

## Evaluation the Relationship Between Serum and Salivary Levels of 25(OH)Vit.D with Type II Diabetes in Newly Diagnosed Diabetics

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### Abstract

**Introduction:** The International Diabetes Federation (IDF) Announces 415 million people around the world are suffering from diabetes. There is a high proportion of UDM (undiagnosed diabetes) at the level of the world and particularly in developing countries. The number of people with UDM in Iran in 2015 are 2197.96 per 1000. Vitamin D<sub>3</sub> deficiency is associated with increased risk of type 2 diabetes and for a long time, been recognized as a risk factor for glucose intolerance. Salivary composition, as the mirror of oral health, its use as a diagnostic tool is increasing and diabetes is also can be effective on the flow rate of saliva and its compounds. Analysis of saliva can be used as part of the evaluation of endocrine function.

**Material and Methods:** In this case-control study in 2016 in Hamadan, we selected 57 newly diagnosed patients with type 2 diabetes mellitus with mean aged 47.73 years and 57 healthy controls with mean aged 45.36 years. By using Spitting method, 5ml of completely unstimulated saliva samples were collected from diabetic patients and control subjects. The serum and saliva 25(OH)Vit.D concentrations were measured by ELISA. The results are analyzed by SPSS 16.

**Results:** Significant difference was found in serum concentrations between the two groups ( $p < 0.001$ ). But in unstimulated whole salivary 1, 25(OH) 2D<sub>3</sub> concentrations between the two groups, difference was not significant and the relationship, was reversed. There was a significant correlation ( $P = 0.013$ ) between serum and saliva 1, 25(OH) 2D<sub>3</sub> concentrations in the control group. In other words, the correlation was approximately 0.33. Correlation between serum and saliva 1, 25(OH) 2D<sub>3</sub> concentrations in case group was not significant. Serum levels of 1, 25(OH) 2D<sub>3</sub> in 21.1% of control group, showed the inadequate level (Vit.D<sub>3</sub> = 20-29ng/ml) and in the case group, showed the critical situation and overall 91.2% of the newly diagnosed diabetics, suffered from lack of vitamin D<sub>3</sub>. According to the salivary levels of 1, 25(OH) 2D<sub>3</sub>, in general, a total of 58% of the case group, have deficiency of vitamin D<sub>3</sub>.

**Conclusion:** The results was confirmed vitamin D<sub>3</sub> deficiency in participating in the study population (both case and control). The findings showed that there is lower concentration of 1, 25(OH) 2D<sub>3</sub> in serum and after that in saliva in diabetic patients that newly diagnosed. Saliva would play a helpful diagnostic role in the early detection, the monitoring and progression of diabetes, but still serum is the better method for detecting vit.D<sub>3</sub> levels and more research needs to be done on saliva for detecting Vit.D<sub>3</sub> concentrations.

