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ANTIOXIDANT AND ANTI-INFLAMMATORY PROPERTIES OF MELATONIN AND MICRONUTRIENTS IN PATIENTS WITH PERIODONTAL DISEASE

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Abstract

Periodontal disease is a chronic disease with a complex etiology that includes bacterial colonization, excessive inflammation and oxidative stress. The hormone melatonin has antioxidant properties and could help alleviate chronic diseases by reducing stress. The aim of this study was to investigate and analyze the effect of exogenous melatonin on patients with periodontitis. More detailed studies are needed to expand the therapeutic possibilities of melatonin as a premedication in dentistry.

Keywords: *melatonin, the effect of melatonin in periodontal disease, periodontal disease, inflammatory markers, antioxidant enzymes*

Scope

The scope of this study was to investigate the anti-inflammatory and antioxidant properties using melatonin supplements by measuring the clinical status of selected patients affected by periodontitis. Improving inflammatory and antioxidant parameters.

Methode

The study was performed on 9 patients (4 men and 5 women) with moderate gingivitis and periodontitis, resistant to treatment. They were between 30 and 70 years old. They were asked to rinse with a solution containing melatonin and 2 tablets of Melatonin 3 mg (Melatonin 5 mg., fillers (Dicalcium phosphate, Microcrystalline cellulose), stabilizer (Hypromellose), anti-caking agent (Vegetable Magnesium Stearate)) to put under the tongue one hour before bedtime. The time was 8 weeks followed by a reassessment of periodontal status. Patients were notified each night by a written message that they should take the pills.

1.1. Melatonin (N-acetyl-5-methoxy tryptamine)

Melatonin is synthesized by the pineal gland in the brain. In a healthy individual, melatonin is released in a rhythmic cycle, with more melatonin being produced at night when light entering the retina begins to decrease. That's why melatonin is

also called the "dark" hormone. Melatonin levels vary in 24-hour cycles.

Normally, it starts to increase in the late afternoon, stays up almost all night and then drops in the early hours of the morning. Melatonin is transported through the blood to different areas of the body, signaling the body's need to sleep. Nocturnal melatonin levels are at least 10 times higher than during the day.

The secretion of melatonin by the pineal gland varies significantly with age. It begins in the third or fourth month of life and coincides with the consolidation of sleep at night. After a rapid increase in secretion, nocturnal melatonin levels peak at 1-3 years of age, then decrease slightly until they reach a plateau that persists throughout the young adult period. After a steady decline in most people, nocturnal melatonin levels in a 70-year-old person reach only a quarter of those seen in young adults. In some elderly people only a very small amount of melatonin is secreted, and in others not at all. [1], [2], [44] [23]

Nocturnal melatonin secretion is inhibited by relatively dim light when the pupils are dilated. It is considered that this is the main way in which prolonged use, before bed, of devices such as laptops and smartphones can have a negative impact on melatonin secretion, circadian rhythm and sleep.

Light is an important regulator of melatonin production in the pineal gland. In humans and other mammals, the daily rate of melatonin production is determined by the internal circadian clock. This "clock" is located in a region of the brain called the suprachiasmatic nuclei. During the day, the suprachiasmatic nuclei stop melatonin synthesis by sending inhibitory messages to the pineal gland. At night, however, the suprachiasmatic nuclei are less active, and the inhibition exerted during the day is reduced, resulting in the production of melatonin by the pineal gland.

Melatonin is important in regulating the sleep-wake rhythm of the body's internal clock. In humans, nocturnal melatonin secretion initiates and maintains sleep and is often referred to as the "sleep" hormone. Although not essential for sleep, we sleep better as long as melatonin is secreted. [15], [18], [19]

Also, in many animals (mammals and birds), melatonin secreted by the pineal gland is essential for regulating seasonal biological rhythm (eg, breeding, hibernation behavior, and fur growth in winter) in response to changing day lengths. Melatonin is secreted in greater quantities in autumn and winter, when the nights are longer, and in smaller quantities in spring and summer. [3], [4], [5] [24] [31]

Melatonin is an active component with antioxidant, anti-inflammatory properties.

