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The Potential Role of Vitamin D Deficiency and Insufficiency Status in the Occurrence of Recurrent Aphthous Ulcer and Insidious Oral Candidiasis

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Abstract:

Objectives: To explore the potential relationship between Vitamin D status and idiopathic orofacial conditions including recurrent aphtous ulcer (RAU), burning mouth syndrome (BMS), orofacial pain (OFP) and dry mouth (DMo) because of endocrinologists' opinion that Calcitriol is a fat-soluble steroid hormone affecting most of systems.

Methods: The prospective clinical trial collected sixty-five comparative cases from Oral Pathology Specialty clinic in Nova Scotia, Canada. Cases were fitted into two groups based on Vitamin D levels. Each group was distributed into four subgroups of RAU, BMS, OFP, and DMo. Data were analyzed by the sign test of single proportions.

Results: Remarkable findings include, 100% complex type RAU with Vitamin D insufficiency (VDI) status healed rapidly after taking Vitamin D 1000 IU plus 500 mg Calcium (VDC) only and had no recurrence in one-year. Moreover, 100% idiopathic BMS with Vitamin D deficiency or insufficiency status have insidious oral candidiasis, accordingly the burning mouth symptom disappeared after two-week protocol of Clotrimazole lozenges and VDC treatment. The OFP participants with unilateral short condyle heads showed VDI status. Their orofacial pain subsided after taking VDC for one-month. Dry mouth group had no significant findings.

Conclusions: Vitamin D deficiency or insufficiency status may be one of underlying causes of idiopathic RAU (complex type) and insidious oral candidiasis (one type of idiopathic BMS). A further prospective study with a large database from multiple research centers is necessary.

Keywords: Vitamin D deficiency, Vitamin D insufficiency, Recurrent Aphthous Ulcer, Insidious Oral Candidiasis, Idiopathic Burning Mouth Syndrome

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Introduction

The prevalence of 25-Hydroxyvitamin D (Calcidiol) deficiency plus insufficiency in Canadian Adults was 20.4%, while the data will be over 50% if adding Vitamin D suboptimal status in [1]. The data came from the Canadian Multicentre Osteoporosis Study in 2011. Large clinical trials and meta-analyses have proved Vitamin D deficiency is associated with osteoporosis, fracture and muscular weakness, while retrospective researches indicated Vitamin D insufficiency is associated with malignancy, Diabetes Mellitus, Multiple Sclerosis and impaired immune response [2]. Endocrinologists and dermatologists believe 1, 25- Dihydroxyvitamin D (Calcitriol) is a fat-soluble steroid hormone affecting most of systems [3][4]. Is it possible that Vitamin D status are related to common idiopathic oral conditions, such as recurrent aphthous ulcer, burning mouth syndrome, orofacial pain and dry mouth? The purpose of this study is to explore the potential relationship.

Materials and Methods

Data source of Participants

Participants were selected from clinic patients of an Oral Pathology Specialty Clinic in Halifax who were referred by dentists in Nova Scotia

of Canada between February 1st, 2017 and October 30th, 2019. The Oral Pathology Specialty Clinic is held and managed by a Certified Oral Pathologist who practices exclusively under regulations and standards of Royal College of Dentists of Canada (RCDC), Provincial Dental Board of Nova Scotia (PDBNS), and Faculty of Dentistry of Dalhousie University.

Definitive diagnoses for common idiopathic oral conditions were obeyed to diagnostic criteria indicated in Neville's Oral and Maxillofacial Pathology 4th edition. Participants' demographic information and medical history were collected from reliable resources such as health care cards, pharmacy medication lists and laboratory examination reports. All participants were adult Canadians and lived in Nova Scotia, Canada where foods and drinks haven't been fortified by Vitamin D ingredient yet.

Inclusion

1.Participants had one of following oral conditions:

a.Idiopathic recurrent aphthous ulcer (RAU), complex type

b.Idiopathic burning mouth syndrome (BMS)

c.Idiopathic orofacial pain (OFP)

d.Idiopathic dry mouth (DMo)

2.Participants didn't take Vitamin D supplement or supplements containing Vitamin D components.

3.Participants have non-known medical condition.

4.Or participants have one or more medical conditions that doesn't affect the natural course of selected oral conditions:

a.Controlled gastroesophageal reflux disease (cGERD)

b.Controlled hypothyroidism (cHTD)

c.Controlled diabetes mellitus (cDM)

d.Controlled hypertension (cHTN)

Exclusion

1.Participants had selected oral conditions with following situations:

a.RAU complex type as a sign of systemic conditions, such as Behcet's disease, Sweet's disease, Lupus, Reiter's disease, inflammatory bowel diseases, AIDS and psoriasis.

b.BMS as a sign of systemic or local illness, such as vitamin B12 deficiency, hyperkalemia, multiple sclerosis, fibromyalgia, and visible lesions of oral candidiasis.

c.OFP caused by myalgia, arthralgia, neuralgia or atypical odontalgia, and no orofacial traumatic history.

d.DMo caused by oncotherapy, sialadenosis, sialadenitis, Sjogren's syndrome and uncontrolled endocrinopathy.

