

# Effect of Low Level Laser Therapy on Local Bone Resorption During Orthodontic Treatment. A Randomized Controlled Trial

Efecto del Laser Terapéutico en la Reabsorción Osea Local Durante Tratamientos de Ortodoncia. Un Ensayo Clínico Aleatoriamente Controlado

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DOMINGUEZ, Á.; LEÓN, P.; ARISTIZABAL, J. F. Effect of low level laser therapy on local bone resorption during orthodontic treatment. A randomized controlled trial. *Int. J. Odontostomat.*, 10(3):483-490, 2016.

**ABSTRACT:** The aim of this study was to assess whether the application of low-level laser therapy (LLLT) during the first stage of orthodontic treatment has an effect on local bone resorption and is detectable at the systemic level by measuring deoxyypyridinoline levels (Pyrilinks) in urine. This was a randomized (1:1), double-blind, active-controlled, parallel-group trial. 28 adult patients who were going to start orthodontic treatment were randomly divided into the control group (n: 13) and the experimental group (n: 15), the latter of which received LLLT. All of the subjects underwent testing of urine samples: the first one on the day before the beginning of orthodontic treatment (T0), and the second one 5 days after bracket placement to measure Pylilinks values (Dpd/Cr) in urine. Group differences were evaluated with Student's paired t-test. At the beginning of the study, the Pylilinks were in the normal range for 53.57 % of the patients, and 46.43 % had elevated values according to the normal ranges. Only taking into account the normal values at (T0), the average Pylilinks for control group (T0) were  $5.75 \pm 1.20$  nM/mM, (T1):  $6.02 \pm 3.00$  nM/mM. For experimental group, (T0) was  $5.71 \pm 0.72$ , and it was  $6.63 \pm 0.73$  in (T1). There were no significant differences in the Pylilinks changes. ( $p = 0.75$ ). In the experimental group levels raised statistically significant ( $p = 0.009$ ). LLLT on patients starting orthodontic treatment with normal Pylilinks levels have a statistically significant increment on their levels 5 days post irradiation.

**KEY WORDS:** orthodontic movement, pyrilinks, low level laser, deoxyypyridinoline, bone reorption.

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## INTRODUCTION

The application of Low-level laser therapy is a noninvasive alternative that has shown to be effective not only to reduce pain caused by the application of separators (Burns *et al.*, 2001; Aihara *et al.*, 2006; Cattaneo *et al.*, 2009; Altan *et al.*, 2012; Artés-Ribas *et al.*, 2013; Bister & Meikle, 2013) in the initial stages of treatment (Chen *et al.*, 2011), during canine retraction (Cruz *et al.*, 2004; d'Apuzzo *et al.*, 2013) and following activation of orthodontic final archwires (Dominguez *et al.*, 2012) but also to reduce the overall orthodontic treatment time (Dominguez *et al.*, 2009; Domínguez-Camacho & Velásquez-Cujar, 2010; Doshi–Mehta & Bhad–Patil, 2012; Domínguez & Velásquez, 2013).

Tooth movement by orthodontic force application depends on remodeling at the periodontal ligament and alveolar bone. Orthodontic movement should be described as a continual and balanced process characterized by bone deposition and bone resorption (Evidence-Based Medicine Working Group, 1992).

Low-level laser therapy accelerates the bone remodeling process by stimulating osteoblastic and osteoclastic cell function and proliferation during orthodontic tooth movement. These effects are due to its ability to stimulate cell metabolism, angiogenesis, bone formation and osteoclastogenesis (Garnero *et al.*,

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Funding. This investigation was proclaimed the winner of the internal Universidad del Valle research call for 2012. All of the funding was provided by the university dean's office.

1994; Fassbender *et al.*, 2009; Fujita *et al.*, 2008.; Fujiyama *et al.*, 2008; Habib *et al.*, 2012; Genc *et al.*, 2013).

Collagen cross-link molecules such as pyridinoline (PYD), deoxypyridinoline (DPD), and N-terminal cross-linked peptides (NTX) have been measured in urine as indices of bone resorption (Ju *et al.*, 1997). Deoxypyridinoline (DPD) is a derivative of hydroxypyridinium, which is released during bone resorption into the blood stream and is eliminated unmodified with urine. A further collagen-derived marker of bone resorption is the C-terminal telopeptide of type I collagen, which is released in bone resorption and almost entirely excreted by the kidney (Kawasaki *et al.*, 2000).