Topical administration of melatonin promotes the healing of tooth extraction holes and can also prevent the progression of oral cancer. [10], [11], [12]

1.2 Chronic periodontitis

Chronic periodontitis is a chronic multifactorial inflammatory condition, which if left untreated can lead to irreversible damage to the supporting tissues [26] [28] (periodontal ligaments, alveolar bone) and can lead to tooth loss. Periodontal disease leads to increased plasma levels of glucose. Oxidative stress leads to the activation of inflammation in periodontal disease.

The etiology of oral inflammatory diseases is multifactorial [[7], [8], [9]] and usually involves a microbial component [10,11]. Numerous potential modifiable and non-modifiable risk factors associated with oral inflammatory disorders have been identified, including smoking, alcohol consumption, stress, poor oral hygiene, systemic health, genetics, and epigenetic factors [7, [12], [13], [14]], [15]]. The severity and progression of oral diseases depend on these risk factors [16].

1.3 Antioxidation and oxidative stress

Ideally there is a balance between free radicals, antioxidants in the body and neutralizing mechanisms.

Our body has a natural defense system against these free radicals. The body's own protective enzymes are part of this system. These include superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) and glutathione S-transferases (GST). [37] [38] [39]

In addition to enzymes, other antioxidant factors such as vitamins A, E and C and various compounds present in plants such as flavonoids, tannins and lignins with different degrees of antioxidant competence also participate in antioxidant processes. All these antioxidant factors work together cooperatively. [40], [41], [42] [43]

When these mechanisms no longer cope with the action of free radicals, they can no longer be effectively neutralized and begin to accumulate - so we are witnessing a process called oxidative stress. [44], [45], [46], [47]. [49]

The results of prolonged exposure to oxidative stress are degradation and genetic mutations at the cellular level (abnormal cell growth being a first step in cancer) and as a direct effect premature aging, inflammation - especially in the vessels and arteries, cardiovascular disease, autoimmune and neurodegenerative diseases such as Alzheimer's and Parkinson's - more and more common conditions. [50], [51], [52], [53], [54], [55], [56]

Antioxidant nutrients prevent the production of free radicals and stabilize and eliminate existing free radicals [56,57]. Free radicals cause an oxidative chain reaction that leads to cell damage and death [[57], [58], [59]]. Antioxidants interrupt this chain reaction by modulating oxidative stress found to be significantly associated with periodontal disease [[60], [61], [62], [63], [64]]. A wide variety of studies, including longitudinal, cross-sectional, and randomized clinical trials, have explored the role of antioxidants in oral inflammatory diseases [[65], [66], [67], [68]].

2.Materials and methods

2.1 Materials

Consultation sheets highlighting gum damage, inflammation and the status of periodontal pockets.

Fact sheets with analyzes for micronutrient deficiencies in the body (nutrigenetic test).

Consultation kits

Treatment prescriptions

2.1. Subjects

To find out the micronutrient deficiencies in the DNA, nutrigenetics tests were performed on 9 patients (4 men and 5 women) with gingivitis and moderate periodontitis aged 36-71 years.

All subjects were systemically healthy, with no symptoms of infection and did not take antibiotics for at least 3 months before the experiment.