2.Participants had one of following situations:

a.Taking Vitamin D supplement or supplements containing Vitamin D components.

b.Having a medical condition that is not mentioned in inclusion items.

Prospective clinical trial

Patients who matched inclusion and exclusion requirements clinically were chosen to be potential participants. They were investigated by objective methods. Qualified participants were selected when potential participants' investigation results matched all requirements of inclusion and exclusion. After treatments, their overall situations were assessed, documented and ready for the statistical analysis. The whole process was conducted by the certified oral pathologist (YG) and was assisted by a research assistant (TB) and a clinical assistant (Mr. JW).

1.Potential participants with BMS needed smear testing. Results were reported by the Oral Pathology Biopsy Service (OBS) of Faculty of Dentistry of Dalhousie University.

2.Potential participants with OFP needed Panoramic imaginings, which were analyzed by the certified oral pathologist (YG).

3.All potential participants needed laboratory examinations. Reports were issued by the Nova Scotia Health Authority's Pathology and Laboratory Medicine. Items included routine hematology panel, fasting glucose (Glucose AC), Calcium, Potassium, Iron, Calcidiol (Vitamin D), B12 and B9. In addition, Hemoglobin A1c (HgA1c), Free thyroxin (T4) and Thyroid stimulating hormone (TSH) will be checked if potential participants have related medical conditions.

4.Group I: Qualified participants who had Vitamin D deficiency (Calcidiol < 25 nmol/L), insufficiency (Calcidiol 25-50 nmol/L) or suboptimal status (Calcidiol 50-75 nmol/L) were required to take Vitamin D3 1000 IU plus 500 mg Calcium supplement (VDC) once a day for six-month. Other treatment protocols were conducted if something else were confirmed.

5.Group II: Qualified participants who had Vitamin D optimal status (Calcidiol 75-125 nmol/L) [7] were treated based on clinical findings and diagnoses.

Data and Statistical method

We screened vitamin D levels to 72 potential participants. Only 56 qualified participants were collected regarding the standard of inclusion and exclusion. They were fitted into two groups based on Vitamin D levels. Each group was distributed into four subgroups of idiopathic RAU (iRAU), idiopathic BMS (iBMS), idiopathic OFP (iOFP), and idiopathic DMo (iDMo). For the comparison and contrast purposes, subgroups had similar health backgrounds. **Please see details in Table 1 and 2.** Data were analyzed by the sign test of single proportions.

Result

Ten qualified participants with complex type of RAU were in iRAU subgroup. The complex type of RAU showed the typical clinical feature "one healed and another developed". Five of them had hematologic findings including macrocytic anemia, thrombocytopenia, leukocytosis, leukopenia and iron deficiency anemia, but their Vitamin D levels were in the optimal status. Another five participants only had Vitamin D insufficiency (VDI) status without hematologic abnormalities. Please see details in table 2 and 3. The remarkable finding is the 100% complex type RAU in Group I healed rapidly in one-week and had no recurrence in one-year after taking VDC only. We only followed up them for one-year. **Please see Figures 1.**

	Group I: Vitamin D deficiency (VDD), insufficiency (VDI) & suboptimal status (VDS)	Group II: Vitamin D optimal status (VDO)	Total
Number of participants	28 (2 VDD; 23 VDI; 3 VDS)	28	56
Gender (Female: Male)	16:12	27:1	43:13
Age: range (average)	21 y/o-77 y/o (50.27 y/o)	25 y/o-84 y/o (52.67 y/o)	
Subgroup 1: iRAU	5 (VDI)	5	10
Subgroup 2: iBMS	7 (1 VDD; 6 VDI)	7	14
Subgroup 3: iOFP	5 (1 VDD; 3 VDI; 1 VDS)	5	10
Subgroup 4: iDMo	11 (9 VDI; 2 VDS)	11	22

Table 1. Demographic data

Note: idiopathic recurrent aphthous ulcer (iRAU); idiopathic burning mouth syndrome (iBMS); idiopathic orofacial pain (iOFP); idiopathic dry mouth (iDMo); Vitamin D deficiency (VDD); Vitamin D insufficiency (VDI); Vitamin D suboptimal status (VDS); Vitamin D optimal status (VDO); Years-old (y/o).

