UNIVERSIDADE PAULISTA
PROGRAMA DE PÓS-GRADUAÇÃO EM ODONTOLOGIA

IMPACTO DO TRATAMENTO DE SUPERFÍCIE DO PILAR INTERMEDIÁRIO DE IMPLANTES DO TIPO CONE MORSE NO PROCESSO INICIAL DE REPARO ÓSSEO. ESTUDO CLÍNICO, PROSPECTIVO, CONTROLADO, RANDOMIZADO E DE BOCA DIVIDIDA

Dissertação apresentada ao Programa de Pós-Graduação em Odontologia da Universidade Paulista – UNIP, para a obtenção do título de Mestre em Odontologia.

ANDRE SEFERIAN OBICE

SÃO PAULO
2017

UNIVERSIDADE PAULISTA
PROGRAMA DE PÓS-GRADUAÇÃO EM ODONTOLOGIA

IMPACTO DO TRATAMENTO DE SUPERFÍCIE DO PILAR INTERMEDIÁRIO DE IMPLANTES DO TIPO CONE MORSE NO PROCESSO INICIAL DE REPARO ÓSSEO. ESTUDO CLÍNICO, PROSPECTIVO, CONTROLADO, RANDOMIZADO E DE BOCA DIVIDIDA

Dissertação apresentada ao Programa de Pós-Graduação em Odontologia da Universidade Paulista – UNIP, para a obtenção do título de Mestre em Odontologia com Área de Concentração em Clínica Odontológica (Subárea: Periodontia), sob orientação do Profa. Dra. Suzana P. Pimentel

ANDRE SEFERIAN OBICE

SÃO PAULO
2017

Obice, Andre Luis Seferian.
Impacto do tratamento de superfície do pilar intermediário de implantes do tipo cone morse no processo inicial de reparo ósseo. Estudo clínico, prospectivo, controlado, randomizado e de boca dividida. / Andre Luis Seferian Obice. - 2017.
26 f. il. color.

Dissertação de Mestrado Apresentada ao Programa de Pós-Graduação em Odontologia da Universidade Paulista, São Paulo, 2017.

Área de Concentração: Periodontia.
Orientador: Profª. Drª. Suzana Peres Pimentel.

1. Implantes dentários. 2. Pilar intermediário. 3. Tratamento de superfície. 4. Osso. 5. Marcadores biológicos. 6. Análise de proteínas. I. Pimentel, Suzana Peres. (orientador). II. Título.

ANDRE SEFERIAN OBICE

IMPACTO DO TRATAMENTO DE SUPERFÍCIE DO PILAR INTERMEDIÁRIO DE IMPLANTES DO TIPO CONE MORSE NO PROCESSO INICIAL DE REPARO ÓSSEO. ESTUDO CLÍNICO, PROSPECTIVO, CONTROLADO, RANDOMIZADO E DE BOCA DIVIDIDA

Dissertação apresentada ao Programa de Pós-Graduação em Odontologia da Universidade Paulista – UNIP, para a obtenção do título de Mestre em Odontologia.

Aprovado em:

BANCA EXAMINADORA

_____ ___/___/201__.
Profa. Dra. Suzana Peres Pimentel (Orientadora)
Universidade Paulista - UNIP

_____ ___/___/201__.
Prof. Dr. Márcio Casati
Universidade Paulista - UNIP

_____ ___/___/201__.
Prof. Dr. Sergio Gerhke
Universidade Católica/Uruguai

DEDICATÓRIA

Dedico este trabalho aos meus pais, Jose Antonio e Daisy, e também a minha esposa, Karina, que estiveram ao meu lado a cada segundo para conclusão desse sonho.

AGRADECIMENTOS

A Deus, por me confirmar sobre essa oportunidade, e mesmo com as maiores dificuldades me manter em paz, e ter conduzido para a conclusão deste trabalho, sem Deus eu não chegaria até aqui.

Aos meus pais José Antonio Vital Óbice e Daisy Seferian Óbice, por me oferecerem tudo para que eu chegasse até aqui, e pelo simples fato de acreditarem no meu trabalho;

A Profa. Dra. Suzana Pires Pimentel, orientadora deste trabalho, por ter me aceitado como orientado, e ter me ensinado como realizar uma pesquisa com excelência.

