의학석사 학위논문

수근관증후군에서 활막하 결체조직내 비타민 D 수용체의 발현

Evaluation of Vitamin D Receptor in

Subsynovial Connective Tissue of Carpal Tunnel Syndrome

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Abstract

Introduction :

Studies suggest that the pathophysiology of carpal tunnel syndrome (CTS) is associated with pathologic changes in the vascularity and physical properties of the subsynovial connective tissue (SSCT) in the carpal tunnel. Aside from its classic action in musculoskeletal system, broad range of roles of vitamin D has been reported, including anti-inflammatory, anti-cancer, neuroprotective role and even cardiovascular benefits. In this study we aimed to evaluate whether vitamin D receptor (VDR) is present in the SSCT endothelial cells in patients with CTS, and whether its expression is associated with clinical features of CTS.

Patients & Methods :

During open carpal tunnel release, specimens of SSCT from 54 patients with CTS were obtained, and stained for VDR in the SSCT endothelial cells using immnunohistochemistry. We evaluated correlation of VDR expression with clinical variables such as serum vitamin D level, age, body mass index and symptom duration, electrophysiologic severity in terms of motor conduction velocity and distal motor latency.

Results :

Diverse expression of VDR was observed in endothelial vessels of SSCT. VDR expression was found to be significantly correlated with age, symptom duration, and distal motor latency, but not with other variables.

Discussion :

This study found that VDR exists in the endothelial cells of the SSCT in patients with CTS. The association of a higher VDR expression with age, symptom duration, and electrophysiologic severity of the disease suggests that VDR may be up-regulated and contribute to disease progression by provoking angiogenesis. Further studies are necessary to confirm the role of vitamin D and VDR in patients with CTS, and to determine whether vitamin D supplementation could be helpful for prevention and treatment of CTS.

Keywords: vitamin D receptor; carpal tunnel syndrome; subsynovial connective tissue; distal motor latency;

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Introduction

Carpal tunnel syndrome (CTS) is a common compressive neuropathy in the upper extremity, with symptoms including tingling sensation and muscle weakness in the thenar area. Among many potential mechanisms that can cause CTS, idiopathic is the most common, where the median nerve compression occurs by an elevate pressure in the carpal tunnel due to reduction of its cross sectional area or increment of its volume.[1,2] In the carpal tunnel, radial and ulnar bursa exist, surrounding the flexor pollicis longus and the other flexor tendons, respectly. Studies suggest that the critical pathophysiology of idiopathic CTS could lie in subsynovial connective tissue (SSCT), which separates bursa from flexor tendons with a meshwork of areolar connective tissue and its associated vasculature, with the median nerve affected secondarily as a result of the changes in the vascularity and physical properties of SSCT.[3-6] Most of studies on pathological changes in idiopathic CTS report that inflammatory cells are rare and that edema and nonspecific fibrosis are the most common histological findings, as well as vascular lesions such as vessel wall thickening and intimal hyperplasia area common in CTS.[3,7]

Recently, in addition to its classic actions in regulating bone metabolism, broad range of roles of vitamin D have been established, including anti-inflammatory, anti-proliferative actions, prodifferentiation, and cardiovascular benefits.[8-10] Vitamin D exerts its biological activity by binding to and activating the vitamin D receptor

(VDR).[11] Several studies reported that endothelial cells express VDR, as well as 1α-hydroxylase, implying that they possess the capacity for coordinating local vitamin D–dependent regulatory activity.[8,12,13] Studies suggest a possible link between endothelial function and regulatory activity through the liganded VDR.[10,14]

The study on proteome alterations in serum found that vitamin D binding proteins were down-regulated in patients with CTS.[15] Another study reported a potential link between serum vitamin D status and the occurrence of CTS in women younger than 50 years.[16] However, VDR itself in the SSCT has not been evaluated in patients with CTS. In this study, we evaluated whether VDR is present in the endothelial cells of the SSCT in patients with CTS, and whether its expression is associated with clinical features of CTS.

Subjects & Methods

Subjects

Our institutional review board approved this study and informed consent for specimen collection was obtained from all participating patients. We included consecutive 54 patients undergoing open carpal tunnel release after diagnosis of idiopathic CTS. The diagnosis of CTS was based on both clinical symptoms such as paresthesia or numbness over the median nerve territory and a positive electrophysiological study. Exclusion criteria were patients with previously diagnosed rheumatoid arthritis, associated nerve compression such as cubital tunnel syndrome or cervical radiculopathy, workers compensation issue, and those treated with osteoporosis medication or calcium/vitamin D supplementation and those diagnosed with a disease influencing metabolism, such as chronic kidney disease, hyperparathyroidism, malignancy, inflammatory arthritis, liver disease and diabetes mellitus.