Pyridinium cross-links have proven to be specific and sensitive bone resorption markers for evaluation of metabolic bone diseases such as osteoporosis, hyperthyroidism and hyperparathyroidism (Lim *et al.*, 1995; Marquezan *et al.*, 2010; Kim *et al.*, 2013; Marini *et al.*, 2015).

The aim of this study was to assess if the effect on bone metabolism and the application of Low-level laser therapy (Ga-Al-As) in humans in the first stage of orthodontic treatment, is detectable at systemic level by measuring the levels of Deoxypyridinoline (Pyrilinks) in urine.

## MATERIAL AND METHODS

This was a randomized (1:1), double-blind, active-controlled, parallel-group trial.

The study began in February 2013. 50 subjects were assessed for eligibility who attended to start corrective orthodontic treatment in the Postgraduate program of Orthodontics, School of Dentistry in Univalle University. A total of 41 patients were eligible for randomization into the study. Analyzed total, distribution and follow up are shown in the CONSORT (Consolidated Standards of Reporting Trials) Diagram (Fig. 1).

Randomization was made under prior consecutive patient list submission to <http://www.random.org/lists>. By a different subject from the one that made the patient intervention, patient assignment was hidden from the lab, data operator, and to the STATESMAN, and was implemented by one of the researchers. Control group patients received inactive

laser applications in order to blind this group. Laser manipulation was done by one subject for every patient.

Following randomization, 15 patients received the Low-level laser therapy and 13 formed the control group. The patients were all treated with brackets and tubes Orthos™ (Ormco, SA de CV Mexico) and initial arch wire Cu-NiTi 0.014 inch (Ormco, SA de CV Mexico). All subjects had to be tested on urine samples, the first one, on the day before treatment (T0), and the second one, was taken 5 days after brackets and archwire placement. The final sample consisted in 15 patients as the experimental group and 13 patients as the control group.

### Inclusion Criteria

- Patient with Ages between 18 to 40 years at the time of treatment.
- Patients without periodontal compromise.
- Without metabolic bone diseases.
- No history of fracture or orthopedic surgery 6 months before the study.
- No medication.
- Patients who initiated conventional orthodontic treatment in clinical orthodontic of the Universidad del Valle.

### Exclusion Criteria

- Pregnancy.
- Patients with history of kidney or liver disease.
- Orthopedic Trauma during the study.
- History of orthopedic surgery or fractures less than 6 months.
- History of use of Bisphosphonates.
- Patients with Thyroid disease.
- Menopause.

**Ethical Considerations.** The study was part of Resolution 8430 of 1993, by which the scientific, technical and administrative standards for the health research are set. The project was approved by the Institutional Review Committee of Human Ethics Faculty of Health, Universidad del Valle.

**Laser protocol.** Experimental subjects were irradiated with laser therapy PhotonLase III (DMC equipment; Sao Carlos Brazil) with wavelength of 808 nm, 80 J/cm<sup>2</sup> and 100 mW, for 22 seconds, 1 mm from the gingiva following buccal surface of all teeth of both the upper arch and the lower arch and 22 seconds following the same protocol for the palatal / lingual surface. All of them were made by the same operator.