A minha esposa, Karina Seferian Obice, me suportou e me deu apoio em todos os momentos durante todo o curso.

Agradeço à equipe de implantodontia da APOIO, que em 2010 acreditou em mim e me proporcionaram, com ajuda de Deus, completamente a mudança do meu futuro profissional; Agradeço ao Prof. Dr. Fabiano Ribeiro Cirano, Hsu Shao Feng, Fernando Hayashi, Alexandre Conte e Márcio Zaffalon Casatti.

À toda equipe de Periodontia da UNIP/SP: Dra. Mônica Grazieli, Dra. Fernanda Vieira Ribeiro pelo suporte e pela paciência durante todo o trabalho;

RESUMO

O objetivo deste estudo foi comparar prospectivamente o impacto do tratamento de superfície do pilar intermediário de implantes tipo cone morse no: processo inicial de reparo ósseo, por meio da avaliação da liberação de marcadores relacionados à osteoblasto/vasculogênese e reparo de tecido mole no fluido peri-implantar. Para este estudo controlado, randomizado, duplo cego e de boca dividida, foram selecionados 15 pacientes que necessitavam de implantes unitários em áreas posteriores de mandíbula bilateralmente. Os implantes forma aleatoriamente divididos em dois grupos: **Usinado** - implante instalado no mínimo 1mm infra ósseo, com pilar intermediário convencional de superfície usinada; **Tratado** - implante instalado no mínimo 2mm infra ósseo, com pilar intermediário com colar de 1,5mm de superfície tratada. Para a avaliação do processo inicial de reparo ósseo após a instalação do pilar intermediário, foram realizadas coletas do fluido peri-implantar 3, 14 , 30 e 60 dias após a inserção dos implantes, para avaliação dos níveis de marcadores relacionados à osteoblasto/vasculogênese e formação de tecido mole: fator de crescimento epidérmico (EGF), proteína óssea morfogenética-9 (BMP-9), endotelina-1 (ET-1), fator de crescimento fibroblástico (FGF), fator de crescimento placentário (PlGF) e fator de crescimento endotelial (VEFG) , por meio de plataforma Luminex/Magpix. Após a obtenção dos níveis de cada marcador, os dados foram submetidos à análise estatística, considerando-se o nível de significância de 5%. A análise dos resultados demonstrou diferença significativa entre os grupos, com maiores níveis de EGF, BMP-9, Endothelina-1, FGF e PlGF no grupo tratado, aos 30 dias após a instalação do implante ($p<0.05$). Além disso, os níveis de PlGF apresentaram-se mais elevados no grupo tratado também no tempo 60 dias ($p<0.05$). Na análise intragrupo, foi possível verificar diferença significativa nos níveis de endotelina-1 e FGF entre os tempos de 3 e 30 dias e entre 3 e 60 dias, no grupo tratado ($p<0.05$). Além disso, houve diferença nos níveis de VEFG no grupo tratado entre os dias 3 e 60 ($p<0.05$). Para o grupo usinado, observou-se diferença significativa nos níveis de ET-1, FGF, PlGF e VEGF entre o tempo de 3 e 60 dias ($p<0.05$). Adicionalmente, observou-se diferença significativa na concentração de PlGF entre os tempos de 14 e 60 dias, para o grupo usinado ($p<0.05$). Pode-se concluir que o tratamento de superfície do pilar com TiO_2 influenciou significativamente a liberação de marcadores relacionados à formação óssea, à angiogênese e reparo tecidual durante o reparo peri-implantar inicial.

Palavras-Chave: Implantes dentários. Pilar intermediário. Tratamento de superfície. Osso. Marcadores biológicos. Análise de proteínas.