**Keywords:** Newly diagnosed diabetes, vitamin D<sub>3</sub> deficiency, saliva and serum

## 1. Introduction

The prevalence of diabetes in the world, is rapidly increasing. 415 million people (one out of every 11 people adult) have diabetes. There is the number of people with diabetes in 2015, 215.2 million in men and 199.5 million in women. that in 2040, increased to 328.4 million in men and 313.3 million in women and one of the two adults with diabetes is undiagnosed (Atlas, 2015b). There is a high proportion of undiagnosed diabetes (174/8 million) especially in developing countries in the world (Rahimi et al., 2016). By 2015, totaling 6.4 million (43.8%) have diabetes in Iran ("International Diabetes Federation - Search," 2017). Also in Iran, 7.7% of adults between the ages of 64-25 years (2 million) have diabetes, that half of them are undiagnosed (Gu et al., 2003). According to the International Diabetes Federation estimation in 2015, the number of people with undiagnosed diabetes (20-79 years) in Iran is 2197.96 in 1000 (Atlas, 2015b). In a study of over 2.7 million adults in Iran, about half of the cases were newly diagnosed diabetic (Esteghamati et al., 2009). In recent decades a large number of non-skeletal diseases with vitamin D<sub>3</sub> deficiency, including type 2 diabetes have been reported (Zittermann, 2006). Vitamin D<sub>3</sub> plays a major role in maintaining normal glucose homeostasis and its deficiency is associated with increased risk of type 2 diabetes (Danescu, Levy, & Levy, 2009; Pittas, Lau, Hu, & Dawson-Hughes, 2007). Vitamin D<sub>3</sub> deficiency, caused by the loss or partial resistance to it, is known as the risk factor for glucose intolerance in a long time (Boucher, 1998; Zittermann et al., 2003). Daniel mouse (2015) reported that 25 (OH) D deficiency could be implicated in the pathogenesis of type 2 diabetes and the exact mechanism still is unclear. High Body mass index (BMI) and less physical activity (Known risk factors for type 2 diabetes) is associated with deficiency of 25 (OH) D And 33% of people with diabetes, newly diagnosed cases of diabetes (Mauss, Jarczok, Hoffmann, Thomas, & Fischer, 2015). Lesser amounts of vitamin D<sub>3</sub> in newly diagnosed diabetic patients with type 2 diabetes in a study in New Zealand, was observed (Scragg et al., 1995). Lack of vitamin D<sub>3</sub> depending on the level of deficiency, may affect glucose homeostasis, insulin secretion and insulin resistance (J Boucher, 2011). The average level of vitamin D<sub>3</sub> in patients with type 2 diabetes generally is lower than healthy individuals (Rahimi et al., 2016). Administration of vitamin D<sub>3</sub> supplementation (once a week) for 8 weeks at dose 50000IU in patients with type 2 diabetes, Can improve the inadequate levels of vitamin D<sub>3</sub> to be effective, improve blood sugar control index and increase insulin sensitivity (Baziar et al., 2014; talaei, mohamadi kelishadi, & adgi, 2011). There are 1 billion people with (30-87%) deficiency or insufficiency of vitamin D<sub>3</sub> around the World (Makariou, Liberopoulos, Elisaf, & Challa, 2011; Mauss et al., 2015). The maximum amount of vitamin D<sub>3</sub> deficiency is from the Middle East. The cause of the lack of 25(OH) D levels Less than 15 ng / ml in the Middle East (72.8%) that amount was much lower (83.9% in women and 48.5% in men) is related to the culture and religious activities that lead to less sun exposure in women compared to men. Nursing home residents (60%) and hospitalized patients (57%) in the United States of America had vitamin D<sub>3</sub> deficiency (Tangpricha & Khazai, 2010). The trend of the prevalence of vitamin D<sub>3</sub> deficiencies in Iran is on the rise (Saeidinia et al., 2013). In the urban population living in Tehran, serum vitamin D<sub>3</sub> plays a significant role in cardiovascular disease (Hosseiniapanah et al., 2011). The latest criteria for assessing the extent of the deficiency of vitamin D<sub>3</sub> Is considered severe deficiency (<10ng/ml), Moderate deficiency (10-19.9ng/ml), Insufficiency (20-29.9ng/ml) and normal ( $\geq$  30ng/ml) .Vitamin D<sub>3</sub> deficiency screening is not recommended for healthy adults, while, at present, according to the Endocrine Society screening guidelines can be used for people at risk for type 2 diabetes (Mauss et al., 2015). Salivary fluid, such as serum or plasma as unique and complex at the same time the body is considered (Krishna, Ashalatha, Baghirath, Kanth, & Malathi, 2010). The use of saliva as a mirror of oral health as a diagnostic method is on the rise. Salivary flow rate and composition in patients with type 2 diabetes, affected by diabetes, salivary flow rate and composition is affected by diabetes in patients with type 2 diabetes and analysis of saliva can applied Endocrinology as part of the performance evaluation and Recently, whole saliva and related compounds is considered, as a new tool in the hormone testing (Carda, Mosquera-Lloreda, Salom, Gomez de Ferraris, & Peydró, 2006; Greabu et al., 2009; Higashi, Hijikuro, Yamagata, & Ogawa, 2013). Vitamin D<sub>3</sub> is found in saliva and the average is 434 pg/ml, the values fluctuate throughout the day and the quantity of vitamin D<sub>3</sub> may be related to food and ethnic origin (Fairney & Saphier, 1987). Due to the high incidence of deficiency of vitamin D<sub>3</sub> in Iran and the Middle East region with the highest prevalence of deficiencies in the world, As well as the prevalence of 5.4 million people with DM in Iran (Atlas, 2015a; Tangpricha & Khazai, 2010), Close relationship between deficiency of vitamin D<sub>3</sub> with diabetes, and the importance of assessing levels of vitamin D<sub>3</sub> in this patients to prevent and reduce complications associated with vitamin D<sub>3</sub> deficiency, this study was designed. Aimed to evaluate levels of salivary and serum 25 (OH) D in patients with newly diagnosed type 2 diabetes and its relation to diabetes, this study was designed in Hamedan regarding included in the common areas row of the deficiency of vitamin D<sub>3</sub> in Iran. Also, other objectives of this review was compare the salivary levels of vitamin D<sub>3</sub> with serum levels of it, to verify the measurement accuracy through saliva, and replace this method by measuring the serum. Having in mind the benefits with the measurement of 1, 25 (OH) 2D<sub>3</sub> in saliva, Including the speed and ease of doing it, Being a low-cost, As well as being a non-

