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Research Article

Role of 1,25(OH)2D On Cytochromes CYP27A1 and CYP27B1 in Periodontitis: A Clinical Study

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ABSTRACT

Background: Vitamins have a great impact on metabolis. **Aims:** To determine the role of 1,25(OH)2D On Cytochromes CYP27A1 and CYP27B1 in Periodontitis. **Material and Method:** The investigation was carried out on 45 participants of ages within the range of (30-45 years) who were attending the private dental clinics. Diagnosis of chronic periodontitis was established depending on dental history, clinical examinations (periodontal indices). All participants were examined by the same dentist. They were classified into three groups: Group 1 (control negative): (15) participants with normal serum vitamin D3 level and with pocket depth ≤3 mm, good oral health and normal periodontal tissues and no previous history of periodontal diseases. Group 2 (control positive): (15) participants with normal serum vitamin D3 level and periodontitis with pocket depth ≥5 mm, they received placebo medication orally, Group3(treatment): (15) participants with vitamin D3 deficiency (below 30 IU), and periodontitis with pocket depth ≥5 mm, they received oral Vitamin D3 fast acting liquid soft gel capsule 2000 IU /day for 3 months. 3 blood samples were taken from each participant at 0,45,90 days, for research examinations. CYP27A1, CYP27B1 serum levels was measured for each sample in three groups by ELISA kit. **Result:** there was a highly significant reduction in CYP27A1 serum level in the treatment group at the ninety days of the study while there was no significant elevation CYP27B1 serum level in all groups during 45,90 days of the study. **Conclusion:** The present study suggested that the 1,25(OH)2D has effects on serum levels of both Cytochromes CYP27A1 and CYP27B1 and this was associated with periodontitis.

Key words: Cytochrome, CYP27, Periodontitis, Vitamin D.

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INTRODUCTION

Cells require ATP (Adenosine Triphosphate) for essential metabolic processes. Glucose is broken down into pyruvate through glycolysis in aerobic organisms. The Electron Transport Chain (ETC) consists of electron transport proteins in the inner membrane of mitochondria. This chain produces 34 molecules of ATP, which the cell uses for survival.[1,2] Cytochromes CYPs P450 (P450s) are a diverse group of enzymes found in various organisms, including prokaryotes, eukaryotes, and viruses.[3] They play a crucial role in many biological processes, such as the production of steroid hormones and the metabolism of foreign substances in humans. These enzymes are capable of catalyzing a wide range of reactions, converting different substrates like steroids, terpenes, and fatty acids.[4,5] CYPs can be classified into two subtypes based on their location within the cell: microsomal or mitochondrial.[6] One specific enzyme, CYP27A1, found in the liver mitochondria, is responsible for hydroxylating vitamin D3-25 and 1α-OH-D3.[7] Another enzyme, CYP27B1, is involved in the hydroxylation of 25-OH-D2 and 25-OH-D3 to produce the active form of vitamin D.[8]

Its documented that the multifunctional nutrient Vitamin D3 (VD3) and its role in calcium and phosphate homeostasis, as well as various physiological and pathological processes.[9] It explains how VD3 is converted to its active form, 1α,25-dihydroxyvitamin D3 (1,25-D3), and deactivated by enzymes.[10] The periodontitis, a chronic disease caused by an imbalance between oral microbes and the individual's inflammatory response. It highlights the significant impact of periodontitis on connective tissue and bone support, as well as the negative effects on quality of life.[11] The multifunctional enzyme CYP27A1, which is involved in cholesterol metabolism and the bio-activation of vitamin D3 in various tissues.[12] It suggests potential roles of local vitamin D production in cellular gene regulation. Lastly, it states that the aim of the research is to determine the effect of vitamin D3 on the serum levels of CYP27A1 and CYP27B1 in patients with periodontitis.[13]

MATERIALS AND METHODS

The samples were obtained from forty-five patients, their ages ranged between (30-45 years), recruited from the private dental clinics in Mosul city. They were classified into three groups: Group 1 (control negative): (15) participants with normal serum vitamin D3 level and with ≤3 mm, good oral health and normal periodontal tissues and no previous history of periodontal diseases. Group 2 (control positive): (15) participants with normal serum vitamin D3 level and periodontitis with pocket depth ≥5 mm, they received placebo medication orally, Group3(treatment): (15) participants with vitamin D3 deficiency (below 30 IU), and periodontitis with pocket depth ≥5 mm, they received oral Vitamin D3 fast acting liquid soft gel capsule 2000 IU /day (Poland) for 3 months. Three blood samples were taken from each participant at 0,45,90 days, for research examinations. The criteria of patients' selection included: They were healthy individuals, non-pregnant or lactating females. Vitamin D

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deficiency (below 30 IU), there was no history of vitamin D allergy and did not take any medication or supplements or herbals for the last 1month, non-smoking, and non-alcoholic. Scaling and polishing had been carried out for each volunteer to reach the base line. A written instruction was supplied to each patient about standard oral hygiene home care. After centrifuging of all samples for serum collection, (CYP27A1, CYP27B1) serum levels was measured for each samples in three groups by ELISA kit.