ABSTRACT

The aim of this randomized, double blind, split-mouth controlled clinical trial was to evaluate the influence of abutments surface treatment of cone morse implants on the profile of osto-angiogenesis and tissue repair. Fifteen patients received single mandibular implants bilaterally. Implants were randomly assigned into two groups: **Machined** - implant installed at least 2mm below bone, with conventional intermediate drilled surface abutment; **Treated** - implant installed at least 1mm below bone, with 1.5mm surface treated collar abutment. Levels of Epidermal Growth Factor (EGF), bone morphogenetic protein 9 (BMP-9), endothelin-1 (ET-1), fibroblast growth factor (FGF), placental growth factor (PlGF) and vascular endothelial growth factor (VEGF) in the the peri-implant fluid were quantified at 3, 14, 30 and 60 days. Intergroup comparison showed higher levels of EGF, BMP-9, Endothelin-1, FGF and PlGF in the treated group, at 30 days after implant insertion ($p < 0.05$). In addition, PlGF levels were higher in the treated group at 60 days ($p < 0.05$). Intragroup analysis revealed significant difference in the levels of ET-1 and FGF between 3 and 30 days and between 3 and 60 days in the treated group ($p < 0.05$). In addition, it was observed difference in the levels of VEGF in the treated group between days 3 and 60 ($p < 0.05$). Significant difference was observed in ET-1, FGF, PlGF and VEGF levels between day 3 and 60 ($p < 0.05$) in the machined group. Additionally, a significant difference in PLGF concentration was observed between day 14 and 60 in the machined group ($p < 0.05$). It can be concluded that abutment surface treatment with TiO_2 significantly influenced the levels of osteo-angiogenesis-related markers during early peri-implant repair.

Keywords: Dental implants. Abutment. Surface treatment. Bone. Biological markers. Protein array.

SUMÁRIO

1 INTRODUÇÃO

A perda óssea peri-implantar pode ser associada com a presença de um espaço entre o pilar intermediário e o implante, denominado *microgap*. Essa região permite acúmulo e proliferação de bactérias orais (Jones & Cochran 2006), que provocam a inflamação do tecido mole, com invasão do infiltrado inflamatório e reabsorção óssea de 1.5 a 2 mm (Abrahamsson et al., 1997). Além disso, o *microgap* influencia no recrutamento e localização de células inflamatórias e na relação anatômica dos tecidos moles e duros em torno do implante (Jones et al 2006).

Após a instalação do pilar, observa-se geralmente uma perda óssea de 1.5 a 2 mm, com perda subsequente de 0.1 mm a cada ano, na região da primeira rosca do implante (Berglundh & Lindhe, 1996; Hermann et al 1997; Hermann et al 2000; Hermann et al 2001). Os tecidos moles peri-implantares executam um papel protetor de selo biológico, reduzindo a colonização bacteriana e, consequentemente, prevenindo a perda óssea peri-implantar. Embora logo após a inserção do implante, o epitélio juncional peri-implantar esteja em contato tanto com o corpo do implante, como com o pilar, ao longo do tempo, esse contato restringe-se somente ao corpo do implante, devido à perda óssea decorrente da instalação do pilar e estabelecimento da inflamação (Atsuta et al., 2016; Berglundh & Lindhe, 1996). Com o objetivo de reduzir o efeito negativo da presença do microgap e, consequentemente, reduzir a perda óssea peri-implantar, alternativas de osseointegração na região da junção implante/pilar começaram a ser estudadas. (Comut et al. 2001; Schwarz et al. 2007a, 2007b; Weiner et al 2008; Alexander et al 2009; Nevins et al. 2008, 2010; Tete et al. 2009; Kloss et al. 2011). A rugosidade da superfície do pilar poderia auxiliar no processo de quimio-atração de plaquetas e na formação de um coágulo de fibrina mais denso, resultando em maior velocidade de osseointegração (Cooper FL., 2000). Além disso, o tratamento de superfície do pilar poderia proporcionar maior volume de tecido ósseo na região da crista óssea, melhorando a adesão dos tecidos moles e a inserção de fibras e, consequentemente, a capacidade de selamento biológico.

Estudos prévios verificaram o efeito de microtexturas na superfície do implante tratadas com fatores de crescimento, como o TGF-β, na inserção, distribuição, orientação e crescimento de fibroblastos de osteoblastos. Os autores verificaram que as microtexturas controlaram a direção do crescimento ósseo, sugerindo que esse tipo de textura poderia favorecer a inserção de tecido mole e ósseo por meio do control da inserção, proliferação e diferenciação celulares (Frenkel SR., et al 2002). Além disso, Simmons et al. 2002

observaram que a presença dessas texturas estimula a fosforilação da tirosina e expressão de RNAm para fibronectina.