invasive and non-stress method, to evaluate the levels of vitamin D3 with a rapid, cheap and without stress and anxiety method for diabetic patient, and in order to find the relationship between the level of vitamin deficiency and diabetes-related complications, in each patient, this study was designed.

## 2. Materials and Methods

In this case control study, 57 patients with newly diagnosed type 2 diabetes (in accordance with the standards of the Diabetes Association of America "ADA") (Association, 2014) were selected by the physician endocrinologist with check FBS and HbA1C (Table 2). Immediately after the confirmation of the diagnosis and before receiving any treatment of anti-diabetic and after measurement of height and weight and calculate BMI (body mass index) using the formula  $\text{Kg/m}^2$  (weight/height<sup>2</sup>), a sampling of the saliva of these people was conducted. Sampling of 57 persons healthy saliva of healthy patients as partners during the past three months have no history of any systemic diseases such as diabetes or taking medications, calcium and vitamin D<sub>3</sub> supplements and were smoking. Criteria for inclusion include the confirmation of the diagnosis of type 2 diabetes cases by specialist physicians, lack of receiving treatment for disease control before proceeding to sampling, the desire to collaborate in research and the completion of the questionnaire. Exclusion criteria included lack of desire to participate in the study, have any systemic diseases including liver disease, chronic kidney disease or any creatinine levels outside the normal range of 0.6-2.1 mg/dl, More or less than normal amount of calcium (9-11mg/dl), Malignancy, pregnancy or breastfeeding, taking any medication like calcitonin, bisphosphonates, steroids, supplements of calcium and vitamin D<sub>3</sub> as well as alcohol and cigarettes in the last 3 months And BMI greater than 40 Kg/m<sup>2</sup> (Obesity). To check the status BMI and obesity, weight was measured using a special scale. To measure the height, the tape was used standing, one without shoes and with a touch of heel and thigh and scapula with the wall. Collect saliva samples was performed using Spitting (Greabu et al., 2009). In addition, to collect samples of unstimulated, so ensure that people refrain from eating and drinking or any oral stimulation (e.g., chewing gum) for 90 minutes prior to sample collection for 90 minutes prior to sample collection and it typically every 60 seconds for 5-15 minutes to do. To minimize variations in the sample, sampling at a specified time limit and was conducted in the spring and summer. Put the sample inside the container contains ice, were transferred to the laboratory immediately and in order to isolate debris and squamous cells, the samples were centrifuged for 10 min at 4 °C (at 2500 g speed) and then to collect all samples for testing, at the temperature of -20° C, were frozen. The salivary and serum samples were measured with Human vitamin D ELISA Kit, manufacturing company "Bioassay Laboratory technology" China. The serial number of the Cat. No: E1537Hu. The kit uses a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of Human Vitamin D<sub>3</sub> in samples.

