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Deoxypyridinoline bone height after oral implant surgery in menopause women

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ABSTRACT

The ratio Deoxypyridinoline / Creatinine measured in urine (DPD/Cr) is the most sensitive and specific marker of early metabolic breakdown of collagen I, and therefore, of osteopenia and bone resorption. The normal values change with age and gender; in male adults the normal range is 2.3 to 5.4 nmol/mmol and in women is 3.0 to 7.4 nmol/mmol. It has been shown that osteopenia can lead to osteoporosis and to failure of implant osseointegration. The objective of this study was to associate levels of DPD/Cr in urine with bone height measured by tomography before surgery and three months after oral implant surgery in menopausal women. 20 healthy or systemically controlled postmenopausal women who underwent surgery implants, were selected by convenience for the study. All implants were: Titanium SIS® Implants (CIEO Foundation, Colombia) customized according to the patient requirements indicated in the CBCT. The implant length varied in the range 5 to 15 mm, internal diameter: 3 to 5 mm, internal hexagon: 2.4 mm, and screw: 1.85 × 0.35 mm. DPD values in urine were measured by a Chemical Luminescence Immune test and bone height in mm was measured in a tomography on implant zone before the surgery and 3 months after implant surgery. The average age of the patients was 61.2 ± 17.31 years and the number of implants 1-4/patient. The ratio DPD/ Cr showed a high average of 9.594 ± 0.475 nmol/mmol. Average pre-surgery bone height was 15.23 ± 1.41 mm and post-surgery decreased to 13.78 ± 1.16 mm. This difference was significant (t paired, p = 0.001). The Pearson correlation test showed a high association (p = 1) between the elevation of DPD/Cr and the decrease in bone height. There is a significant association between the change in concentrations of urinary creatinine-corrected deoxypyridinoline and bone resorption in menopausal women, three months after oral implant surgery.

Keywords: Bone resorption, creatinine, deoxypyridinoline, oral implants, oral surgery.

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INTRODUCTION

One of the main causes of oral implant failure is the lack of integration of the implant into the bone tissue that is related to some factors such as the patient's systemic health, where the hormonal participation of estrogens in women and testosterone in men, life style and surgical techniques, play an important role. Osteopenia can lead to the development of osteoporosis with a higher prevalence in women than in men. In Bogotá, the prevalence of osteopenia in women aged over 50 has been assessed in terms of the backbone (49.7%), hip (47.55%), reporting osteoporosis 15.7% and osteopenia 11.4% (Orjuela et al., 2018; Cepeda et al., 2014; Suarez, 2012; Norman and Meng, 2017; Pu and Tan, 2017; Finkelstein et al., 2008).

The bone is in a permanent process of regeneration and resorption regulated by the activation of osteoblasts

and osteoclasts; 80% of the skeleton is formed by cortical bone and only 20% by trabecular bone, which provides the highest percentage of bone replacement in the entire skeleton. The upper jaw bone is characterized by having the highest content of trabecular bone; therefore, its process of bone formation and resorption is accelerated (Giro and Coelho, 2010; Ross, 1998; Chou et al., 2017).

The ratio of *Deoxypyridinoline / urinary Creatinine (DPD)* is currently considered to be the most sensitive and specific assay for early detection of osteopenia. Normal values change with age and gender; for adult men, they range between 2.3 to 5.4 nmol/mmol of creatinine and for adult women from 3.0 to 7.4 nmol/mmol (Barba, 2011; Cepeda et al., 2010). Pyridinoline, hydroxyproline and deoxypyridinoline are defined as products derived from cross-link places of union between chains in the molecule of collagen type I. When collagen is metabolically degraded pyridinoline (PD) or deoxypyridinoline (DPD) are released. Deoxypyridinoline cross-links (DPD) are specific to bone tissue (Pallesen et al., 2002). DPD occurs almost exclusively in bone and dentin; therefore urinary DPD is more specific as a marker of bone resorption. Unlike other markers of bone resorption, DPD excretion is not affected by diet (collagen ingested is not eliminated in urine) or by the degree of activity of tissues other than bone (Barba, 2011) because it is released to blood circulation from collagen breakdown and then, unmetabolized in the liver, is eliminated only by urine. Its excretion is dependent of the kidney function; therefore the results must be corrected by the rate of creatinine urinary excretion.

PD and DPD are excreted in urine, in free form (40%) or peptide linked (60%) (Pallesen et al., 2002). Therefore, urinary levels correlate well to bone resorption indexes, that is with osteoclastic activity and are considered as early biomarkers for osteopenia. Fasting is not required for the analysis

Pyridinolines excretion follows a circadian rhythm, presenting higher values during the night, probably due to the 30% crosslinks degradation between 8 and 13 h. Therefore, the time of urine sampling is important to obtain comparable results. The reference values of urinary DPD change according to the analytical technique.