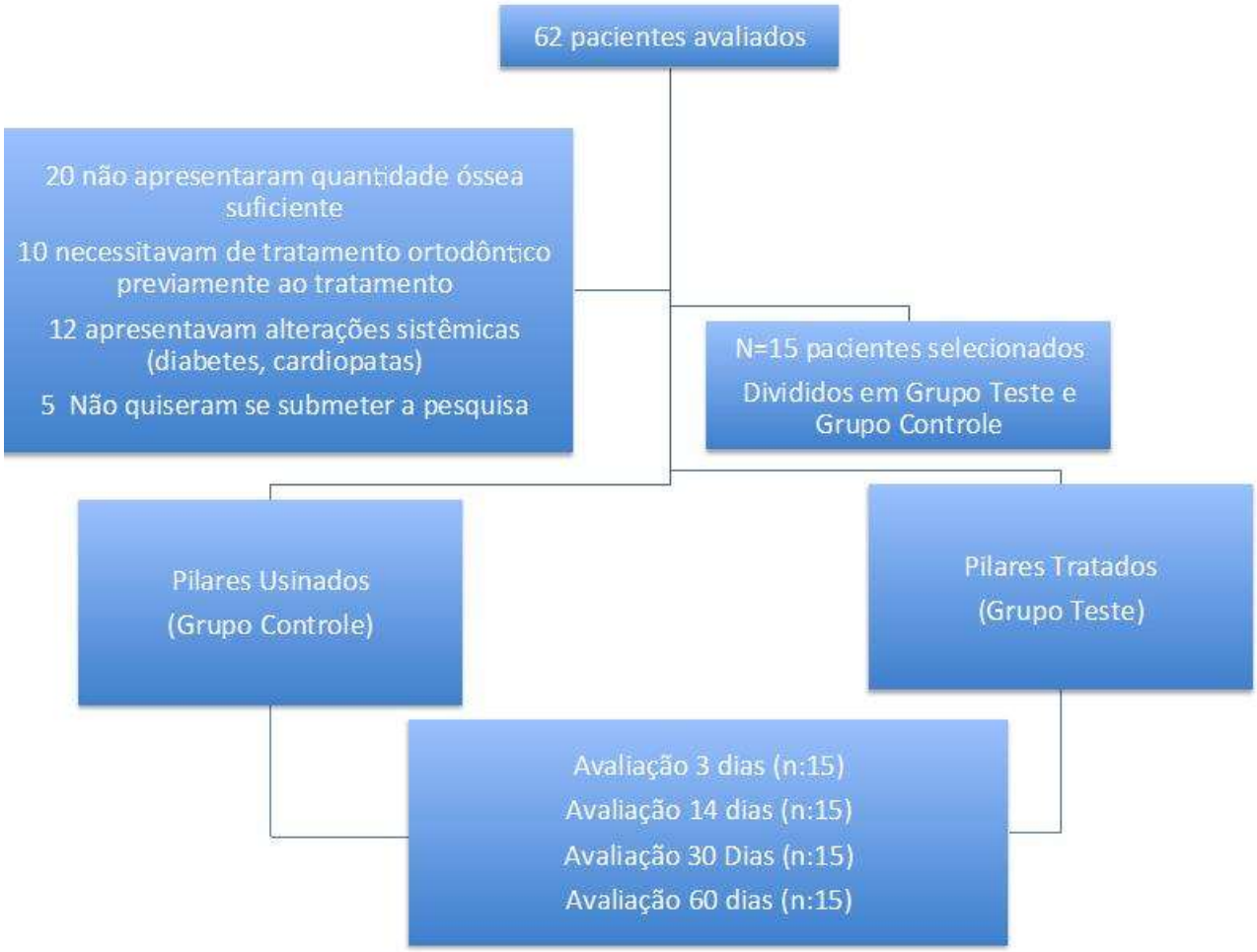
Diante disso, estudos em modelo animal (Weiner et al 2008; Geherke et al 2016) avaliaram o comportamento do tecido ósseo, do tecido conjuntivo e das células epiteliais após a utilização de pilares com colar de superfície tratada. Esses estudos mostraram maior altura e adesão do tecido ósseo, bem como maior estabilidade do tecido mole e menor atividade osteoclástica.