RESULTS

In this study significant differences in the means of CYT27A1 serum level were observed in the treatment group throughout study periods. while There were no significant differences in the means of CYT27A1 serum level in both control groups throughout study periods. In this study no significant differences were observed between all study groups throughout study period in CYT27B1 serum level. which means different response to the vitamin D3 supplement in periodontitis (Figure 1).

The Comparison between Periodontal Disease Index's into Each Group: In this study highly, significant reduction in the means of periodontal index were observed in the treatment group and significant elevation in control negative throughout study periods while we observed no significant in control positive group (Table 1).

DISCUSSION

Periodontitis is a chronic infectious disease caused by microorganisms in dental plaque, leading to inflammation and destruction of periodontal

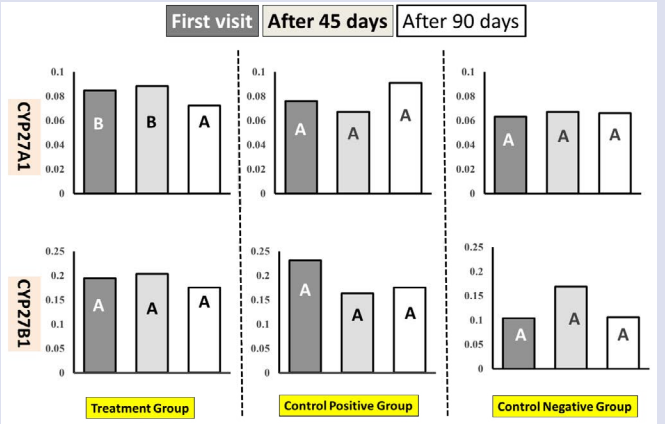

Figure 1: The levels of serum CYP27 during (0,45,90) days in control negative groups, control positive group, and treatment group.

Table 1: The periodontal disease index's in control negative groups, control positive group, and treatment group.

	Gender (M/F)		Sum of Squares	df	Mean Square	F	p value
treatment group	5/10	Between Groups	18.433	2	9.217	50.099	0.000**
		Within Groups	7.727	42	0.184		
Positive Group	6/9	Between Groups	0.134	2	0.067	0.280	0.757
		Within Groups	10.029	42	0.239		
Negative Group	5/10	Between Groups	0.339	2	0.170	2.480	0.036*
		Within Groups	2.872	42	0.068		

* Significant at p-value ≤ 0.05. ** Highly Significant at p-value ≤ 0.01.

support tissues.[14] Connective tissue destruction and alveolar bone resorption are mainly mediated by the release of pro-inflammatory cytokines and inflammatory mediators in response to bacterial challenge.[15] The progression and severity of periodontal disease can be influenced by environmental and genetic factors that modify the host's immune response. Vitamin D2 and D3 are prohormones that undergo hydroxylation in the liver and kidneys to become the active forms, 25-hydroxyvitamin-D2/3 and 1α,25-dihydroxyvitamin-D2/3. These active forms bind to the vitamin D receptor (VDR) and can exert genomic and non-genomic actions on target cells and tissues.[14,15] Hydroxylation at C1α occurs in the mitochondria of kidney cells by the action of 1α-hydroxylase CYP27B1. This enzyme is also found in other tissues and cell types. Local production of 1,25(OH)2D2/3 plays a role in identifying extra-skeletal functions of vitamin D. The active form of vitamin D, 1,25(OH)2D, binds to the nuclear vitamin D receptor (VDR) and heterodimerizes with retinoid X receptor (RXR). This complex acts as a transcription factor, regulating target genes with a vitamin D response element. Additionally, 1,25(OH)2D can bind to the plasma membrane VDR, leading to non-genomic actions such as stimulating intestinal calcium transport.[16-18]

Vitamin D signaling plays a crucial role in maintaining calcium balance for bone health and has additional functions in various tissues. Disruptions in vitamin D signaling are associated with numerous diseases. The activity of cytochrome P450 enzymes, which facilitate the conversion of vitamin D3 into its active form, is essential for vitamin D signaling and its proper functioning.[12] The study found significant differences between the treatment and control groups. The treatment group showed a significant increase in CYP27A1 at 45 days, indicating a positive response and improvement in periodontal tissues. However, there were no significant differences observed in the control groups. This can be explained by the fact that the bioactive form of vitamin D, 1,25-dihydroxyvitamin D3, binds to the vitamin D receptor (VDR) in the cytosol, forming a VDR-RXR complex. This complex regulates the transcription of genes, including cytochrome P450 (CYP) enzymes, in liver and intestinal cells.[19]