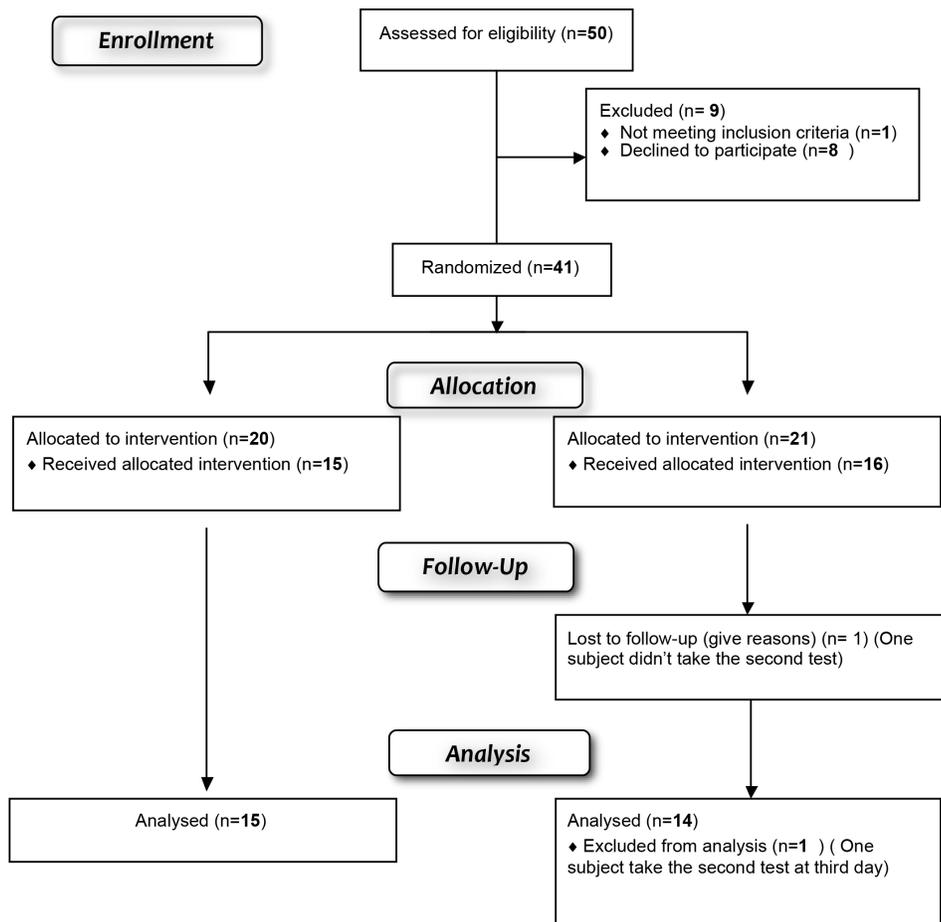


Fig. 1. Flow Diagram LLT-PyriLinks Sample.

**Evaluation of local Bone resorption.** The effect on local bone resorption was evaluated by determination of Deoxypyridinoline levels in urine following this protocol:

Each sample of 30 ml (first urine of the day) was sent to the laboratory. The sample was protected from ultraviolet light to prevent deterioration of the Deoxypyridinoline. Samples were stored at  $-80^{\circ}\text{C}$  until immunoassay testing according to manufacturer's instructions. The test was performed in a Sandwich Immunoassay using a monoclonal antibody as a reagent for Deoxypyridinoline (D-PyriLinks - MetranBiosystems, USA). Deoxypyridinoline in the sample competes with the Alkaline Phosphatase - Deoxypyridinoline and the reaction is detected by the p-nitrophenyl phosphate substrate. Through colorimetry, the amount of color is reverse to the amount of Deoxypyridinoline sample. Following correction for urine creatinine, normal values ranging

from 2.5 to 5.5 nM of urine creatinine D-Pyr/nM for males and 2.5 to 6.5 nM of D-Pyr/nM for female.

Two urine tests were made, one prior to the orthodontist appointment (T0) and the second 5 days post irradiation (T1).

**Statistical Analysis.** Data on the levels of DPD were corrected by creatinine (Deoxypyridinoline / Creatinine) and obtained in nM / mM, then they were tabulated and statistically analyzed, including age and gender with STATA software version 13 to determine the characteristics of the sample.

The changes in the levels of DPD / Cr in urine were compared by paired t-test because the data were parametric (no units because it is a ratio). To evaluate the difference between t0 and t1 in each group the Past versión 2010 Excel was used showing a normal distribution.

## RESULTS

The age average of the sample was 30.42 years ( $\pm 6.24$ ). Doing the Two-sample t test with equal variances, it was found that the age average in the control group was 29.84 years ( $\pm 8.44$ ) while in the experimental group was 30.93 years ( $\pm 3.6$ ). No statistically significant age differences were found between groups (Table I). The distribution of participants by gender showed a percentage of 64.29 % women and 35.71 % for men. The age distribution in both genders was normal according to the Shapiro-Wilk test (Table II).

At the beginning of the study Pylilinks values were in the normal range for 53.57 % of the patients and 46.43 % had elevated values according to the normal ranges

The Pylilinks average levels for the control group before the procedure (experiment) (T0) were  $7.45 \pm$

$2.72$  nM / mM and 5 days after the experiment (T1) were  $6.59 \pm 2.4$  nM / mM. For the experimental group (laser group) the initial values had an average of  $7.59 \pm 2.92$  (T0), and  $7.24 \pm 1.57$  in T2 (Table III).

