The Influence of Vitamin D Serum Concentration on Third Molar Extraction Outcome: a Pilot Study

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ABSTRACT

Background: In the academic world, the debate continues on the subject of how far a lack of vitamin D can affect the healing of various wounds. Objective: To determine if basal serum levels of vitamin D significantly influence clinical parameters linked to post-extraction wound healing after surgical removal of impacted/semi-impacted third molars. Methods: A total of 23 patients were included in this study. Clinical outcome parameters were: edema, trismus, pain, soft tissue healing, and dry socket signs. The research was divided into four stages. Results: Due to the high prevalence of hypovitaminosis D (91%), patients were classified into an insufficient (≥ 20 ng/ml) or a deficient group (<20 ng/ml). The results showed no statistically significant differences in pain, edema, trismus, or soft tissue healing between those two groups. A slight statistical interaction was observed in the clinical parameters related to edema and trismus assessment, but not statistically significant. We did not notice signs of "dry socket" on any of the patients. Conclusion: Within its limitations (low number of patients, high prevalence of vitamin D deficiency), this pilot study failed to find a significant influence of serum vitamin D concentrations in wound healing or post-surgery symptom (pain, edema, trismus) development after third molar extraction. Further clinical investigations are necessary to elaborate on this function of vitamin D more precisely. Keywords: Vitamin D deficiency, Third molar, Pain Measurement, Trismus, Wound Healing.

1. BACKGROUND

Vitamin D (calciferol) is a liposoluble biomolecule, which plays a vital role in the regulation of the metabolism of calcium and phosphate (1). Vitamin D appears in two forms: vitamin D3 or cholecalciferol, which is synthesized in the skin or taken in with food, and ergocalciferol or vitamin D2, which is exclusively absorbed through food. The largest proportion of the need for vitamin D, 80–90%, is met by production in the skin (2). Vitamin D3 or cholecalciferol is synthesized from the precursor 7-dehydrocholesterol by the action of ultraviolet B rays with a wavelength of 290-315nm. The activation of vitamin D3 occurs under the control of enzymes through two phases, the first in the liver, and the second in the kidneys (3).

Vitamin D mainly appears in the circulation as 25(OH)D bound to the vitamin D binding protein. 25(OH)D has a half-life of two to seven weeks, in contrast to 1.25(OH)2D, whose half-life is only four hours, which is why 25(OH)D is deemed to be the primary diagnostic marker for determining vitamin D levels (4, 5).

Serum vitamin D concentration is designated as sufficient (physiological) at > 30ng/ml. Insufficient values are in the range of 29-21ng/ml, of deficiency 20-10ng/ml, whilst a value of 10-0ng/ml is described as severe deficiency (6, 7). The most active form, 1.25(OH)2D, exercises most of its functions by binding to the widespread vitamin D receptors (VDR), which are primarily localized in the nucleus of the target cell (4, 8). Although daily exposure of 35% of the skin surface to the sun for 13 minutes is sufficient to prevent a shortage, more than one billion people around the world are at risk of vitamin D deficiency (9). In view of its many functions in the organism, vitamin D deficiency is linked to an increased risk of many diseases, such as rickets in children and osteomalacia in adults,
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hyperparathyroidism, osteoporosis, diabetes mellitus, cardiovascular diseases, autoimmune diseases, and cancers (1, 7). During the current COVID-19 pandemic, a shortage of vitamin D has been linked to a severe clinical picture of the disease (10).

Vitamin D is also of significant importance for oral health. It plays a role in the mineralization of teeth during their development, it is important for the health of the periodontal tissue, and it has an important role in the formation of enamel, dentine, and bone tissue (4, 11-18). Vitamin D deficiency may also be linked to the occurrence of chronic periodontitis, caries, and a tendency for oral cancer (11, 19). In modern dentistry, there is an increasing amount of research linking the failure of osseointegration of dental implants with a deficiency of 25(OH)D (20-23).