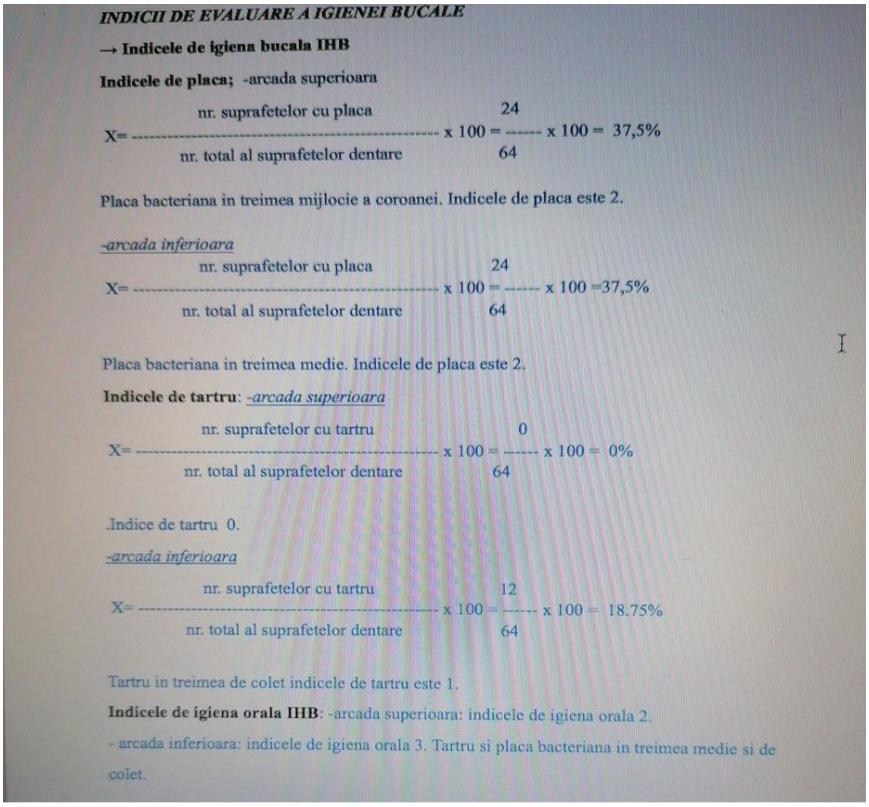
Vitamin therapy has started - almost all vitamins are used: vit. A, vit. C, vit. E ,, in the form of multivitamins and Tarosin, which contains vitamins C + P. Vitamins activate capillary circulation, optimize vascular permeability, metabolic exchanges and oxidation-reduction reactions, cell regeneration.

The administration of melatonin 3mg, 2 sublingual pills one hour before bedtime, melatonin acts on antioxidants and periodontal inflammation.

All subjects were informed about the purpose of the study and participated voluntarily.

2.2. Procedure

2.2.1. Performing the oral examination by the dentist with the preparation of the periodontal file in which the gingival status and the periodontal pockets were noted before the treatment (example Fig: 1,2,3)



INDICII DE EVALUARE A IGIENEI BUCALE

→ Indicele de igiena bucala IHB

Indicele de placa; -arcada superioara

$$X = \frac{\text{nr. suprafetelor cu placa}}{\text{nr. total al suprafetelor dentare}} \times 100 = \frac{24}{64} \times 100 = 37,5\%$$

Placa bacteriana in treimea mijlocie a coroanei. Indicele de placa este 2.

-arcada inferioara

$$X = \frac{\text{nr. suprafetelor cu placa}}{\text{nr. total al suprafetelor dentare}} \times 100 = \frac{24}{64} \times 100 = 37,5\%$$

Placa bacteriana in treimea medie. Indicele de placa este 2.

Indicele de tartru: *-arcada superioara*

$$X = \frac{\text{nr. suprafetelor cu tartru}}{\text{nr. total al suprafetelor dentare}} \times 100 = \frac{0}{64} \times 100 = 0\%$$

.Indice de tartru 0.