CYP27A1 is believed to play a role in the metabolism of certain forms of vitamin D at high concentrations, but its involvement at normal physiological levels is unclear.[20] Cytochrome P450 enzymes, including CYP27A1, are essential for various processes such as cholesterol production, steroid synthesis, and drug metabolism.[21] CYP27A1 is active in converting vitamin D3 into 25-hydroxylated metabolites, while also forming 24- and 27-hydroxylated metabolites of vitamin D2.[22] It has been suggested that CYP27A1 may be involved in periodontal immune defense and contribute to gingival inflammation and bone loss.[23] On the other hand, the enzyme CYP27B1 is responsible for producing the most potent form of vitamin D, 1,25(OH)2D, which accounts for the majority of its biological effects.[12,20]

The study found that there was a significant increase in the CYP27B1 serum level after 45 days, but this increase was not considered significant when compared to the level after 90 days. The higher levels of 25(OH) D and bone CYP27B1 expression were associated with a stronger plate-like structure in bones, supporting the idea that 1,25(OH)2D levels from bone supply can improve bone health.[24] The production of 1α,25(OH)2D3 from 25(OH)D3 is influenced by parathyroid hormone, Ca2+, Pi, and 1α,25(OH)2D3 itself, which explains the decrease in CYP27B1 serum level after 90 days of treatment. The expression of CYP27B1 and synthesis of 1α,25(OH)2D3 play a crucial role in the development of APCs (dendritic cells and macrophages), indicating a direct involvement of vitamin D3 in the body's immune system.[25] The 1,25(OH)2D, a form of vitamin D, is produced and acts on keratinocytes in the oral epithelium.[26] This signaling affects the growth, differentiation, and death of these cells, as well as local immune responses. Vitamin D3, the active form of vitamin D, functions as a hormone and regulates genes involved in various processes such as

detoxification, energy metabolism, immunity, and calcium balance. Vitamin D deficiency can lead to health issues like bone malformations and weakened immune system.[27]

The text discusses the expression of the CYP27B1 protein in gingival tissues and its correlation with periodontal inflammation. The study found that CYP27B1 was expressed in both gingival fibroblasts and epithelial cells. The expression of CYP27B1 mRNA and staining scores were higher in diseased individuals compared to the control group.[28] The text also mentions that parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) regulate vitamin D metabolism. PTH stimulates bone turnover and upregulates 1,25(OH)2D levels by inducing CYP27B1 expression in the kidneys.[29] On the other hand, FGF23 inhibits CYP27B1 in the kidneys, reducing calcitriol production. The CYP enzymes play a crucial role in maintaining vitamin D levels, and factors such as age, climate, sun exposure, genetics, and environment can affect vitamin D levels.[30] The most affected may be females because females are always struggling with vitamin D and their consequences especially females with polycystic ovarian syndrome.[31] The elevation of CYP27A1 and CYP27B1 serum levels in the treatment group led to an improvement in periodontitis, while the control group showed different changes in serum levels.[30] The vitamin D The local milieu of oxygen supply and presence of bioactive factors intrinsically secreted by cells will ultimately shape the fate of the diseases outcomes.[32,33] Moreover, other adipokines, such as, adiponectine, obestatin, and redox status may intervene resulting in further complicating the condition.[34,35]

CONCLUSION

In conclusion, the findings of the present study suggested that the 1,25(OH)2D has effects on serum levels of both Cytochromes CYP27A1 and CYP27B1 and this was associated with periodontitis. It may give an evidence to confirm that the severity of periodontal tissue damage may be a consequence of the presence of the cytochromes.

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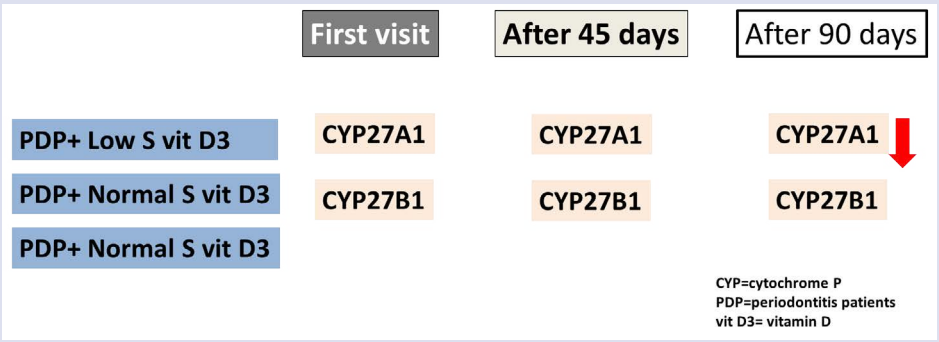
GRAPHICAL ABSTRACT



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