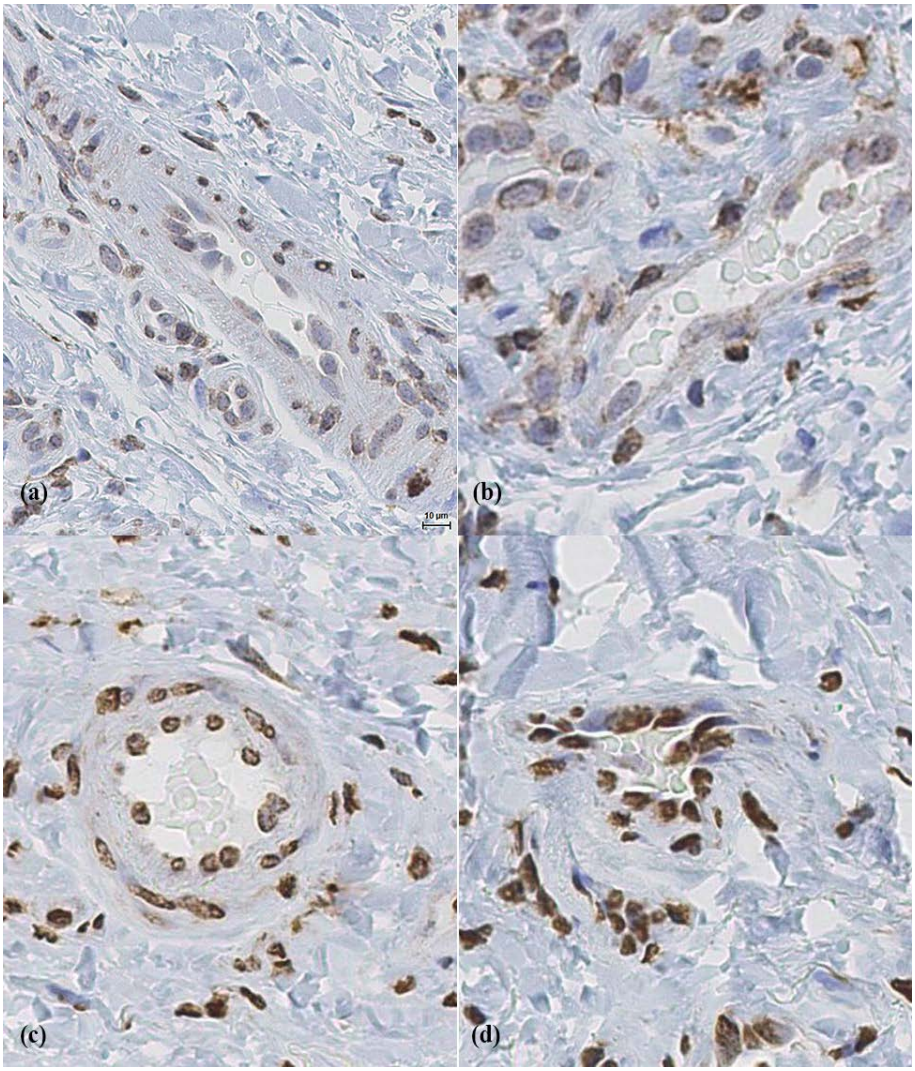
Immunohistrochemical analysis of VDR in the SSCT

Specimens of SSCT were obtained from patients with idiopathic CTS during open carpal tunnel release. The specimens were formalin-fixed and paraffin-embedded. Four-micrometer serial sections were cut and processed for immunohistochemical staining for VDR. Using the Discovery XT automated immunohistochemistry stainer (Ventana Medical Systems, Inc., Tucson, AZ, USA), slides were stained. Detection was done using the DAB Map Kit (Ventana Medical Systems). Sections were deparaffinized using EZ Prep solution. CC1 standard (pH 8.4 buffer containing Tris/Borate/EDTA) solution was used for antigen retrieval. Inhibitor D (3% H_2O_2, Endogenous peroxidase) was blocked for 4 minutes at 37°C temperature. Slides were incubated with primary antibody (Rat monoclonal antibody to Vitamin D Receptor, abcam, Cambridge, USA) for 32 minutes at 37°C, and the secondary antibody (Omimap anti Mouse HRP, rat,) for 20 minutes at 37°C. Slides were incubated in DAB and H_2O_2 substrate for 8 minutes at 37°C followed by Hematoxylin and Bluing reagent for counterstain at 37°C. Reaction buffer (pH 7.6 Tris buffer) was used as washing solution.