Table 1. Gender distribution

gender distribution		groups		Total	Chi-Square Tests
		Control	Case		
Female	Count	39	34	73	X <sup>2</sup> = 0.952 df = 1
		68.4%	59.6%	64.0%	
Male	Count	18	23	41	P = 0.329
		31.6%	40.4%	36.0%	

Table 2. Comparison of blood parameters in both case(n=57) and control groups

	groups	Mean	Std. Deviation
		Age	control
	case	47.7368	12.98285
Height	control	1.6568	.06185
	case	1.6661	.07161
Weight	control	71.7018	8.43878
	case	75.0175	13.94439
BMI	control	26.0960	2.60719
	case	26.9640	4.49713
FBS	control	91.3684	6.68322
	case	217.252	115.48133
HbA1c	control	5.6167	.82075
	case	.7229	2.35300
serum_Ca	control	9.4404	.66409
	case	9.1789	.47799
Serum_Creatinin	control	.7561	.22758
	case	.8333	.22939

Table 3. Relationship between the amount of serum and salivary vitamin D3 with diabetes

	groups	Mean±sd	t-test
<b>serum vitamin D3</b>	control	37.6351±8.61028	
	case	15.3105±7.46902	T=14.787
<b>salivary vitamin D3</b>	control	20.8807±3.95296	df = 109.809
	case	27.9053±10.91476	P<.000

Table 4. compare the values of serum vitamin D3 in the case and control groups

<b>serum vitamin D3 (ng/dl)</b>		Control n(%)	case n(%)
Severe Deficiency	≤10	0 .0%	18 31.6%
Moderate deficiency	11-19	0 .0%	26 45.6%
Insufficiency	20-29	12 21.1%	8 14.0%
Normal	≥30	45 78.9%	5 8.8%

Table 5. compare the values of salivary vitamin D3 in the case and control groups

<b>salivary vitamin D3 (ng/dl)</b>		Control n(%)	case n(%)
Severe Deficiency	≤10	0 .0%	4 7.0%
Moderate deficiency	11-19	29 50.9%	8 14.0%
Insufficiency	20-29	25 43.9%	21 36.8%
Normal	≥30	3 5.3%	24 42.1%

### 3. Findings

57 patients with newly diagnosed type 2 diabetes, with an average age of 47.73 years (34 women and 23 men) And 57 healthy volunteers (39 females and 18 males) with an average age of 45.36 years, participated in the study (Table 1&2). The average serum levels of vitamin D<sub>3</sub> in the control group, 37.6 ng/ml and in the case group was 15.3 ng/ml. The average level of saliva was 20.8 in the control group, and in the case group was 27.9ng/ml. In comparison, the average serum vitamin D<sub>3</sub> in healthy people with diabetics, the difference was significant (P<0.001). This communication about average vitamin D<sub>3</sub> in saliva, was reversed. There is a direct and significant correlation between serum and salivary vitamin D<sub>3</sub> in control group (p=0.013) and the correlation between serum and salivary vitamin D<sub>3</sub> is about 0.33 that in case group, this correlation was reversed. (Table 3) In Evaluation of Serum Levels of vitamin D<sub>3</sub> (Table 4), the deficiency was observed in both groups that in 21.1% of cases in control group, was insufficient (20-29ng/ml). There were no severe deficiency of vitamin D<sub>3</sub> (<10ng/ml) as well as moderate deficiency (10-19ng/ml) and in 78.9% based on more than 30 ng/ml and was normal. But the situation in the case Group (newly diagnosed diabetic patients) was more critical. 31.6% have severe deficiency of vitamin D<sub>3</sub> (<10ng/ml) and 45.6% have moderate deficiency (10-19ng/ml). There were inadequacy of vitamin D<sub>3</sub> (20-29ng/ml) in 14% and normal levels (>30ng/ml) in 8.8% of the cases. Overall 91.2% of newly diagnosed diabetics, suffered from a lack of vitamin D<sub>3</sub>. The results generally confirms the prevalence of deficiencies of vitamin D<sub>3</sub> in the statistical community participant (case and control) And the extent and severity of this deficiency among newly diagnosed diabetic patients is far greater than was healthy people and the relationship between vitamin D<sub>3</sub> deficiency and diabetes, was direct and meaningful relationship. Investigation of salivary amounts of vitamin D<sub>3</sub>(Table 5) in the control group, briefly showed that there had been severe lack of vitamin D<sub>3</sub> and moderate deficiency in 50.9%, inadequate Vitamin D<sub>3</sub> in 43.9% and normal levels of vitamin D<sub>3</sub> in 5.3% of cases was reported. In case group, 7% had severe lack of vitamin D<sub>3</sub> and 14% had moderate deficiency. There were seen, inadequate vitamin D<sub>3</sub> in 8.36%, and 42.1% normal level of vitamin D<sub>3</sub> of cases. It is generally based on the results of salivary amounts of vitamin D<sub>3</sub>, a total of 58% of newly diagnosed diabetes patients had a deficiency of vitamin D<sub>3</sub>.