There were not significant differences in the Deoxypyridinoline level change comparing before and after in the control group, neither in the experimental group ( $p > 0.05$ ).

There were also no significant differences between groups before or after the procedure (experiment) ( $p > 0.05$ ).

The control group showed a decrease of 69.23 % in the Pylilinks levels and they increased in 23.08 %. While in the experimental group the increase was 53.33 %.

Table I. Average age of the sample.

Group	Obs	Mean	Std. Err.	Std. Dev.	(95% Conf. Unten/al)	
Control	13	29.84615	2.342052	8.044388	24.70326	34.94905
Experimental	15	30.93333	.948516	3.673587	28.89897	32.9677
Combined	28	30.42857	1.180114	6.244574	28.00718	32.84996
Difference		-1.087179	2.401903		-6.020361	3.850002

diff= mean(Control) - mean(Experimental) t = -0.4526

Ho: cIff =0

degrees of freedom=26

Ha: diff < 0

Ha: diff!=0

Ha:diff > 0

Pr (T < t) = 0.3273 Pr( |TI| > |tI| ) = 0.6546 Pr(T > t) = 0.6727

Table II. Deoxypyridinoline Concentration (all subjects included).

	Control			Experimental	
T0	Average $\pm$ SD	7,45 $\pm$ 2,72	nM/mM	7,59 $\pm$ 2,92	nM/mM
T1	Average $\pm$ SD	6,59 $\pm$ 2,4	nM/mM	7,24 $\pm$ 1,57	nM/mM

Table III. Deoxypyridinoline Concentration for subjects with normal levels in T0.

	Control			Experimental	
T0	Average $\pm$ SD	5,75 $\pm$ 1,2	nM/mM	5,71 $\pm$ 0,72	nM/mM
T1	Average $\pm$ SD	6,59 $\pm$ 2,4	nM/mM	6,63 $\pm$ 0,73	nM/mM

## DISCUSSION

To evaluate if the effect on bone metabolism and the LLLT is detectable in urine, Pylilinks values were measured before the initial activation of orthodontic

archwires and 5 days later, finding changes in the results of a test that should not change in such a short time, unless a procedure is done, and has an effect on

bone turnover. In this case orthodontic treatment with or without low level laser therapy application.

This evaluation method was selected because urinary measurement of free Deoxypyridinoline (DPD) exhibits the least biological variability day-to-day, within individuals across the diurnal cycle, and within a healthy premenopausal population (Marquezan *et al.*, 2010).

The results showed no significant difference in the level changes of Pyrilinks comparing before and after between the control and the experimental group. These results suggest that on the fifth day of starting orthodontic treatment the bone turnover is detectable in urine but due to the series of events involved after the application of an orthodontic force, probably on this day an increase occurs in the proliferation of osteoblast more than a promotion of pre osteoclasts aggregation to become osteoclasts.

At the beginning of the study, Pyrilinks values were in the normal range for 53.57 % of the patients and 46.43 % had elevated values according to the normal ranges. This may explain the large individual variation of the different movement speed in patients under orthodontic treatment that depends on the particular state of their bone metabolism. Some patients may have increased osteoclast activity from the beginning of their treatment which may influence the rate of tooth movement.

The results also suggest that on the fifth day of irradiation, it cannot be found an increase in osteoclastogenesis, but there can also be a predominant proliferation of osteoblasts that were previously found in irradiating normal human osteoblast cell cultures having a peak at the same day in vitro (Oppenheim, 1942), without any cytotoxic effect on the pre-osteoclasts (Reitan & Kvam, 1971).

In the clinical trials that analyzed osteoclastogenesis (Robins *et al.*, 1991; Sackett *et al.*, 1996; Sarno *et al.*, 1999) the process was detected from days 2–19, whereas Marquezan *et al.* did not find differences.

It is possible that day five was too early to detect an increment in osteoclastogenesis. Seibel *et al.* (1993) found that osteoclastogenesis was statistically significant higher than the control group on day 7 and 13. However, a significant increase in the proliferation of Osteoblasts could achieve an increase in RANKL and subsequently by the feedback this increase

osteoclastogenesis, being the expression of RANK-RANKL the mechanism by which the application of laser stimulates the velocity of the movement as was reported by Fujita *et al.* (Sousa *et al.*, 2014).