	Group I	Other positive findings	Group II	Other positive findings	Total	Ratio	Sign test difference
iRAU	5	Non	5	Hematologic findings	10	5:5	Yes
iBMS	7	Fungal hyphae positive	7	Non	14	7:7	Yes
iOFP	2	Unilateral condyle head shortness	2	Short lingual frenulum	4	2:2	Yes
	3	Head Forward Posture habit	3	Head Forward Posture habit	6	3:3	No
iDMo	7	Side effects of drugs, or substance abuse, or less-water intake	9	Side effects of drugs, or substance abuse, or less-water intake	16	7:9	No
	4	Pre- Diabetes Mellitus	2	Pre- Diabetes Mellitus	6	4:2	No
Total	28		28		56	28:28	

Table 2. Vitamin D status and other positive findings

Note: idiopathic recurrent aphthous ulcer (iRAU); idiopathic burning mouth syndrome (iBMS); idiopathic orofacial pain (iOFP); idiopathic dry mouth (iDMo); Group I: Vitamin D deficiency (VDD), Vitamin D insufficiency (VDI) and Vitamin D suboptimal status (VDS); Group II: Vitamin D optimal status (VDO).

	Group I (VDD or VDI)	Group II (VDO)	Total	Treatment and result
Subgroup 1: iRAU	Healthy: 5 cases Vitamin D levels: 40.4; 39.9; 43.0; 29.4 and 26.5 nmol/L Age: 21-34 y/o (average 26.4 y/o) Female: Male = 2:3 Negative finding in hematologic panel.	Healthy: 3 cases cHTN and cGERD: 1 case cHTD: 1 case Vitamin D levels: over 75 nmol/L Age: 26-75 y/o (average 45.4 y/o) Female: Male = 5:0 Hematologic findings: macrocytic anemia; thrombocytopenia; leukocytosis; leukopenia; Iron deficiency anemia.	10	Group I: Taking Vitamin D 1000 IU and 500mg Calcium for six-month; Rapidly healed in one week and no recurrence in one-year. Group II: Variable treatment protocols based on findings.
Subgroup 2: iBMS	Healthy: 2 cases cHTN and cDM: 1 case cGERD and cDM: 1 case cGERD: 1 case cHTN: 1 case cHTN, cDM and cGERD: 1 case Vitamin D levels: **43.5; 18.8; 35.7; 37.9; 40.0; 39.8; and 42.5 nmol/L** Age: 47-77 y/o (average 62.2 y/o) Female: Male = 4:3 Fungal hyphae positive	Healthy: 3 cases cHTD: 2 cases cHTN: 1 case cGERD and cHTD: 1 case Vitamin D levels: over 75 nmol/L Age: 31-84 y/o (average 56.57 y/o) Female: Male = 7:0 Fungal hyphae negative	14	Group I: Taking Vitamin D 1000 IU and 500mg Calcium for six-month and Clotrimazole lozenges for two-week; Burning sensation disappeared in two weeks and no relapse. Group II: Variable treatment protocols based on findings.
Subgroup 3: iOFP	Healthy: 1 case cHTN: 1 case Vitamin D levels: **44.7 and 30.5 nmol/L** Age: 36-62 y/o (average 49 y/o) Female: Male = 1:1 Unilateral condyle head shortness	Healthy: 2 cases Vitamin D levels: over 75 nmol/L Age: 53-75 (average 64 y/o) Female: Male = 2:0 Symmetric condyle heads, but short lingual frenulum	4	Group I: Taking Vitamin D 1000 IU and 500mg Calcium for six-month; Unilateral orofacial pain subsided in one month and no relapse. Group II: Frenectomy, orofacial pain subsided after one-month.

Table 3. Comparison of demographic data, positive findings, medical history and treatments

Note: idiopathic recurrent aphthous ulcer (iRAU); idiopathic burning mouth syndrome (iBMS); idiopathic orofacial pain (iOFP); Vitamin D deficiency (VDD); Vitamin D insufficiency (VDI); Vitamin D optimal status (VDO); Years-old (y/o); Controlled gastroesophageal reflux disease (cGERD); Controlled hypothyroidism (cHTD); Controlled diabetes mellitus (cDM); Controlled hypertension (cHTN).