-arcada inferioara

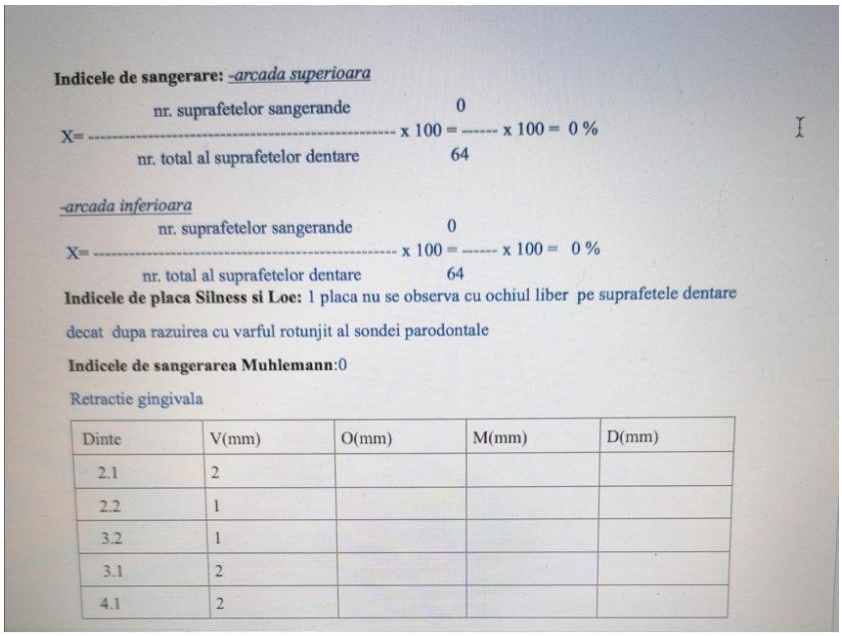
$$X = \frac{\text{nr. suprafetelor cu tartru}}{\text{nr. total al suprafetelor dentare}} \times 100 = \frac{12}{64} \times 100 = 18.75\%$$

Tartru in treimea de colet indicele de tartru este 1.

Indicele de igiena orala IHB: -arcada superioara: indicele de igiena orala 2.

- arcada inferioara: indicele de igiena orala 3. Tartru si placa bacteriana in treimea medie si de colet.

Fig.1 F.O. Pac no. 1 P.M. (66 years ,sex M) Evaluation of oral hygiene indices



Indicele de sangerare: *-arcada superioara*

$$X = \frac{\text{nr. suprafetelor sangerande}}{\text{nr. total al suprafetelor dentare}} \times 100 = \frac{0}{64} \times 100 = 0\ \%$$

-arcada inferioara

$$X = \frac{\text{nr. suprafetelor sangerande}}{\text{nr. total al suprafetelor dentare}} \times 100 = \frac{0}{64} \times 100 = 0\ \%$$

Indicele de placa Silness si Loe: 1 placa nu se observa cu ochiul liber pe suprafetele dentare decat dupa razuirea cu varful rotunjit al sondei parodontale

Indicele de sangerarea Muhlemann:0

Retractie gingivala

Dinte	V(mm)	O(mm)	M(mm)	D(mm)
2.1	2			
2.2	1			
3.2	1			
3.1	2			
4.1	2			

Fig 2 F.O. Pac. no 1:P.M.(66 years ,sex M) Evaluation of oral hygiene indices continued fig.1 and bleeding index.

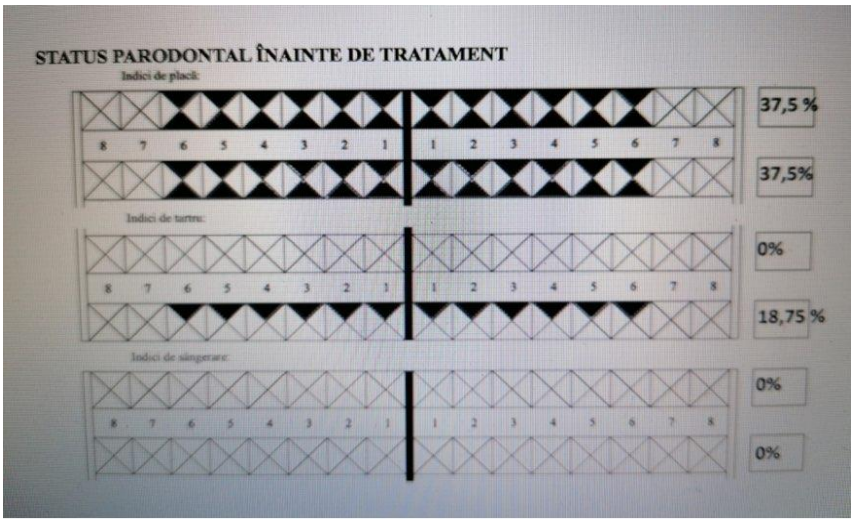


Fig.3 F.O. Pac. no 1: P.M.(66 years, sex M) Assessment of periodontal status before treatment