For quantitative analysis, tissue sections were examined under a microscope, and evaluated for both staining intensity and percentage of VDR positive cells, with a previously described scoring method.[17,18] Positive cells in the four areas were counted using a 400 × objective, and the percentage of immunoreactive cells among endothelial cells in each field were calculated. Staining intensity was classified as follows: 0

(negative), 1 (weak), 2 (moderate), or 3 (strong). Figure 1 shows representative cases. The percentage of positive cells was scored as 0 (≤ 5%), 1(6 – 25%), 2 (26 – 50%), 3 (51 – 75%), and 4 (76 –100%). The staining intensity and percentage of stained cells were then multiplied to generate the staining index (SI) for each case, ranging from 0 to 12.

Figure 1. Representative cases showing varying degree of VDR staining index (a) negative (b) weak (c) moderate (d) strong. Scale of 10um is shown in (a)



Two physician who were blinded to the clinical information examined each sample. Whole scoring procedure were repeated three times and average value of SI was used. We evaluated the inter-rater reliability using intraclass correlation coefficients (ICCs) and the value was 0.868 which indicates excellent agreement.

Measurement of serum vitamin D level

Serum 25(OH)D (25-hydroxyvitamin D) levels were measured in all patients preoperatively using Diels Alder derivatization and ultrahigh-performance liquid chromatography-tandem mass spectrometry (Waters, Milford, MA, USA), which is the gold standard for 25(OH)D measurement. Calibration was performed with standard reference material 972 from the National Institute of Standards and Technology; the intra-assay and inter-assay coefficients of variation at 29 ng/mL were 4.0% and 7.7%, respectively. Concentration of vitamin D below 20.0 ng/mL was viewed as ‘deficient’ and concentration equal to or above 20.0 ng/mL as ‘non-deficient’. All the sampling was performed during daytime.

Evaluation of clinical features of CTS

Symptom severity was measured using the Disabilities of the Arm, Shoulder, and

Hand (DASH) questionnaire. DASH scores range from 0 to 100 and higher score indicates greater disability, and have been used for symptom severity and outcomes for CTS.[19-21] Electrophysiology exam was conducted in all patients before operation. We recorded median nerve motor conduction velocity and distal motor latency, which are suggested to be corresponding to neurophysiological severity of the disease.[23,24]

Statistical analysis

Results were reported as mean and standard deviation (SD) unless otherwise indicated. Staining index (SI) of VDR expression was correlated with serum vitamin D level, and clinical features such as age, body mass index (BMI), symptom duration, electrophysiologic variables (MCV and DML), and preoperative symptom severity (DASH). Pearson correlation coefficient was evaluated with variables. Variables with *P* values less than 0.1 by univariate analysis were included as independent variables in the multivariate analysis, which was performed using the stepwise elimination procedure. Goodness-of-fit was presented as adjusted R^2, which reflect the percentage of overall variability. All statistical tests were two-sided and *P*-values of less than 0.05 were considered significant. Software program SSPS (version 21.0 for windows, SPSS Inc., Chicago, TL, USA) was used.

Results

Patient clinical characteristics

The mean age was 58 years (SD 10 ; range, 40-83 years). There were 52 women and 2 men. Symptom duration averaged 10 months (SD 9 ; range, 6 to 48 months). Mean serum vitamin D level was 14.9 (SD 7.5 ; 5.9 - 38.2) ng/ml. Forty-two patients were vitamin D deficient (<20 ng/ml) while twelve were vitamin D non-deficient. (≥ 20 ng/ml). The mean preoperative DASH score was 39 (SD 21 ; range 3 to 79). The mean motor conduction velocity (MCV) was 53.3 m/s (SD 5.8 ; range, 36.6 - 66.1 m/s), and the mean distal motor latency was 5.1 ms (SD 5.1 ; range, 3.1 - 12.8 ms).

Immunohistrochemical analysis of VDR in the SSCT

Diverse expression of VDR was observed in endothelial vessels of SSCT. The mean staining index (SI) of VDR in endothelial cell of SSCT was 5.2 (SD, 3.1; range, 0.5 - 11.5).