Embora a literatura mostre resultados positivos com o tratamento de superfície do pilar no comportamento do tecido ósseo, com menor perda óssea marginal e no comportamento dos tecidos moles, com maior adesão dos mesmos na região coronária, não há informação quanto à influência desse tratamento nos níveis de mediadores angiogênicos e osteoblastogênicos no fluido peri-implantar, durante as fases iniciais de reparo peri-implantar. Essas moléculas são marcadores importantes no processo de reparo tecidual e a análise do seu padrão de liberação poderia elucidar de forma importante os benefícios do uso de pilares tratados. Além disso, este é o primeiro estudo que utiliza essa abordagem clinicamente.

Desta forma, o objetivo deste estudo clínico-laboratorial foi avaliar prospectivamente o impacto do tratamento de superfície do pilar intermediário de implantes do tipo cone morse, com tratamento com dióxido de titânio (TiO2), no processo inicial de reparo ósseo e dos tecidos peri-implantares por meio de análise imuno-enzimática.

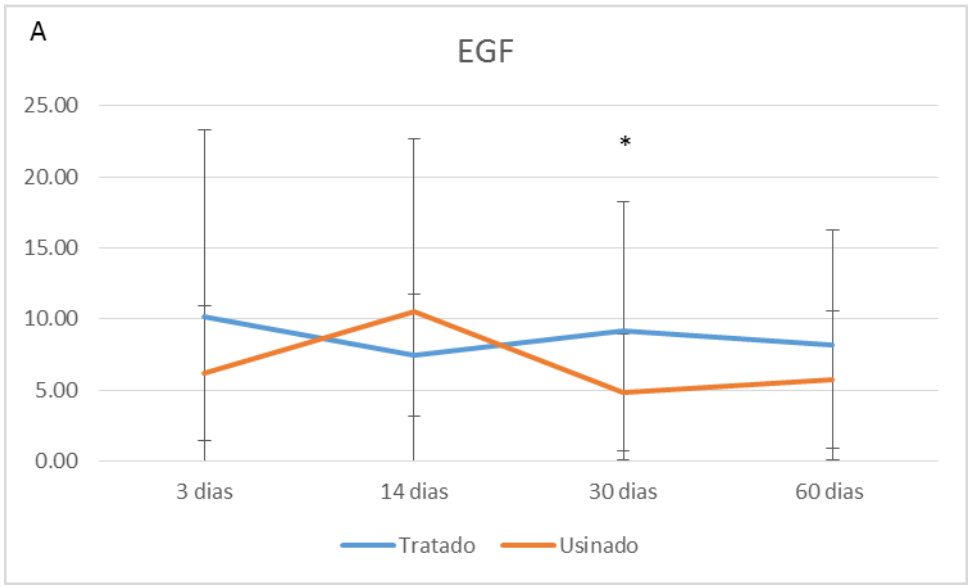
2 FIGURAS

1. Ilustração esquemática do desenho experimental - Fluxograma

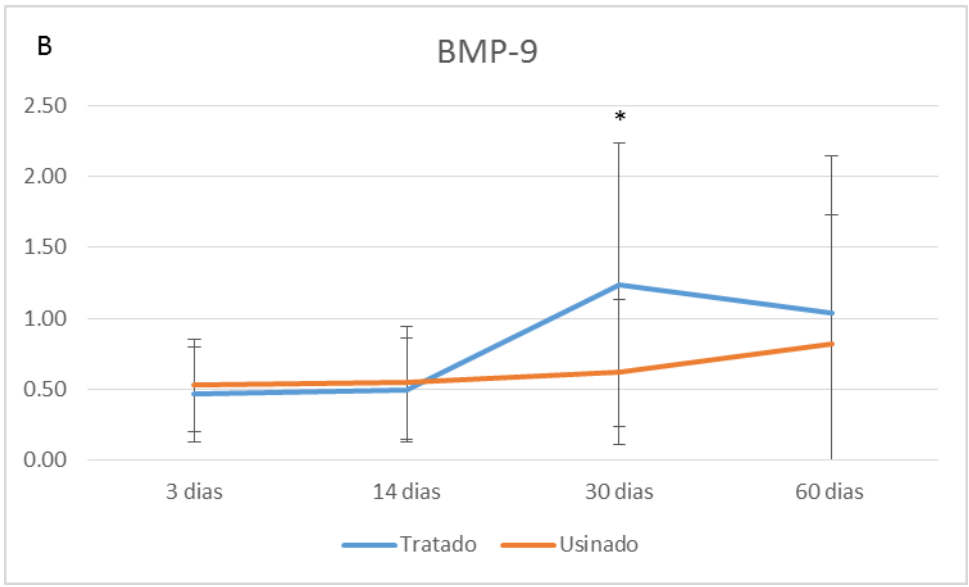


2. Figuras

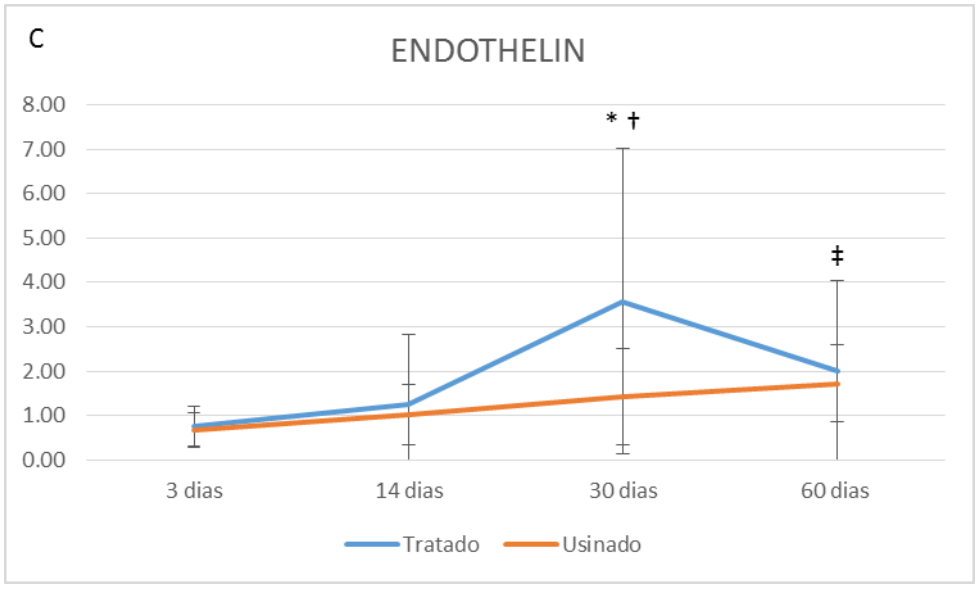
Figura 2 - Níveis de Fator de Crescimento Epidérmico (EGF) (A), Proteína óssea morfogenética-9 (BMP-9) (B), Endotelina-1 (ET-1) (C), Fator de Crescimento Fibroblástico (FGF) (D), Fator de Crescimento Placentário (PlGF) (E), Fator de Crescimento Endotelial (VEFG) (F) no fluido peri-implantar (pg/ml) de implantes com pilar intermediário com colar de 1,5mm de superfície tratada e implantes com pilar intermediário convencional de superfície usinada.