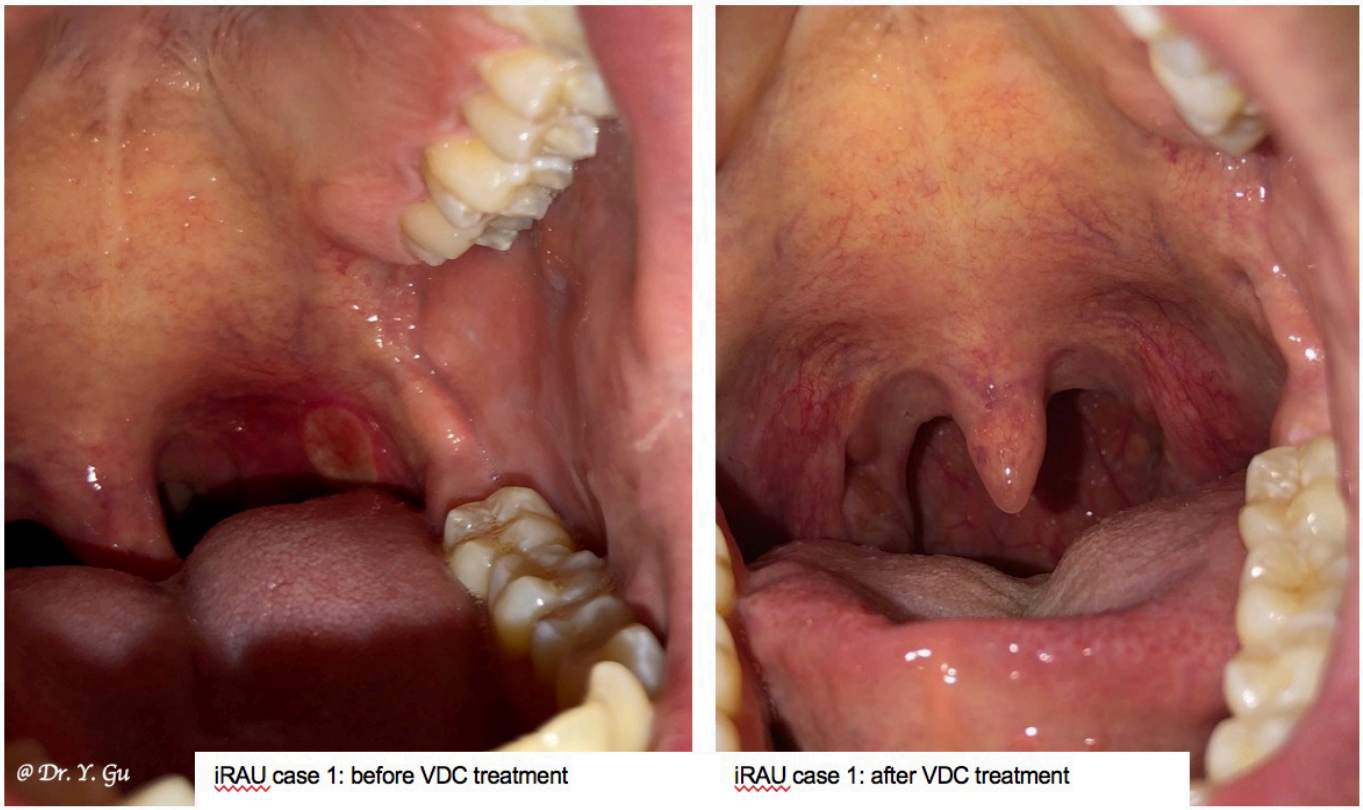


Figure 1: One case in iRAU subgroup of Group I (VDD or VDI)

Note: iRAU: idiopathic recurrent aphthous ulcer; VDD: Vitamin D deficiency status; VDI: Vitamin D insufficiency status; VDC: Vitamin D 1000 IU plus Calcium 500 mg per day treatment plan.

Fourteen participants were in iBMS subgroup. Seven of them with positive fungal hyphae were found, one in vitamin D deficiency (VDD) status and six in VDI status. Another seven cases with Vitamin D optimal (VDO) status had negative findings clinically and systemically. **Please see details in Table 2 and 3.** The significant finding is 100% idiopathic BMS with VDD or VDI status have insidious oral candidiasis, which only had burning mouth symptom, but didn't show common clinical appearances of oral candidiasis and didn't have systemic and local risks related to oral fungal infection. Their burning mouth symptom completely disappeared after two-week protocol of Clotrimazole lozenges and VDC, moreover, no relapse. **Please see Figures 2.**

Ten qualified participants were selected into iOFP subgroup. Three of six participants who had habits of head forward posture showed VDO status. Two participants with VDI status were only found to have unilateral condyle head shortness and four-year history of orofacial pain prominently on the same side, while another two cases with VDO status were only found to have short lingual frenulum. Please see details in Table 2 and 3. The remarkable finding is OFP participants with unilateral short condyle heads showed VDI status. Their orofacial pain subsided significantly after taking VDC for one month, furthermore, no relapse. **Please see Figure 3**

Twenty-two participants were collected in iDMo subgroup. All of them had same underlying causes of pre-DM (higher levels of Glucose AC), substance abuse (smoking, alcohol, coffee and cannabis), side effects of drugs (antidepressants, diuretics and antihistamine) or drinking less water. 50% of participants presented with VDO status. **Please see details in Table 2.** There was no significant difference in this subgroup.