In the academic world, the debate continues on the subject of how far a lack of vitamin D can affect the healing of various wounds (24).

2. OBJECTIVE

In view of the fact that impacted and sub-impacted wisdom teeth are a frequent reason for oral surgery, we decided to examine the effect of serum concentrations of 25(OH)D on the healing of the extraction wounds from surgically removed third molars. In this research we clinically tested whether serum concentrations of vitamin D have any significant effect on the clinical parameters accompanying the healing of post-extraction wounds following surgical removal of impacted and sub-impacted wisdom teeth. We also investigated the potential role of vitamin D deficit as a predisposing factor for the occurrence of dry socket. In line with these aims, the research hypothesis was that serum values of vitamin D affect the healing of extraction wounds following surgical removal of wisdom teeth.

3. PATIENTS AND METHODS

Participants

The research included adult patients of both sexes who came to the Clinic for Oral Surgery of the Faculty of Dental Medicine with Clinics of the University of Sarajevo, with an indication for surgical extraction of impacted/sub-impacted wisdom teeth. All the patients signed informed consent for participation in the study which was approved by a decision of the Ethics Committee of the Faculty of Dental Medicine with Clinics in Sarajevo, no. 02-3-4-59-1-9/2020.

A total of 43 patients were examined. Of them, 23 met all the necessary criteria and were therefore included in the research. The indications for extraction were pain and preparation for orthodontic treatment. According to the exclusion criteria for involvement in the research, the following were excluded: patients with blood dyscrasias, uncontrolled diabetes mellitus, patients on anticoagulant and antiplatelet therapy, bisphosphonate, and immunosuppressive therapy, chemotherapy, radiotherapy, pregnant women, nursing mothers, and patients taking vitamin D supplements. Individuals who did not agree to the terms of the research, and who did not respect the research protocol were also excluded from the study.

The stages of the research

The research was conducted in four stages: S0, S1, S2, S3. The first, S0, the pre-operative stage, involved collection of general information on the patient by means of medical history. So, in this stage, we registered the names and surnames, age and sex of the patients, the drugs they were taking, any harmful habits such as smoking and alcohol consumption, the position of the tooth in the arch, and the indication for extraction. Before the surgery, an orthopantomogram (OPG) was performed to assess the position and morphology of the impacted tooth, its relationship with the surrounding anatomic structures, for assessment of the condition of the periapical tissue, and for planning the surgical procedure. In addition, we examined the plaque index (Silness and Löe), determined the Pederson index of the difficulty of the extraction, undertook a detailed clinical examination, and established any presence of gingivitis, caries, periapical lesions, or other pathologies (25-31). At this stage, the reference values of the clinical indicators (TL – tragus-comissura labial, TP – tragus-pogonion, the interincisal distance) were recorded, on that basis of which, through check-up examinations, the development of edema and the occurrence of trismus was monitored.

We quantified edema as a clinical indicator by measuring the distances between the anthropometric points of the tragus and the labial commissura. The measurements were undertaken using a tape measure and are expressed in millimetres (Figure 1). The development of trismus as a clinical indicator was tracked by measuring the interincisal distance between the mesial incisal angle of the upper central incisor and the same point on the antagonist tooth, with the mouth open as fully as possible, using dental calipers. After the initial examination was performed, all patients were sent for laboratory testing of serum concentrations of 25(OH)D, PTH (parathormone), and free calcium in the serum. According to the levels of vitamin D found, the serum concentrations were categorized into four groups (physiological/normal values, insufficiency, deficiency, and severe deficiency) (6, 7).

