu et al., 2001). Patients with IC had higher iNOS mRNA expression and NO production than controls (Koskela et al., 2008). NO is a smooth muscle relaxant and vasodilator; however, NO can also be toxic when produced in excess for a prolonged time, leading to increased free radical formation and subsequent cellular damage (Koppenol et al., 1992). Increased iNOS over-production has been suggested to cause barrier dysfunction in several tissues (Han et al., 2004). In granulomatous diseases, macrophage 1-hydroxylase activation results in an increase in calcitriol, which inhibits iNOS expression and reduces NO production by LPS-stimulated macrophages (Chang et al., 2004). Calcitriol production by macrophages may provide protection against oxidative injuries caused by NO bursts. Calcitriol is known to inhibit LPS-induced immune activation in human endothelial cells (Equils et al., 2005). Table 2 summarizes the non-genomic role of vitamin D in interstitial cystitis.

Table 2. Summary of the Non-Genomic Role of Vitamin D in Interstitial Cystitis (IC)

Interstitial cystitis	Vitamin D
<p>Bacillus Calmette-Guérin (BCG) Vaccination *Intra-vesical BCG treatment has been used in IC patients (Irani et al., 2004; Propert et al., 2008; Saianen et al., 2009). *BCG treatment improves symptoms as measured by the Wisconsin Interstitial Cystitis Inventory, but did not affect 24-hour urinary frequency in patients with IC (Matsuoka et al., 2012).</p>	<p>*BCG-vaccinated infants are almost 6 times more likely to have sufficient vitamin D concentrations than unvaccinated infants 3 months after BCG vaccination. Among the vaccinated group, there was a strong inverse correlation between the IFN- response to <i>M. tuberculosis</i> PPD and vitamin D concentration; infants with higher vitamin D concentrations had lower IFN-responses (Lalor et al., 2011). *Tuberculosis in cattle usually presents with a rapid transient increase in serum calcitriol within the first two weeks following infection (Rhodes et al., 2003). *During tuberculosis infection, alveolar</p>

Mast cells and Histamine

- *Activated mast cells were increased in IC patients compared with controls. A relationship between mast cell and the inflammatory process was demonstrated in IC patients (Theoharides et al., 1995).
- *The histamine content of bladder washings was strongly correlated with the number of mast cells in patients with classic IC compared with non-ulcerative IC (Enerbäck et al., 1989).
- *Urinary histamine and methyl-histamine levels were increased in the spot and 24-hour urine samples in IC patients compared with normal volunteers (el-Mansoury et al., 1994).

Prostaglandins (PGs)

- *Urinary PGE₂ excretion is increased in IC patients (Lynes et al., 1987).
- *PGE₂ induces bladder pressure and has a direct contraction effect on the detrusor smooth muscle of the bladder (Ishizuka et al., 1995).
- *COX-2 is up-regulated in epithelial cells explanted from IC bladder biopsies compared with control tissues (Yang et al., 2011).

macrophage-produced calcitriol plays a beneficial role by limiting inflammation-mediated tissue injury, potentiating nitric oxide (NO) production by stimulated monocytes/macrophages, inhibiting INF- γ production by stimulated CD4⁺ cells, and suppressing *M. tuberculosis* growth (Ametaj et al., 1966; Rockett et al., 1988).

- *Rats fed a vitamin D-deficient exhibit an increase in the hypotensive response to histamine (De Novellis et al., 1994).
- *VDR expression was identified in all samples of canine cutaneous mast cell tumors that contained reactive mast cells (Russell et al., 2010).
- *The mast cell density in peripheral tissues revealed a moderate increase in the number of mast cells in the skin of VDR-deficient mice compared with wild-type animals (Baroni et al., 2007).
- *Calcitriol can induce mast cells to up-regulate IL-10 mRNA and IL-10 protein secretion levels (Yu et al., 2011), which can contribute to the mast cells' capacity to suppress inflammation and skin pathology at chronic UV-B irradiation sites (Biggs et al., 2010).
- *Calcitriol selectively inhibits stem cell factor-dependent mast cell proliferation and colony formation, and reduces histamine release induced by calcium ionophore A23187 (Toyota et al., 1996).
- *Calcitriol has been reported to regulate the expression of several key genes involved in PG pathways, which causes a decrease in PG synthesis (Moreno et al., 2005).
- *Calcitriol and its analogs have also been shown to selectively inhibit COX-2 activity (Aparna et al., 2008).
- *Elocalcitol decreased COX-2 expression and PG E₂ production in benign prostatic hyperplasia cells (Penna et al., 2009).

Reactive Oxygen Species (ROS)

*ROS have been suggested to play a role in IC (Furuta et al., 2012).

*In CP-treated animals, all oxidative stress parameters were altered, including as elevated protein carbonyl content, protein thiol, malondialdehyde (MDA), conjugated dienes, and lipid peroxidation; however, thioredoxin reductase and glutathione peroxidase were decreased (Abraham et al., 2009; Rezvanfar et al., 2010; Zhang et al., 2006).

*Calcitriol has been reported to exert a receptor-mediated effect on the hydrogen peroxide secretion by human monocytes (Cohen et al., 1986).

*Calcitriol could also protect non-malignant prostate cells from oxidative stress-induced cell death by eliminating ROS-induced cellular injuries (Bao et al., 2008).

*Vitamin D metabolites and vitamin D analogs were reported to induce lipoxygenase mRNA expression, lipoxygenase activity, and ROS production in a human bone cell line (Somjen et al., 2011).

*Vitamin D may reduce the extent of lipid peroxidation; additionally, it induces superoxide dismutase (SOD) activity in the rat hepatic antioxidant system, enhances intracellular glutathione (GSH) pools, and significantly reduces LPD-induced nitrite production (Sardar et al., 1996; George et al., 2012; Garcion et al., 1999).

Inducible Nitric Oxide Synthase (iNOS)

*Urinary NO concentration is markedly elevated in IC patients compared with controls (Jansson et al., 1998; Ehrén et al., 1999; Logadottir et al., 2004).

*There is a statistically significant correlation between changes in symptoms/problem score and changes in luminal bladder NO in IC patients (Hossenli et al., 2004).

*Patients with IC have higher iNOS mRNA expression and NO production than controls (Koskela et al., 2008).

*In granulomatous diseases, the activation of macrophage 1-hydroxylase results in an increase in 1,25OHD, which inhibits iNOS expression and reduces NO production by LPS-stimulated macrophages (Chang et al., 2004).

4. CONCLUSION

Vitamin D may have a beneficial role in IC and has anti-proliferative and anti-fibrotic effects in inflamed bladder. Genetic studies have provided opportunities to determine the proteins that link vitamin D to IC pathology. Vitamin D also affects IC symptoms through non-genomic mechanisms. Calcitriol is best used to treat IC because of it is the active form of vitamin D₃ and its receptors are expressed in the bladder.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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