Usually, bone mineral density in women is reduced an average of 1% to 5% and in postmenopausal women from 1 to 3% due to the low hormonal flow of estrogens (Norman and Meng, 2017; Pu and Tan, 2017; Finkelstein et al., 2008).

All this has led to carry out preventive studies in order to know the state of bone health especially in postmenopausal women.

In a randomized clinical study, Tanimoto et al. (2004) evaluated the levels of PD and DPD in urine of patients with osteoarthritis at temporomandibular joint (TMJ). Urine samples were obtained from 12 patients with TMJ disorders, concluding that there is a significant increase (t -Student $p < 0.05$) in the levels of PD and DPD in urine in patients with temporomandibular osteoarthritis.

The effect of alendronate on DPD values in postmenopausal patients with osteoporosis or osteopenia has been evaluated (Bella and Cabrera, 2009). The sample of 118 women aged between 41 and 69 was divided into 5 experimental groups; in one of the groups, initial DPD was measured and after 60-day treatment with alendronate, concluding that only the postmenopausal women with osteoporosis medicated with Alendronate 6 months after treatment, presented significant changes (t. Student $p = 0.001$) in the DPD values.

Cepeda et al. (2010) compared the effectiveness of levels of DPD/urinary Creatinine and calcium in serum as early markers of osteopenia in 20 healthy menopausal women who did not take calcium supplements nor were under hormone replacement therapy. DPD was measured in the second sample of urine of the day and calcium in serum. Out of the total sample, 75% showed high levels of DPD/urinary Creatinine and 25% had normal levels. 100% of the sample showed normal calcium levels. The ratio DPD/Creatinine, showed a highly significant difference to the maximum normality values (Wilcoxon test, $p = 0.03$), while calcium levels did not show a significant difference regarding normal ranges (t Student $p = 0.99$).

In a controlled clinical trial (Payne et al., 2011), it was evaluated which bone biomarkers (DPD - calcium) reflect systemic and alveolar bone resorption. The sample of 128 menopausal women with osteopenia and periodontal disease was divided into two groups: case group ($n = 64$ women) medicated with calcium and vitamin D and control group with placebo. After two years, calcium biomarkers in serum and DPD in urine were analyzed again, finding a direct association with bone density loss. It was concluded that not any group showed a decrease in DPD although it was observed a significant increase in bone resorption and alveolar height (t-Student $p < 0.0001$).

Cepeda et al. (2014) compared the ratios of DPD/Creatinine and bone crest height, before and four months after an oral implant surgery. The sample of 28 healthy male and female patients (range of age: 40-75), were undergoing implant surgery and was divided into 2 groups by gender. The DPD in urine and bone heights in tomographic images, was evaluated from the apex of the implant to the margin of the bone crest, before and four months after surgery. In both sexes, the DPD medians were in the upper normal limit (7.5 women, 5.1 men). A significant correlation was found between the increase in DPD and gender ($p = 0.034$) and between gender and initial ($p = 0.010$) and final ($p = 0.035$) bone height, concluding that there is a high correlation between high levels of DPD and the increased bone resorption before implant placement and after it (Spearman $p = 0.005$).

All these studies have demonstrated that the increase in DPD/Creatinine ratio, allows the early and preventive diagnosis of osteopenia, a negative factor in the osseointegration process. Therefore, the objective of this investigation was: To determine the association between levels of DPD corrected for urinary creatinine with the tomographic bone height measured before and three months after oral implants surgery in menopausal women.

MATERIALS AND METHODS

The study was designed as analytical clinical research of a cross-sectional cohort. The protocol was approved by the Institutional Ethics Committee of the *Fundación Universitaria CIEO –UniCIEO* that classified it as a minimum risk investigation. After explaining and signing the informed consent, the protocol to be followed for the collection of urine samples was explained to each patient.

The sample selected by convenience included 20 healthy or systemically controlled menopausal women, who underwent implant surgery in the Oral and Reconstructive Implantology Clinic of the *Fundación Universitaria CIEO -UniCIEO* during 2017-2018. Patients with mental disabilities and not willing to cooperate with the study were excluded.

The same kind of implants was used for all patients: Titanium SIS® Implants (CIEO Foundation, Colombia) customized according to the patient requirements indicated in the CBCT. The implant length varied in the range 5 to 15 mm, internal diameter: 3 to 5 mm, internal hexagon: 2.4 mm, and screw: 1.85 × 0.35 mm.