Discussion

Calcitriol, which is the hormone of Vitamin D, is converted from 7-Dehydrocholesterol within epidermis through three steps: UVB 290-315 nm on epidermis, 1-alfa-hydroxylase (CYP27b1) in proximal tubule cells of kidney and 25-Hydroxylase (CYP2R1) in liver cells. However, experimental researches found the CYP27b1 [5] exists from epithelium [6] to endothelium [7] and expresses from brain [8] to immune system [9]. Vitamin D may affect keratinocyte proliferation, endothelium repair, neuroinflammation and T cell function. Therefore, we shall broaden our vision that bone and intestine are not only organs relying on Vitamin D. **Please see Illustration 1.**

The optimal status of Calcidiol, which is the pre-hormone and the measurable Vitamin D, is 75 nmol/L, equal to 3000 IU [2]. We can obtain 1000 IU Calcidiol if our 25% skin (arms and legs) without sunscreen or clothing is exposed to sunshine (UVB 290-320 nm) for 4 minutes [2]. However, the required power of sunshine can be achieved in the middle of summer before 10:00am and after 3:00pm in the place of latitude 35 degree between north and south. In addition, the sunshine day shall not have cloud and air pollution [2] [10]. The latitude of Canadian large cites is between north 44 and 54 degrees. It is not surprised 50% Canadian adults' Vitamin D level below suboptimal status. Please see Illustration 1.

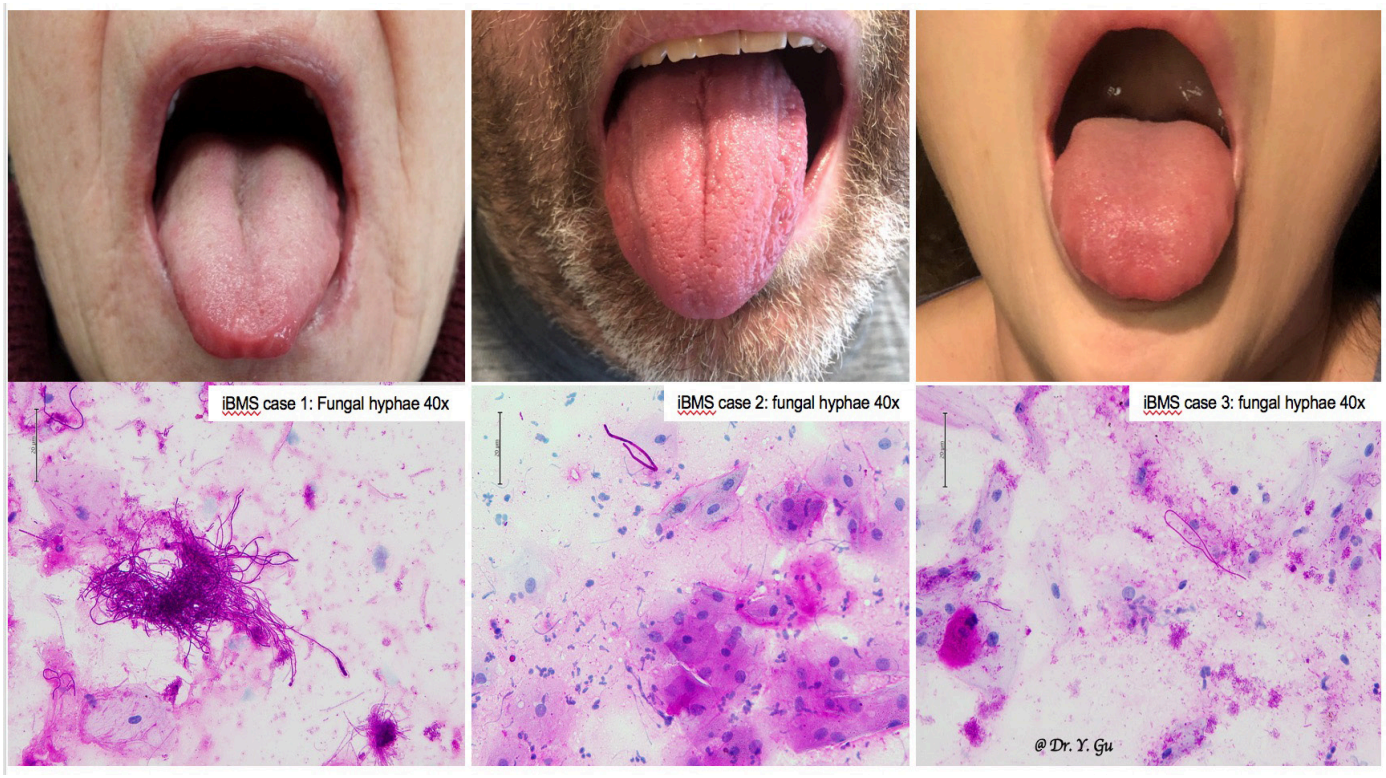


Figure 2: Three cases in iBMS subgroup of Group I (VDD or VDI)
Note: iBMS: idiopathic burning mouth syndrome; VDD: Vitamin D deficiency status; VDI: Vitamin D insufficiency status.