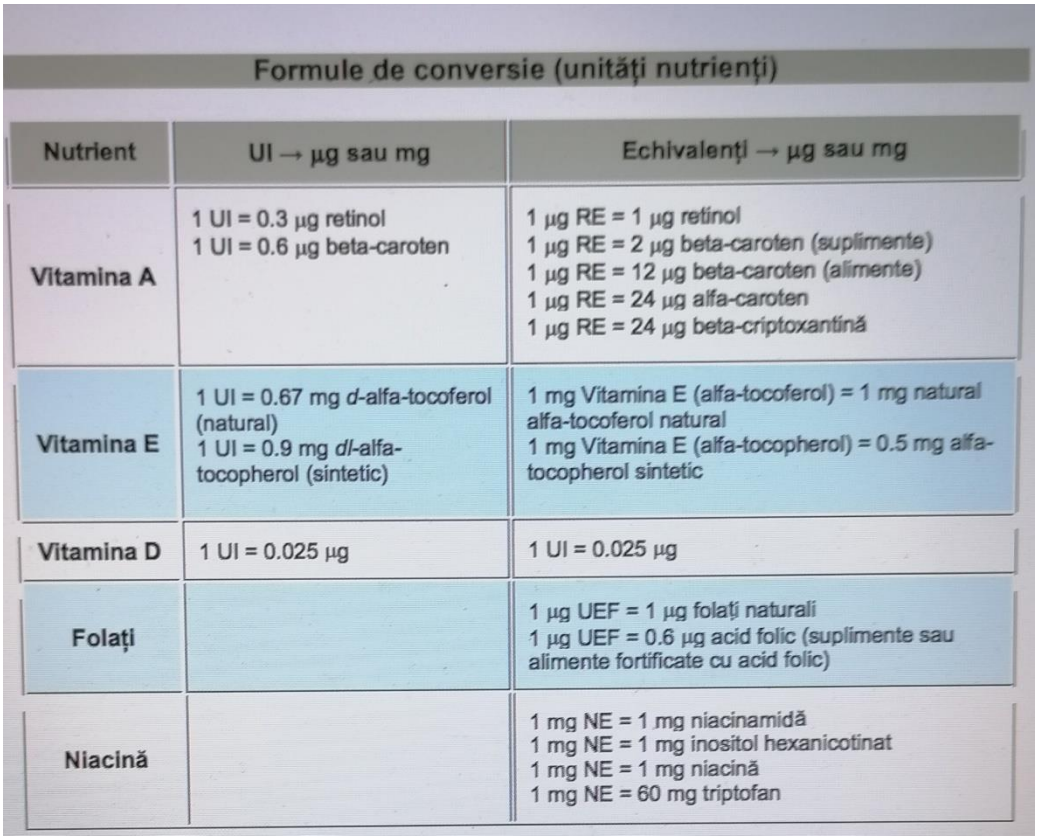
2.2.2. Performing the nutrigenetic test. A simple saliva sample is collected, after which the analysis laboratory generates a report that includes information about the deficiencies that the patient has.

NUTRIENT	UNITĂȚI	BĂRBAȚI	FEMEI	SARCINĂ	LACTAȚIE
Vitamina A	µg/zi	3000	3000	3000	3000
Vitamina C	mg/zi	2000	2000	2000	2000
Vitamina D	µg/zi	100	100	100	100
Vitamina E	mg/zi	1000	1000	1000	1000
Vitamina K	µg/zi	ND	ND	ND	ND
Tiamină	mg/zi	ND	ND	ND	ND
Riboflavină	mg/zi	ND	ND	ND	ND
Niacină	mg/zi	35	35	35	35
Vitamina B6	mg/zi	100	100	100	100
Folați	µg/zi	1000	1000	1000	1000
Vitamina B12	µg/zi	ND	ND	ND	ND
Acid pantotenic	mg/zi	ND	ND	ND	ND
Betaină	mg/zi	ND	ND	ND	ND
Biotină	µg/zi	ND	ND	ND	ND
Colină	mg/zi	3500	3500	3500	3500
Calciu	mg/zi	2500 (<50 ani) 2000 (>50 ani)	2500 (<50 ani) 2000 (>50 ani)	2500	2500
Crom	µg/zi	ND	ND	ND	ND
Cupru	µg/zi	10000	10000	10000	10000
Fier	mg/zi	45	45	45	45
Fluor	mg/zi	10	10	10	10
Fosfor	mg/zi	4000 (<70 ani) 3000 (>70 ani)	4000 (<70 ani) 3000 (>70 ani)	3500	4000
Iod	µg/zi	1100	1100	1100	1100
*Magneziu	mg/zi	350	350	350	350
Mangan	mg/zi	11	11	11	11
Molibden	µg/zi	2000	2000	2000	2000
Seleniu	µg/zi	400	400	400	400
Zinc	mg/zi	40	40	40	40
Sodiu	g/zi	2,3	2,3	2,3	2,3
Clor	g/zi	3,6	3,6	3,6	3,6