The surgical stage, or stage 1, consisted of the surgical procedure itself of extraction of the wisdom tooth, performed by the same surgeon. After applying local anesthesia (Septanest Forte 40 mg/ml, with 0.01 mg adrenaline), an incision was made and the mucoperiosteal flap was raised. If necessary, corticotomy was performed. The extraction of the indicated tooth was performed using an elevator and forceps. After extraction, curettage of the socket and irrigation using NaOCl solution (0.05%) was performed, and the wound was closed with simple interrupted sutures. The duration of the procedure was monitored from the time of application of an anesthesia to the placing of the sutures. After the surgical procedure, the subjective opinion of the surgeon regarding the difficulty of the extraction was registered. The medications administered were: Amoxicillin caps. á 500 mg 4x1 for 8 days per os, Brufen tbl. á 200mg per os, Chymoral forte tablets 3x2 per os).

The first postoperative stage, S2 (the third day after S1), comprised the first check-up examination at which we measured the edema, trismus, pain, assessed the healing of the soft tissue and the existence of postoperative complications (dry socket), and determined the plaque index (Silness and Löe). We tested pain as a subjective symptom using a

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Visual Analogue Scale (VAS) (32). A pain-free state, in the end, was given a value of 0, intensity of pain from 1-3 (mild) a value of 1, intensity of pain 4-7 (moderate pain) a value of 2, and intensity of pain 8-10 (severe pain) a value of 3. The number and dose of analgesics the patient took over this period were also recorded (25). Healing of the wound was monitored using a scale based on Landry (32). Dry socket as a possible postoperative complication was monitored on the basis of the Blum’s criteria (33).

The second postoperative stage, or S3 (10 days after S1), involved a second check-up examination within which another assessment was undertaken of the clinical parameters mentioned above, as well as determination of the Silness and Löe plaque index, with the final removal of sutures.

**Statistical Analysis**

In the statistical analysis of data, 2x3 mixed MANOVA (multiple analysis of variance) for each of the clinical indicators was used, where "2x3" relates to the fact that there were two independent variables in the research. The first variable was the level of 25(OH)D, and it had two levels (because of the division of the subjects into insufficient and deficient groups, with the proviso that in the test sample, there were no subjects with vitamin D values within the physiological/normal range). The second variable was the value of the clinical parameters tested, which had 3 levels (due to the measurement of the subjects at three different stages, that is, S0, S2, and S3). The analysis was mixed because the first variable was inter-group, and the second intra-group. MANOVA analysis was used because it compares groups that are formed on the basis of two or more independent variables (in this case, there were two). We used IBM PSS version 23. All the requirements for this analysis were met.

4. RESULTS

The total number of patients treated in this research was 23, of which 19 (83%) were female and 4 (17%) male. Their average age was 22.47 years; (SD 5.15). The lowest level of 25(OH)D was 7.55ng/ml and the highest 33.69ng/ml. The mean level of 25(OH)D was 21.5ng/ml (SD 6.41).

The prevalence of vitamin D insufficiency and deficiency in this research was 91% (7.55-26.3ng/ml). Since most patients had 25(OH)D concentrations below the physiologically acceptable level, we categorized them whereby the threshold value was 20ng/ml. Therefore, we had two groups: insufficient (>20ng/ml) and deficient (≤20ng/ml). Of the total number of subjects, 11 were in the insufficient group (48%), and 12 patients were in the deficiency group (52%).

The results of testing levels of 25(OH)D are presented below in relation to five clinical parameters (TP – tragus-pogonion, TL – tragus labial commissure, TS – trismus, WHQ – wound healing quality) as shown in Figure 2.

**TP (tragus-pogonion)**

No statistically significant effect was established of 25(OH)D levels, F1 (1.16)= 0.74; p>0.05, on the distance between the TP between the two experimental groups (insufficient and deficient) at the three stages of measurement, but a statistically significant change was found in the clinical parameter tested (TP) over the stages of measurements, regardless of the level of 25(OH)D. Thus, subjects with insufficient levels of 25(OH)D did not differ statistically significantly in relation to the points of measurement (S0, S2, and S3) regarding TP from subjects with deficient levels of 25(OH)D. Therefore, the F-test did not show any statistically significant interaction, F (2.54)= 1.33; p>0.05. The results of the two groups in relation to TP at each measurement are shown in Figure 2A.