Univariate analysis indicated that VDR expression significantly correlates with age, symptom duration, and distal motor latency (DML), but not with serum vitamin D

level, BMI, serum motor conduction velocity, and preoperative DASH scores (Figure 2). These variables and serum vitamin D level were analyzed for multivariate analysis, which showed that only DML was independently associated with VDR expression in endothelial cells of the SSCT (Table 1, adjusted $R^2 = 0.122$, $P = 0.012$,)

Figure 2 Scatter plot for clinical variables and VDR staining index. Trend line is shown only in statistically significant variable. (a) age (b) symptom duration (c) distal motor latency (DML) (d) serum vitamin D level

Table 1 Clinical variable correlation with staining index

Variable	Correlation coefficient	Univariate *P*-value	Multivariate p-value
Serum vitamin D level	0.258	0.062	
Age	0.272	**0.047**	
Symptom duration	0.344	**0.032**	
Body mass index	0.065	0.645	
MCV	-0.202	0.179	
DML	0.377	**0.010**	**0.012**
DASH score	0.066	0.651	

MCV, motor conduction velocity; DML, distal motor latency; DASH, Disabilities of the Arm, Shoulder, and Hand questionnaire

Boldface indicates statistical significance

Discussion

In this study we evaluated the level of VDR expression in endothelial cells of subsynovial connective tissue (SSCT) in patients with CTS and assessed its association with clinical features of CTS. We found that VDR exists in the endothelial cells of the SSCT, and VDR expression significantly correlates with age, symptom duration, and electrophysiologic severity of CTS in terms of distal motor latency (DML). These findings suggest that VDR expression might be associated with the disease progression, as older age, longer symptom duration and prolonged DML possibly all reflect chronicity of the disease.

The histologic findings of idiopathic CTS reveal a non-inflammatory fibrous connective tissue with edema, thickening of vessel walls, intimal hyperplasia, and thrombosis.[3,25] Fibrotic changes in the SSCT increase pressure of the carpal tunnel, followed by ischemic insult and subsequent vascular changes of SSCT. A study reported that immunoreactivities of eNOS, NF-kb, and TGF-b are significantly up-regulated in SSCT of CTS patients, supporting the hypothesis that oxidative stress in SSCT triggers cytokine production in fibroblast and endothelial cells and causes vascular hypertrophy and subsequent tissue fibrosis.[26] In addition, the tenosynovium from intermediate or late-phase of CTS patients are reported to exhibit substantially increased vascularity, vessel hypertrophy, and tenosynovial thickening.[27] These studies

imply that vascular endothelial cells of SSCT could mediate a role in the pathogenesis or progression of CTS.

The most abundant vitamin D metabolite in the circulation and tissue is 25-hydroxyvitamin D (25(OH)D), and the enzyme 25(OH)D-1α-hydroxylase catalyzes activation by hydroxylation of 25(OH)D to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) which is biological active form of vitamin D. Most effects of vitamin D are mediated by the binding of $1,25(OH)_2D$ to the vitamin D receptor (VDR), which promotes or inhibits transcription of vitamin D-responsive genes.[34]

Physiological actions of $1,25\ (OH)_2D$ in various systems, along with the detection of VDR in target cells, have indicated potential role of VDR and VDR ligands in inflammation, cancers and autoimmune diseases, and cardiovascular system. VDR is overexpressed or repressed in several histological types of cancer, demonstrating tissue-type variations in vitamin D signaling and amount of VDR and its capacity to bind to vitamin D are correlated with the antiproliferative and prodifferentiating effects of different types of cancer. [37-39] The expression of the VDR in cardiac myocytes and fibroblasts is upregulated following exposure to hypertrophic stimuli in vitro and in vivo hypertrophied hearts. [12]

The positive correlation between VDR and variables such as age, symptom duration and DML in the current study suggests that VDR related signaling pathway could play a part in the SSCT endothelial cell-mediated disease progression. Possible mechanism

might lie in tissue remodeling by elaborating new vessels as a regeneration process following progressive ischemia. As CTS progress with ischemic changes resulting in putative oxidative stressful environment in the carpal tunnel, VDR in endothelial cells may contribute to tissue remodeling by triggering angiogenesis.

In this study, VDR expression had a positive correlation with serum vitamin D level, although the correlation was not statistically significant (r = 0.258, P = 0.062). This result seems to contradict our previous notion that vitamin D plays a neuroprotective role and that hypovitaminosis D could be associated with the occurrence of CTS. It is possible that up-regulation of VDR in response to ischemic conditions of the SSCT might induce increased synthesis of circulating vitamin D, as 78% of the patients were vitamin D deficient in this study. Meanwhile, previous reports did not find a significant relationship between serum vitamin D concentration and VDR expression in other conditions. Bischoff-Ferrari et al. reported that they were not able to show a relationship between serum vitamin D and VDR expression in human muscle.[28] Also, Kinyamu et al. did not find a relationship between serum vitamin D level and mucosal VDR level in the intestine.[29] Further studies are necessary to find the relationship between serum vitamin D and the tissue VDR, and to determine whether vitamin D supplementation could be helpful for patients with CTS, by down-regulating VDR in endothelial cells and delaying the process of vascular hypertrophy and fibrosis.