* Limita superioară pentru Magneziu reprezintă aportul adus de suplimente și medicamente, și nu reflectă aportul adus de alimente și apă.

ND = nedeterminat

Fig.4 Tolerable upper limits. The table below shows the maximum limits of daily nutrient intake for adults, depending on age, sex and physiological condition. Except for medical advice, these limits should not be exceeded.



Formule de conversie (unități nutrienți)

Nutrient	UI → µg sau mg	Echivalenți → µg sau mg
Vitamina A	1 UI = 0.3 µg retinol 1 UI = 0.6 µg beta-caroten	1 µg RE = 1 µg retinol 1 µg RE = 2 µg beta-caroten (suplimente) 1 µg RE = 12 µg beta-caroten (alimente) 1 µg RE = 24 µg alfa-caroten 1 µg RE = 24 µg beta-criptoxantină
Vitamina E	1 UI = 0.67 mg *d*-alfa-tocoferol (natural) 1 UI = 0.9 mg *dl*-alfa-tocopherol (sintetic)	1 mg Vitamina E (alfa-tocoferol) = 1 mg natural alfa-tocoferol natural 1 mg Vitamina E (alfa-tocopherol) = 0.5 mg alfa-tocopherol sintetic
Vitamina D	1 UI = 0.025 µg	1 UI = 0.025 µg
Folați		1 µg UEF = 1 µg folați naturali 1 µg UEF = 0.6 µg acid folic (suplimente sau alimente fortificate cu acid folic)
Niacină		1 mg NE = 1 mg niacinamidă 1 mg NE = 1 mg inositol hexanicotinat 1 mg NE = 1 mg niacină 1 mg NE = 60 mg triptofan

Fig.5 Conversion formulas (nutrient units)

In the following tables you have highlighted the deficiencies resulting in the 9 tests of the patients before performing the drug treatments. These were tested only once in order to highlight the deficiencies and to draw up treatment plans with supplements, leaving a new set of tests to be performed after the end of each treatment.

Pac1	Normal value	deficiency
vit.A	YES	
vit.C	YES	
vit.E	YES	
melatonina		YES

Table 1. T.N. Pac. no 1: P.M.(66 years, sex M) Interpretation of the nutrigenetic test.

Pac.2	Normal value	deficiency
vit.A	YES	
vit.C		YES
vit.E	YES	
melatonin		YES

Table 2. T.N. Pac. nr 2: V.R.(46 years, sex M) Interpretation of the nutrigenetic test.

Pac.3	Normal value	deficiency
vit.A	YES	
vit.C	YES	
vit.E	YES	
melatonin	YES	

Table 3. T.N. Pac. no 3: A.L.(41 yaers, sex M) Interpretation of the nutrigenetic test.

Pac.4	Normal value	deficiency
vit.A	YES	
vit.C		YES
vit.E	YES	
melatonin		YES

Table 4. T.N. Pac. no 4: A.L.(35 years, sex M) Interpretation of the nutrigenetic test.

Pac.5	Normal value	deficiency
vit.A		YES
vit.C		YES
vit.E		YES
melatonin		YES

Table 5. T.N. Pac. no 5: B.A.(35 years, sex F) Interpretation of the nutrigenetic test.