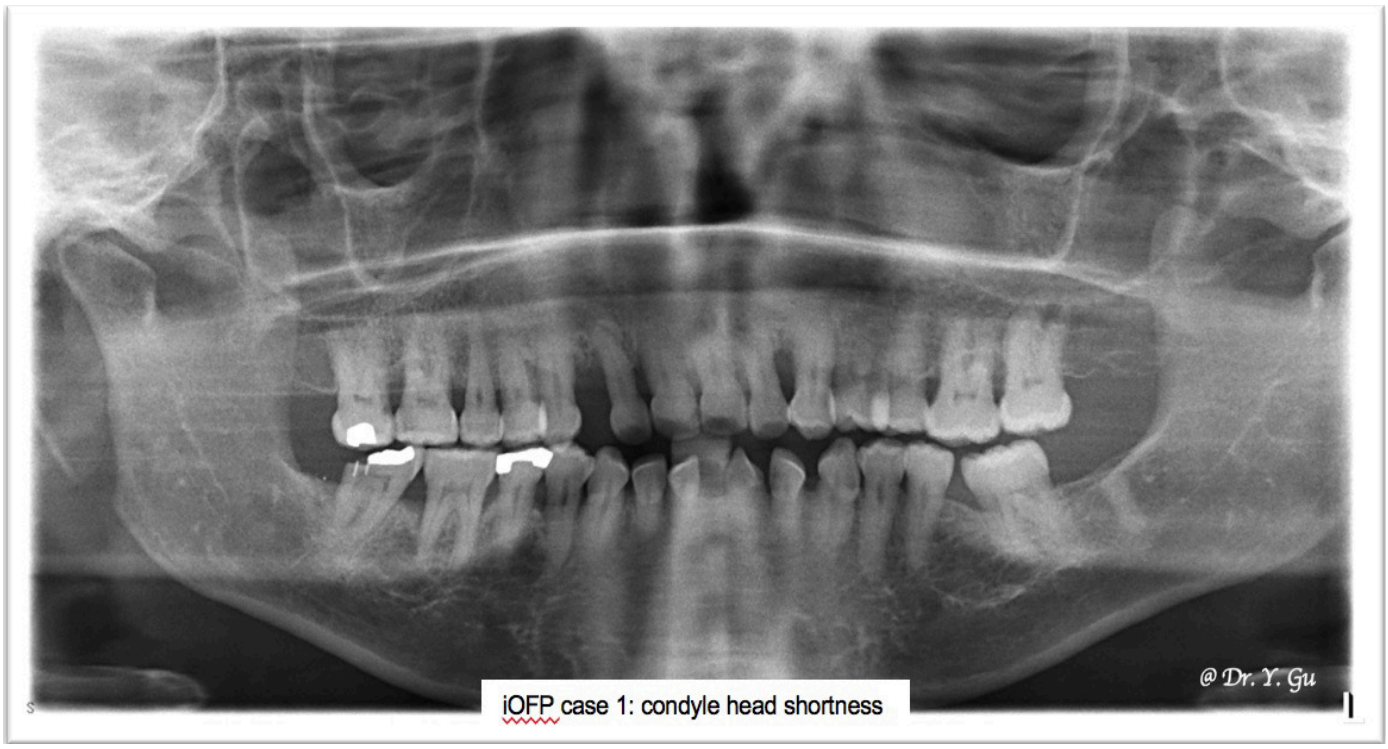