We did not evaluate VDR in the median nerve and its surrounding perineural tissues due to the risk of nerve injury. VDR expression and its role in peripheral neuropathy

has not been lighted in detail up to this date. An animal study in rats reported VDR expression is increased in cytoplasm, nuclei and membranes of dorsal root ganglion neurons in diabetes mellitus.[30] Several previous reports focus on role of vitamin D and VDR complex in central nervous system. Studies showed staining for VDR within neurons and glial cells of human brain as well as 1α-hydroxylase staining in human neurons and glia.[31-33] A study involving multiple sclerosis reported increased VDR and 1α-hydroxylase mRNA expression in active brain lesions indicating a possible endogenous role for vitamin D in suppression of the disease.[34] Future studies on animal model of CTS may reveal the effect of vitamin D and VDR in the neural tissue.

There are several limitations to this study. First, all the included patients were with CTS who had open carpal tunnel release. Therefore, early stage patients are not included and the present study may not represent the general population with CTS. Furthermore, the ratio of men was low in this study. This was because women were more likely to have surgery than men, [35,36] and more men were excluded due to exclusion criteria. However, these may limit the generalizability of the findings. Second, evaluation of the VDR was cross-sectional, so the causal relationship between VDR and pathologic vascular changes of the SSCT cannot be determined. Third, VDR expression was not evaluated in a control group due to the limitations of obtaining the tissue in healthy individuals. Thus the role of VDR in the occurrence of CTS could not be determined.

In conclusion, this study found that VDR exists in the endothelial cells of the SSCT in

patients with CTS. The association of a higher VDR expression with age, symptom duration, and electrophysiologic severity of the disease suggest that VDR may be up-regulated and contribute to disease progression by angiogenesis. Further studies are necessary to confirm the role of VDR in patients with CTS, and to determine whether vitamin D supplementation could be helpful in the prevention or treatment of CTS.

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초록

배경 :

수근관 증후군의 병태생리로 활막하 결체 조직의 혈관분포상태 및 물리적 변화가 관련이 있다는 기존 연구들이 보고되고 있다. 최근 비타민 D의 근골격계에서의 역할 외에도 염증반응을 비롯하여, 암 및 심혈관계 질환, 그리고 신경보호 역할도 갖는다고 알려져있다.

방법 :

본 연구에서는 특발성 수근관 증후군으로 진단을 받고 관혈적 수근관 유리술을 시행하는 54명의 환자에서 활막하 결체 조직을 채취하여 혈관내벽세포의 비타민 D 수용체의 발현 정도를 면역조직화학법을 이용하여 정량화하였다. 정량화된 수용체 발현 수치와 체내 비타민 D 농도, 연령, BMI, 증상이환기간 등의 임상 지표와 운동전도속도 및 원위운동잠시로 표현되는 전기생리학적 지표와의 상관관계를 분석하였다.

결과 :

수근관 증후군 환자의 활막하 결체 조직에서 다양한 범위의 비타민 D 수용체 발현 정도가 관찰되었고 발현 정도와 연령, 증상 지속 기간, 원위부 운동신경 잠시와 통계적으로 유의미한 양의 상관관계가 관찰되었다.

결론 :

본 연구에서는 수근관 증후군 환자들의 활막하 결체 조직내 혈관내 세포벽에 비타민 D 수용체 발현 여부를 확인하였다. 또한 발현 정도가 높을수록 연령, 증상 지속 기간, 원위부 운동신경 잠시가 높아진다는 결과를 바탕으로 비타민 D 가 신생혈관을 유도하거나 혈관분포상태 변화를 유도하는 기전으로 수근관 증후군 진행에 영향을 미친다고 생각할 수 있다. 향후 추가 연구를 통해 비타민 D 가 수근관 증후군 병태 생리에서 갖는 역할을 확인하고 비타민 D 보충으로 수근관 증후군을 예방하거나 치료에 도움을 줄 수 있는지 확인해야한다.

주요어 : 비타민 D 수용체; 수근관증후군; 활막하 결체조직; 원위부 운동신경잠시;

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