Altan *et al.* (in Sousa *et al.*, 2011) reported that LLLT accelerates the bone remodeling process by stimulating osteoblastic and osteoclastic cell proliferation and function during orthodontic tooth movement. This suggests that in terms of acceleration of dental movement, it is important to consider not only osteoclastogenesis but also the increase in the population of osteoblast necessary for an effective bone remodeling process.

The authors do not know about previous reports that have used Pyrilinks to evaluate the effects on bone metabolism, after observing that they can be changed after the application of a force. Although on day 5 not in a statistically significant way, but if is clinically important to begin understanding with a different gaze the interpretation of the biology of tooth movement different from the pressure - tension theory described over 100 years ago (Sun *et al.*, 2001) and based on animal studies (Uebelhart *et al.*, 1990; Tortamano *et al.*, 2009; Sygouros & Acar, 2013) at present these types of studies are not included on the evidence scale or are classified below expert opinion (Yamaguchi *et al.*, 2007; Viecilli *et al.*, 2008; Youssef *et al.*, 2008; Yamaguchi *et al.*, 2010) and this theory has begun to be revalued (Zhu *et al.*, 2002) but it needs contemporary methods to be totally based on human.

So far LLLT as an accelerated treatment modality for orthodontic tooth movement is supported by the systematic review developed by Sousa *et al.* (2014) however it is necessary to perform more randomized controlled clinical trials to clarify the sequence of events that occur every day in the dentoalveolar bone metabolism after the application of an orthodontic force and we suggest performing Pyrilink tests on days 1,3 and 7.

## CONCLUSIONS

- LLLT on patients starting orthodontic treatment with normal Pyrilinks levels have a statistically significant increment on their levels 5 days post irradiation.
- It is suggested that measurement of Deoxypyridinoline levels in urine is a method that can be used to assess

the changes day by day in bone metabolism which occur at the dentoalveolar bone level and can be detectable systemically.

· Not all patients starting orthodontic treatment have a normal range in levels of Deoxyypyridinoline in urine, which means an increase of systemically osteoclastic activity, which may explain the large intra-individual variability in the proportion of tooth movement depending on bone metabolism.

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**DOMINGUEZ, Á.; LEÓN, P.; ARISTIZABAL, J. F.** Efecto del laser terapéutico en la reabsorción ósea local durante tratamientos de ortodoncia. Un ensayo clínico aleatoriamente controlado. *Int. J. Odontostomat.*, 10(3):483-490, 2016.

**RESUMEN:** El objetivo de este trabajo fue evaluar si la aplicación de la terapia láser de bajo nivel (TLBN) durante la primera etapa del tratamiento ortodóncico tiene un efecto sobre la resorción ósea local y es detectable a nivel sistémico midiendo los niveles de desoxipiridinolina en la orina. Se trató de un ensayo aleatorizado (1:1), doble ciego, controlado de forma activa y paralelo. 28 pacientes adultos que iban a iniciar el tratamiento de ortodoncia se dividieron al azar en el grupo control (n: 13) y el grupo experimental (n: 15), el último de los cuales recibió TLBN. Todos los sujetos fueron sometidos a pruebas de muestras de orina: la primera en el día anterior al inicio del tratamiento ortodóncico (T0) y la segunda 5 días después de la colocación del bracket para medir los valores de Pylilinks (Dpd / Cr) en la orina. Las diferencias grupales se evaluaron con la prueba t de Student pareada. Al inicio del estudio, los Pylilinks estaban en el rango normal para 53,57 % de los pacientes, y 46,43 % tenían valores elevados según los rangos normales. Sólo teniendo en cuenta los valores normales en (T0), los Pylilinks medios para el grupo de control (T0) fueron  $5,75 \pm 1,20$  nM / mM, (T1):  $6,02 \pm 3,00$  nM / mM. Para el grupo experimental, (T0) fue de  $5,71 \pm 0,72$ , y fue de  $6,63 \pm 0,73$  en (T1). No hubo diferencias significativas en los cambios de Pylilinks. (P = 0,75). En el grupo experimental los niveles aumentaron estadísticamente (p = 0,009). LLLT en los pacientes que comienzan el tratamiento ortodóncico con niveles normales de Pylilinks tienen un incremento estadísticamente significativo en sus niveles 5 días después de la irradiación.

**PALABRAS CLAVE:** movimiento ortodóncico, pirlilinks, láser de bajo nivel, desoxipiridinolina, reabsorción ósea.

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Received:15-07-2016  
Accepted: 17-10-2016