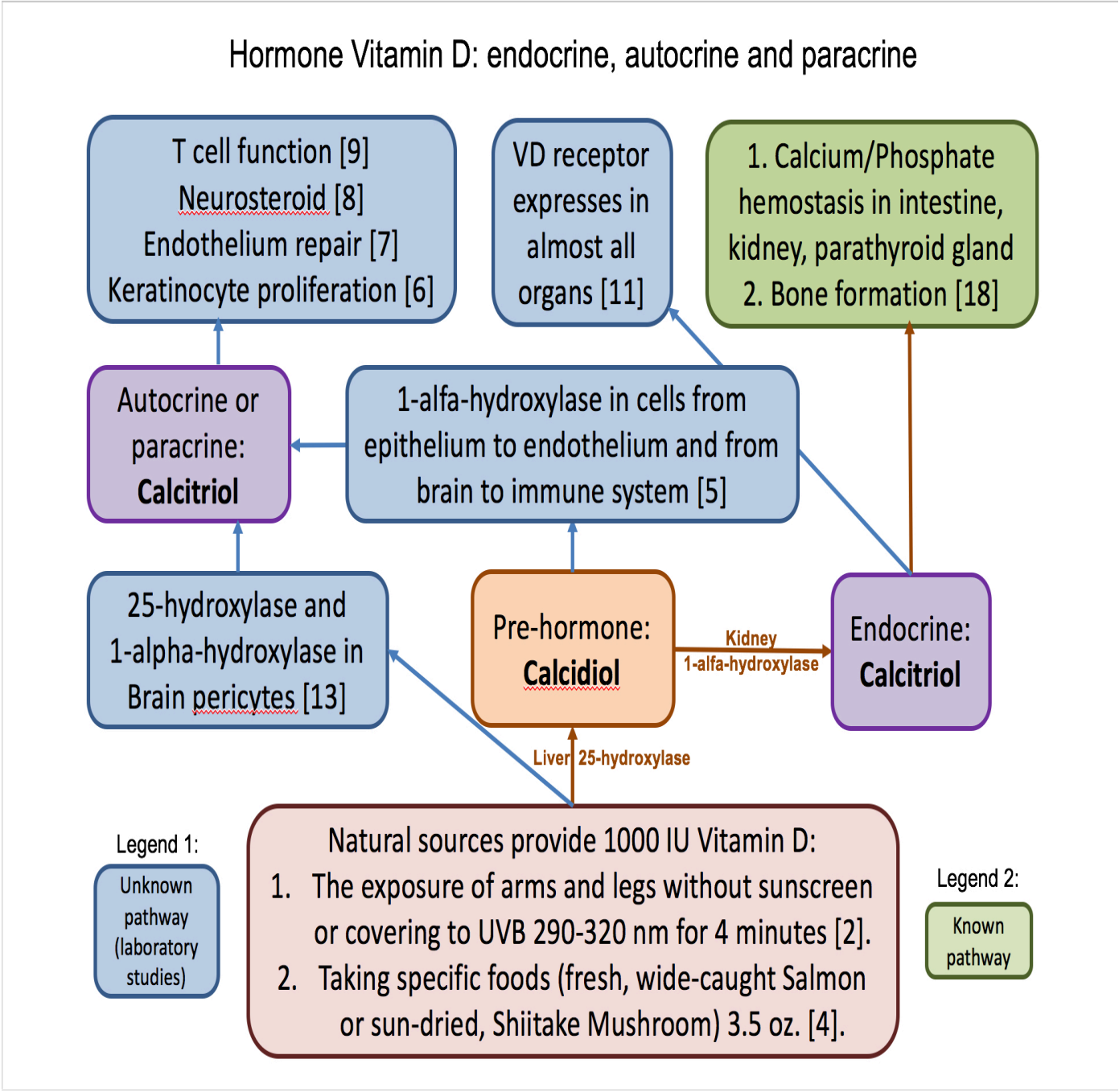