**TL (tragus labial commissure)**

A marginally statistically significant effect of 25(OH)D levels was found, F(2.54)= 1.33; p = 0.09, on the distance between the TL between the two experimental groups (insufficient and deficient) at the three stages of measurement. However, the result was not at the desired level, p>0.05. Further, a statistically significant change was established in the tested clinical parameter (TL) over the stages of measurement regardless of the level of 25(OH)D. Thus, subjects with insufficient levels of 25(OH)D did not differ statistically significantly in relation to the points of measurement (S0, S2, and S3) regarding TL from subjects with deficient levels of 25(OH)D. Therefore, the F-test did

![Figure 1. Measurement of clinical parameters for edema (A, B) and trismus (C)](image)

![Figure 2. a) Tragus–pogonion (TP), b) Tragus–labial commissure (TL), c) Trismus (TS), d) Pain, e) Wound healing quality (WHQ), values between the deficient and the insufficient group measured at three stages (1-50, 2-52, 3-53).](image)
not show any statistically significant interaction, $F(2.34)=1.33; p>0.05$. The results of the two groups in relation to TL at each measurement are shown in Figure 2B.

**TS (trismus)**
A marginally statistically significant effect of 25(OH)D levels was found, $F(1.16)=3.17; p=0.09$, on the interincisal distance, by which we monitored the development of trismus between the two experimental groups (insufficient and deficient) at the three stages of measurement. However, the result was not at the desired level, $p>0.05$. Further, a statistically significant change was established in the tested clinical parameter (TS) over the stages of measurement regardless of the level of 25(OH)D. Thus, subjects with insufficient levels of 25(OH)D did not differ statistically significantly in relation to the points of measurement (S0, S2, and S3) regarding TS from subjects with deficient levels of 25(OH)D. Therefore, the F-test did not show any statistically significant interaction, $F(2.34)=0.14; p>0.05$. The results of the two groups in relation to TS at each measurement are shown in Figure 2C.

**Pain**
No statistically significant effect was established of 25(OH)D levels, $F(1.16)=0.18; p>0.05$, on the VAS scale of pain between the two experimental groups (insufficient and deficient) at the three stages of measurement, but a statistically significant change was found in the clinical parameter tested (pain) over the stages of measurements, regardless of the level of 25(OH)D. Thus, subjects with insufficient levels of 25(OH)D did not differ statistically significantly in relation to the symptom of pain in dependence of the stages of measurement (S0, S2, and S3) from subjects with deficient levels of 25(OH)D. Therefore, the F-test did not show any statistically significant interaction, $F(2.34)=2.21; p>0.05$. The results of the two groups in relation to perception of pain at each measurement point are shown in Figure 2D.

**WHQ (wound healing quality)**
No statistically significant effect of the level of 25(OH)D was found, $F(1.16)=0.13; p>0.05$, on the (WHQ) between the two experimental groups (insufficient and deficient) at the three stages of measurement, but a statistically significant change was found in the clinical parameter tested (WHQ) over the stages of measurements, regardless of the level of 25(OH)D. Thus, subjects with insufficient levels of 25(OH)D did not differ statistically significantly in relation to the points of measurement (S0, S2, and S3) regarding WHQ from subjects with deficient levels of 25(OH)D. Therefore, the F-test did not show any statistically significant interaction, $F(2.34)=0.21; p>0.05$. The results of the two groups in relation to WHQ at each measurement are shown in Figure 2E. None of the patients included two patients with sufficient levels of 25(OH)D in the insufficient group.