Pac.6	Normal value	deficiency
vit.A	YES	
vit.C	YES	
vit.E	YES	
melatonin		YES

Table 6. T.N. Pac. no 6: A.A.(42 years, sex F) Interpretation of the nutrigenetic test.

Pac.7	Normal value	deficiency
vit.A		YES
vit.C	YES	
vit.E	YES	
melatonin		YES

Table 7. T.N. Pac. no 7: L.A.(58 years, sex F) Interpretation of the nutrigenetic test.

Pac.8	Normal value	deficiency
vit.A	YES	
vit.C	YES	
vit.E	YES	
melatonin		YES

Table 8. T.N. Pac. no 8: B.M.(69 years, sex F) Interpretation of the nutrigenetic test.

Pac.9	Normal value	deficiency
vit.A		YES
vit.C		YES
vit.E		YES
melatonin		YES

Table 9. T.N. Pac. no 9: B.R.(32 years, sex F) Interpretation of the nutrigenetic test.

From performing the nutrigenetic tests we were able to create some statistics regarding: vitamin and melatonin deficiency depending on age, sex, and age from which it turned out that both sexes have VitD deficiencies but the higher percentage is in males (100% male / 60% female). Also from here it appears that both sexes have a deficiency in Vit C (50% male / 40% female).) In women compared to men, a deficiency of Vit A, Vit E analyzes show melatonin deficiency found in both sexes with a higher percentage in women (100% F and 80% B).

Male	Pac 1	Pac2	Pac3	Pac4
vit.A				
vit.C		YES		YES
vit.E				
melatonin	YES	YES		YES

TABLE 10. Deficiencies according to sex male. The highest percentage of deficiencies in males of Vit C 50% and melatonin 80%.

Female	Pac 5	Pac6	Pac7	Pac8	Pac9
vit.A	YES		YES		YES
vit.C	YES				YES
vit.E	YES				YES
melatonin	YES	YES	YES	YES	YES

Table 11. Deficiencies depending on the female sex. The highest percentage of deficiencies in females is 60% that is Vit A, followed by Vit C, Vit E in proportion of 40%, and a percentage of 100% melatonin.

In the following 4 tables, namely Table 12, Table 13, Table 14, Table 15 we highlighted the deficiency by age groups and we found that in the interval of 30-40 years we have a deficiency of 100% Vit C and melatonin and 50% Vit.A and Vit.E, 40-50 years we have a deficiency of 50% melatonin and 33.3% Vit.C and also a deficiency of 100% but in the age ranges 50-60 years and 60-70 years we have melatonin.

age 30-40 years	Pac 4	Pac 5	Pac 9
vit.A		YES	YES
vit.C	YES	YES	YES
vit.E		YES	YES
melatonin	YES	YES	YES

Table 12. The deficiency depending on the age range30-40 we have a deficiency of 100% of Vit C and melatonin and 50% of Vit.A and Vit.E

age 40-50 years	Pac 2	Pac 3	Pac 6
vit.A			
vit.C	YES		
vit.E			
melatonin	YES		YES

Table 13. The deficiency depending on the age range 40-50 years we have a deficiency of 50% melatonin and 33.3% Vit.C

age 50-60 years	Pac 7
vit.A	YES
vit.C	
vit.E	
melatonin	YES

Table 14.The deficiency depending on the age range 50-60 years was of 100% in case of VitA and melatonin.

age 60-70 years	Pac 1	Pac 8
vit.A		
vit.C		
vit.E		
melatonin	YES	YES

Table 15. The deficiency depending on the age range 60-70 years was 100% for melatonin.

4.Discutions

The symptoms and treatment of oral inflammatory diseases are mainly influenced by the intake or supplementation of micronutrients. Micronutrients are needed to maintain the health of the mucous membranes and oral structures, as they possess anti-oxidant and anti-inflammatory properties. Deficiency of certain micronutrients can modulate the risk of oral inflammatory diseases. Melatonin supplements along with micronutrients can be effective in improving oxidative and inflammatory conditions. Therefore melatonin and micronutrient therapy may be recommended as part of the therapeutic approach in the control of periodontal disease. more studies are needed.

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