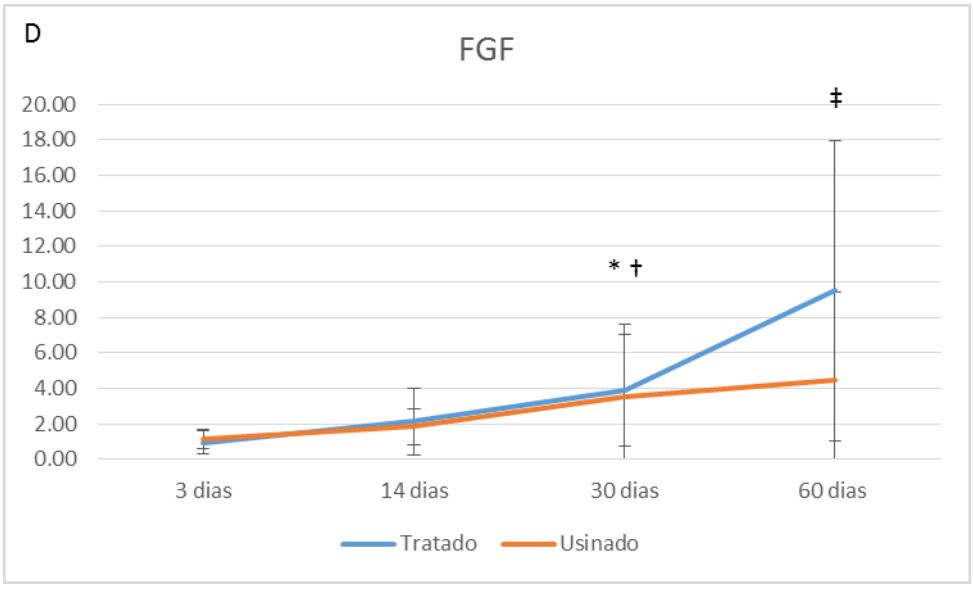
* Indica diferença estatisticamente significativa entre os grupos (Anova Two-way/Tukey, $p<0.05$). Não houve diferença significativa na análise intragrupo (Anova Two-way/Tukey, $p<0.05$).



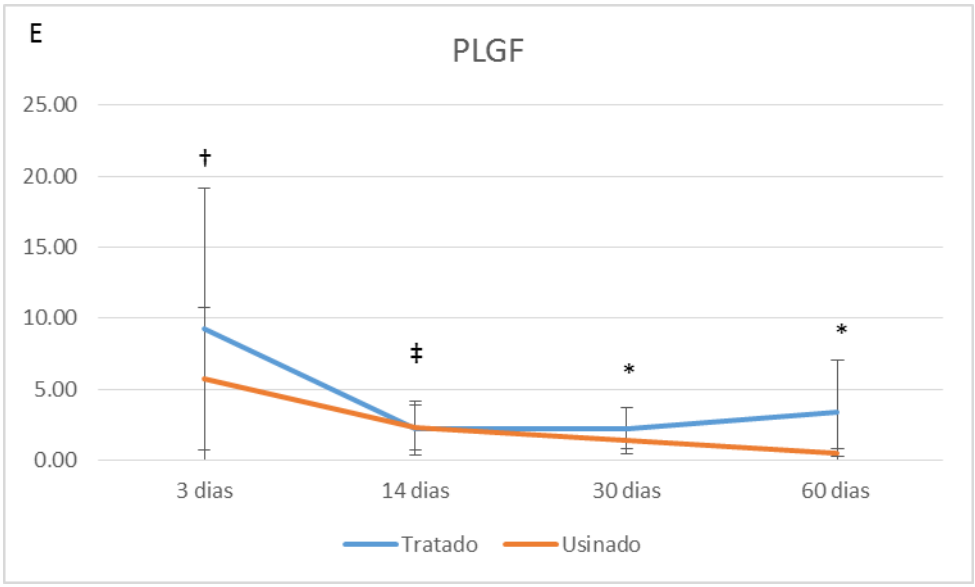
* Indica diferença estatisticamente significativa entre os grupos (Anova Two-way/Tukey, $p<0.05$). Não houve diferença significativa na análise intragrupo (Anova Two-way/Tukey, $p>0.05$).