The results obtained may be explained by the high prevalence of vitamin D deficiency amongst the test patients, which reached 91%. In other words, we did not have a large enough number of sufficient patients in whom we would notice the positive effect of vitamin D on the tested parameters. This is supported by the research by Jagelavičiene E. et al. from 2018, according to which the concentration of 25(OH)D in the plasma necessary for this vitamin to have an effect on the periodontium is 36–40 ng/ml (34). In our pilot study, the range of 25(OH)D was significantly below the necessary concentration, amounting to 7.55–35.0 ng/ml. In 2011, Bashutski JD et al. additionally supported this assertion and stated that before a periodontal surgical procedure, it is necessary to ensure an adequate concentration of vitamin D in order to achieve the best postoperative results (12).

The role of vitamin D in the outcome of periodontal surgical treatment has already been proven in several studies, which ascribe it a key role in the process of postoperative healing (35). In vitamin D sufficient patients, a smaller pocket depth was measured, of 1.4mm, and a greater increase in epithelial attachment, by 1.35mm, in comparison with deficient patients, 12 months after the procedure (12).

According to the research by Oteri et al., the outcome of surgical extraction of wisdom teeth depends on many endogenic and exogenic factors, including serum concentrations of 25(OH)D (35). The same authors tested the effect of administration of high doses of vitamin D on the outcome of surgical extraction of third molars. The sample consisted of 25 patients who underwent bilateral extraction of the lower third molars. In patients with high serum levels of 25(OH)D, the edema was smaller, and the wound healed better and more quickly. Also, in this group, the values of the inflammation markers TNF-α (tumor necrosis factor), IL-1-β (interleukin 1 beta), and IL-6 (interleukin 6) were lower than in the control group. This is explained by the anti-inflammatory effect of 25(OH)D. The intensity of pain did not differ at any of the stages of measurement between the two groups (35).

A potential mechanism for controlling pain, according to research by Helde-Frankling et al., in 2017, is based on the anti-inflammatory effect and suppression of synthesis of the prostaglandin E2 (56). The positive effects of this vita-
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The enzyme CYP27B1, which is needed to convert 25(OH)D into 1,25(OH)2D, is found in macrophages and increased production of antimicrobial peptides (cathelicidin and β-defensin) in these same cells (8). The antimicrobial peptides bind to components of the bacterial membrane and cause lysis (14). Similar to innate immunity, cathelicidin (LL-37) and immunity, calcitriol is capable of stimulating the creation of lipopolysaccharides, and inhibits the growth and adhesion of Porphyromonas gingivalis (14).

The mechanism by which vitamin D can have a positive influence on the outcome of surgical extraction of third molars also includes its direct role in the wound healing process itself (4). The results show that vitamin D exercises its role in the healing of wounds by increasing the function of transforming growth factor beta (TGF-β) in the dermal fibroblasts. This growth factor is vital during the healing of wounds because it stimulates angiogenesis, epithelialization, proliferation of fibroblasts, differentiation of myofibroblasts, synthesis of tissue granulation, and leads to the contraction of the edges of the wound in the phase of maturation (43). In 2016, Oda Y et al. showed that slower healing of wounds was noticed in vitamin D deficient mice, whilst on the other hand the results of the research by Ding J et al. from 2016 suggest that vitamin D supplementation may improve wound healing and regeneration in vitamin D deficient patients (45, 44).

6. CONCLUSION

In view of the fact that this pilot study did not establish statistically significant difference in the development of the clinical parameters (edema, pain, trismus, healing of soft tissue) between the insufficient and the deficient groups, we can conclude that basal serum concentrations of 25(OH)D did not show an effect on wound healing after the surgical extraction of third molars. Moreover, we did not notice signs of alveolitis in any of the patients. However, due to all the limitations which we were facing during the research (the small sample, the high prevalence of vitamin D deficiency, the lack of a group of sufficient patients) and the favorable marginally significant interaction, we believe that additional research is needed on a larger sample to shed light on the true role of vitamin D in the healing of extraction wounds and that this study could be a guidance in this undertaking.
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