#### 4. Discussion

The measurement of higher amounts of vitamin D<sub>3</sub> in saliva, can be attributed to release larger amounts of Protein binding to vitamin D<sub>3</sub> (Protein-bound 25 (OH) D<sub>3</sub>) in saliva (Tatsuya Higashi- 2013) and measuring 25 (OH) D as a common practice, done with the commercial kit using immunoassay. Measurement of salivary 25 (OH) D as a pre-hormone using unstimulated whole saliva (Collected without chewing gum) is beneficial to assess the status of vitamin D<sub>3</sub> (Higashi et al., 2013). So, in the present study, due to higher average levels of vitamin D<sub>3</sub> in saliva than in serum in newly diagnosed diabetic patients, can result from secrete larger amounts of protein-bound 25 (OH) D<sub>3</sub> in saliva or the result of the method of measurement or other unknown causes. Due to the nature of diabetes, vitamin D<sub>3</sub> levels in serum or saliva, May be varying from one person to another and in various social, ethnic groups, in different geographical conditions and under different mechanisms requires extensive research for the understanding of the causes and possible mechanisms. In Agha Hosseini's study (2011) Salivary and serum levels of vitamin D<sub>3</sub> in postmenopausal women may be maintained in the normal range and have nothing to do with the feeling of dry mouth (Agha-Hosseini, Mirzaei-Dizgah, & Mirjalili, 2011). In healthy adults, about 85% of circulating vitamin D<sub>3</sub>, bind to vitamin D binding protein and there are less than 0.1% free in the plasma and plasma proteins to cross salivary membranes, are much larger and only low molecular weight compounds, be able to pass and it can be inferred that identification of higher amounts of vitamin D<sub>3</sub> in saliva, can result from the presence of more vitamin D<sub>3</sub>-binding protein in saliva (Higashi et al., 2013).

#### 5. Conclusions

In general, the deficiency of vitamin D<sub>3</sub> in newly diagnosed diabetics, was observed also in the serum and saliva samples and compare these values together showed that saliva also Such as serum, can be a good indicator to identify the values of vitamin D<sub>3</sub>. But still serum is a better approach for this assessment and more research needs to be done on saliva. According to the results of this study, suggested that taking into consideration the limitations do the research and trying to solve them, design and conduct more studies on the measurement of vitamin D<sub>3</sub> in the saliva. Also, if confirmed the results of this research, based on the prevalence of vitamin D<sub>3</sub> deficiency, it is recommended that Measuring vitamin D<sub>3</sub> routinely included Screening for type 2 diabetes. In the prevention of the progression of the internal disorders to diabetes, or in cases of newly diagnosed diabetes, Supplementation and diets rich in vitamin D<sub>3</sub> at the start of treatment, may be prevented the incidence of many complications of diabetes in more advanced stages of disease, requires further research and more comprehensive to find the relationship between lack of vitamin D<sub>3</sub> and the various complications of diabetes or its relation to diabetes as a risk factor. The incidence and prevalence of dry mouth in diabetic patients, can be one of the reasons for the increase vitamin D<sub>3</sub> concentrations in the saliva. Therefore, more research is needed in this area.

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