DPD/urinary Creatinine values were measured in urine samples obtained with the following protocol: to eliminate the first urine in the morning; after two hours, to collect the second urine in a bottle delivered to the patients instructed to close the lid of the bottle very well, to mark it and not to expose it to direct light. Within the next 3 h, to deliver the sample to the *"Hormonal Research laboratory"* in Bogotá, to perform a quantitative analysis of DPD by "Enzyme-labeled solid phase chemiluminescent immunoassay" (Pyrilinks-D) with an incubation cycle of 1 × 30 min in the equipment IMMULITE 2000™. Each patient underwent a tomography in the implant pre-surgery area and 3 months after implant surgery, to measure and compare bone height in mm. The tomograms were taken with a cone tomography equipment, and with the Galaxis Sidexis software it was measured the length and distance in mm between two selected points of an image. The radiation dose is absolutely safe since it ranges between 277.00 to 681.00 mGycm^2, 85 Kv. The demographic patients' data such as age, sex and date of menopause initiation were obtained from the medical registers.

Statistical analysis

The statistical analysis was performed with the free software R and MINITAB free educational version, with descriptive statistics based on means, standard deviation and medians, and to show if there are significant differences between bone height pre and three months post-surgery of implants was applied the t-paired test, and to determine the association between the DPD/Creatinine ratio and bone heights by the Pearson correlation coefficient.

RESULTS

The average ± standard deviation age in years of the 20 post-menopausal women was 61.2 ± 17.31. The number of implants per patient was: 1-4 implants.

The results of DPD nmol/mmol of urine creatinine, showed a high average of 9.594 ± 0.475 nmol/mmol (Table 1). The average pre-surgery bone height was 15.23 mm ± 1.41 mm and 3 months post-surgery, it decreased to 13.78 ± 1.16 mm. This is a significant difference (t paired p = 0.001) (Table 2). The Pearson correlation coefficient indicates a high association (p value = 0.945) between the increment of DPD/Cr and the decrease of bone heights (Table 3).

DISCUSSION

The results of the present study indicate that it is important for the dentist, particularly for specialists in oral implantology, to know the bone health status in order to predict the beginning of osteopenia through bio-markers such as DPD/Creatinine ratio, in agreement with other studies (Cepeda et al., 2014; Barba, 2011; Tanimoto et al., 2004; Bella and Cabrera, 2009; Payne et al., 2011) and to predict the success of bone integration, particularly in postmenopausal women where the estrogen decrease alters the process of bone regeneration (Orjuela et al., 2018; Pu and Tan, 2017; Medeiros et al., 2017; Onuma et al., 2015; Miazgowski et al., 2012; Rogers et al., 2000).

In this investigation, it was observed that menopausal women have an increase in DPD with an average twice the normal value, which is why three months later there was an increase in bone loss with a value close to the accepted value in literature of 1 mm per year. These data agrees with what has been observed by several researchers (Payne et al., 2011) that also confirmed that women with osteopenia and periodontal disease show an association between calcium biomarkers and DPD with the systemic and alveolar bone loss. Also it was reported (Cepeda et al., 2015) that in both men and women with an average age of 54, the DPD medians were in the normal upper limit of 7.5 nmol/mMol for women and 5.1 nmol/mmol for men and bone resorption was 0.3 and 0.2 mm respectively, concluding that there is a high correlation between levels of DPD and bone resorption before implant placement and after surgery.

It has also been shown that osteopenia hinders bone integration and leads to implant failure, in patients with elevated DPD (Medeiros et al., 2017) in a meta-analysis of 12 studies, 8,859 patients and 29,798 implants, where the objective was to evaluate the survival rate of implants in patients with osteoporosis, concluding that there is a significant difference in marginal bone loss around the implants in patients with and without osteoporosis (p = 0.05).

As observed in these studies, osteopenia should be early diagnosed with DPD biomarkers, in individuals aged over 50, especially in women, in order to do preventive

Table 1. DPD/Cr ratio and bone height. Initial and three months after implant surgery.

Variable	Number of patients	Average	Standard deviation	Difference	Minimum	Median	Maximum
Urinary DPD *Creatinine Ratio (nmol/mmol)*	20	9.594	0.475	2.123	6.500	9.120	14.950
Initial bone height (mm)	20	15.23	1.41	6.28	9.20	12.88	30.80
Bone height 3 months after surgery (mm)	20	13.78	1.16	5.21	8.50	11.98	24.90

Table 2. Comparison of bone height before and 3 months after implant surgery (t-paired).

Average	Difference	Standard deviation	95% CI for the difference	Paired t value	P value
1.448	1.564	0.350	(0.716; 2.180)	4.14	0.001

Table 3. Correlation between DPD and bone heights. Pearson correlation coefficient.

	DPD	Initial height	Height 3 months
DPD	1		
Initial height	-0.337	1	0.945
Height 3 months	-0.316		1

medicine to reduce disabling diseases and improving lifestyle with exercise plans and nutritional habits.

Conclusion

There is a significant negative association between the elevation of the DPD/Creatinine biomarker and the increase in bone resorption in menopausal women, 3 months after oral implant surgery.

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