Figure 3: One case in iOFP subgroup of Group I (VDD or VDI)
Note: iOFP: idiopathic orofacial pain; VDD: Vitamin D deficiency status; VDI: Vitamin D insufficiency status.



Note: If we want to obtain 1000 IU Calcidiol from natural sources, our arms and legs without sunscreen or clothing shall be exposed to sunshine (UVB 290-320 nm) for 4 minutes [2] or we shall take fresh, wide-caught Salmon and sun-dried, Shiitake Mushroom for 3.5 oz [4]. **Calcitriol** is converted from Cholecalciferol by 1-alfa-hydroxylase in kidney and 25-Hydroxylase in liver. The known endocrine pathway is calcium and phosphate homeostasis in kidney, intestine and parathyroid glands. In addition, bone formation is relied on Vitamin D as well [18]. Laboratory studies proved Vitamin D receptors expressed in almost all organs [11] and two enzymes exist in many cells [5] [13]. Vitamin D may have autocrine and paracrine capacity that works on keratinocyte proliferation, endothelium repair, neuroinflammation (neurosteroid-like effect) and T cell function [6][7][8][9].

Fresh, wide-caught Salmon and sun-dried, Shiitake Mushroom for 3.5 oz can provide around 1000 IU Calcidiol. Other foods, such as canned Sardine, Mackerel and Tuna for 3.5 oz can provide around 300 IU Calcidiol [4]. All of them are not common foods in our diet. In addition, the half-life span of Cholecalciferol is two days if it comes from diet, while it is 60 days if coming from skin [2]. Therefore, nature foods can't be the main source of Vitamin D. **Please see Illustration 1.**

Vitamin D receptor (VDR) is a nuclear receptor highly expressed in calcium-homeostasis organs of intestine, bone, kidney and parathyroid glands. However, VDR tissue gene database reported VDRs express in almost all organs, and higher confidence areas include peripheral blood, placenta, lens epithelium, prostate gland epithelium and parathyroid glands [11]. VDRs link to ligands of Calcitriol or Lithocholic acid and then conducts duel functions as an endocrine receptor and a metabolic sensor [12]. Brain pericytes express VDR, 1-alfa-hydroxylase and 25-Hydroxylase together in vitro [13]. It could be a good evidence of Vitamin D as a hormone conducts paracrine and autocrine function as well. **Please see Illustration 1.**

The etiology of Recurrent Aphthous Ulcer (RAU) is unclear, but the occurrence is related to multiple factors, such as hematologic abnormality, malnutrition and endocrinopathy. The histopathological feature of RAU is non-specific inflammation. My hypothesis is ulcers are the consequence of focal ischemic necrosis due to transient micro-thrombosis within small arteries and then following with tissue-damage-mediated inflammation. Vitamin D stabilizes the quiescent endothelium, modulates certain stages of endothelial activation, and is involved in the repair of the damaged endothelium in vitro and in vivo [7]. Is it possible that Vitamin D insufficiency increases the risk of micro-thrombosis? In our study the sole abnormality in RAU subgroup were VDI status. After receiving VDC treatment, the complex type of RAU healed rapidly and didn't recur in one year. Vitamin D insufficiency shall be added in multiple factors that are related to RAU occurrence.

An experimental study proved that the requirement of Candida Albicans yeasts transferring to hyphae (pathogenicity form) is the status of 370C, PH 7, 5% CO_2, serum and starvation [14]. This is a common status of our oral cavity. My hypothesis is fungal hyphae and spores usually sleep together in oral cavity. Candida hyphae invade epithelium in two ways: endocytosis by epithelial cells and degradation of desmosomes by proteolysis via the secretion of aspartyl proteinases [15]. It is understandable that burning sensation shall be the first sign of fungal hyphae invasion. Vitamin D deficiency or insufficiency significantly promoted oral keratinocyte proliferation in vivo and in vitro [6]. Therefore, patients with VDD or VDI status have active oral epithelial proliferation, which provide a good opportunity for fungal hyphae invasion. In our study, fungal hyphae were found only in participants with VDD and VDI status who had burning mouth symptoms, but zero clinical appearance of oral candidiasis. Vitamin D analog significantly increase gingival epithelium to produce human cathelicidin LL-37 20-30% in vitro [16]. In addition, Vitamin D enhances the production of IL-8 in neutrophils and IL-1 beta in macrophage in response to Lipopolysaccharide (LPS) in vivo [17]. It is not surprised that after two-week protocol of Clotrimazole lozenges and VDC treatments their burning mouth symptom completely disappeared and had no recurrence. We named the idiopathic burning mouth syndrome (iBMS) with positive findings of fungal hyphae as insidious oral candidiasis that is related to Vitamin D deficiency or insufficiency status.

Vitamin D promotes bone formation [18]. Our research found Vitamin D insufficiency is the only abnormality for patients who lost the normal height of unilateral condyle heads. The consequence of unilateral condyle head shortness is the coronoid process on the same side protruded into the infratemporal fascial space, which protects contents of infratemporal fossa including maxillary artery, pterygoid venous plexus and mandibular nerve (CN V3). It is understandable that patients had consistent orofacial pain on the same side. After one-month treatment of taking VDC their orofacial pain subsided significantly. The VDC treatment successfully stopped the further bone loss of condyle heads. It is necessary to draw attention to the situation of that unilateral idiopathic orofacial pain (iOFP) could be caused by unilateral condyle head shortness due to Vitamin D insufficiency in adults.

Our study did found the potential relationship between Vitamin D deficiency or insufficiency status and the occurrence of idiopathic RAU, BMS, and OFP. However, a further prospective study with a large database from multiple research centers is expected.

This prospective clinical trial may reach two hypotheses:

1.Vitamin D deficiency or insufficiency status is one of underlying causes of idiopathic recurrent aphthous ulcer complex type.

2.Vitamin D deficiency or insufficiency status is one of underlying causes of idiopathic burning mouth syndrome. It is a new subtype of oral candidiasis, insidious oral candidiasis, that doesn't show oral white pseudomembrane, oral erythematous patches, oral white plaque or granules, but only has mouth burning sensation.

Conflict of Interest

Authors disclose any commercial association. This study is only based on our research interesting and no funding support.

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