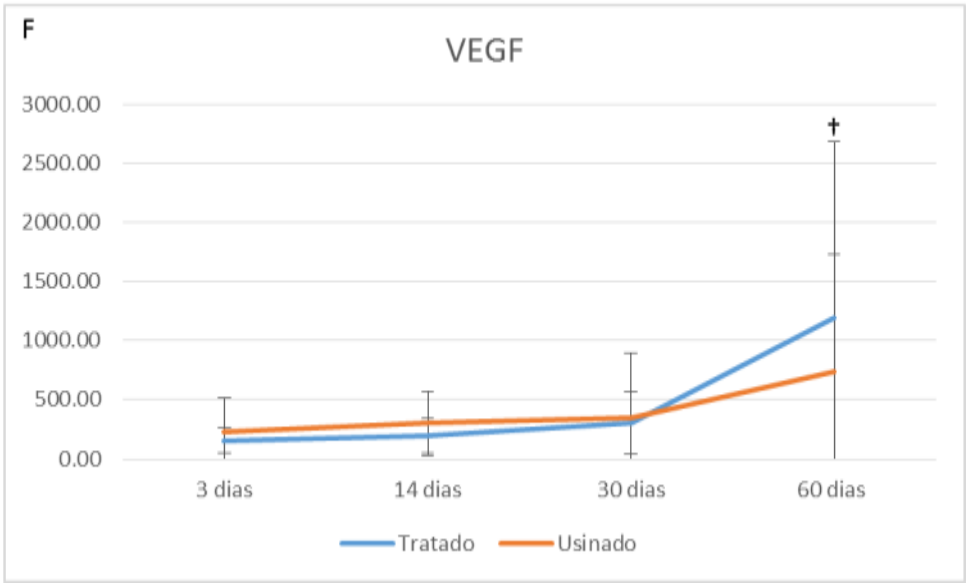
* Indica diferença estatisticamente significativa entre os grupos (Anova Two-way/Tukey, p<0.05).
† Indica diferença estatisticamente significativa entre os tempos de 3 e 30 dias, para o grupo teste (Anova Two-way/Tukey, p<0.05).
‡ Indica diferença estatisticamente significativa entre os tempos de 3 e 60 dias, para os grupos teste e controle (Anova Two-way/Tukey, p<0.05).



* Indica diferença estatisticamente significativa entre os grupos (Anova Two-way/Tukey, p<0.05).
† Indica diferença estatisticamente significativa entre os tempos de 3 e 30 dias, para o grupo teste (Anova Two-way/Tukey, p<0.05).
‡ Indica diferença estatisticamente significativa entre os tempos de 3 e 60 dias, para os grupos teste e controle (Anova Two-way/Tukey, p<0.05).



* Indica diferença estatisticamente significativa entre os grupos (Anova Two-way/Tukey, p<0.05).
† Indica diferença estatisticamente significativa entre os tempos de 3 e 60 dias, para o grupo controle (Anova Two-way/Tukey, p<0.05).
‡ Indica diferença estatisticamente significativa entre os tempos de 14 e 60 dias, para o grupo controle (Anova Two-way/Tukey, p<0.05).



† Indica diferença estatisticamente significativa entre os tempos de 3 e 60 dias, para o grupo teste (Anova Two-way/Tukey, p<0.05).
Não houve diferença estatisticamente significativa entre os grupos teste e controle (Anova Two-way/Tukey, p>0.05).

3. Tabelas

Tabela 1. Dados demográficos dos sujeitos incluídos no estudo.

Idade (média desvio ± padrão; anos)	40±10.41
Feminino (%)	73.33
Masculino (%)	26.66

3 CONCLUSÃO GERAL

Pode-se concluir que o tratamento de superfície do pilar intermediário com TiO2 modula a liberação de marcadores ósseos, angiogênicos e de reparo tecidual.

REFERÊNCIAS GERAIS

1. Abraham DJ, Eckes B, Rajkumar V, Krieg T. New developments in fibroblast and myofibroblast biology: implications for fibrosis and scleroderma. Curr Rheumatol Rep 9: 136–43, 2007.
2. Abrahamsson I, Berglundh T, Lindhe J. The mucosal barrier following abutment dis/reconnection. An experimental study in dogs. J Clin Periodontol. Aug;24(8):568-72, 1997.
3. Adell R, Lekholm U, Rockler B, Brånemark PI. A 15-year study of osseointegrated implants in the treatment of the edentulous jaw. Int J Oral Surg. 1981 Dec;10(6):387-416, 1981 .
4. Ahnstedt H, Stenman E, Cao L, Henriksson M, Edvinsson L. Cytokines and growth factors modify the upregulation of contractile endothelin ET(A) and ET(B)receptors in rat cerebral arteries after organ culture. Acta Physiol (Oxf). 2012 Jun;205(2):266-78. doi: 10.1111/j.1748-1716.2011.02392.x. Epub 2012 Jan 12.
5. Alexander H, Ricci JL, Hrico GJ. Mechanical basis for bone retention around dental implants. J Biomed Mater Res B Appl Biomater 2009; 88:306–311.
6. Alves JB, Ferreira CL, Martins AF, Silva GA, Alves GD, Paulino TP, Ciancaglini P, Thedei G Jr, Napimoga MH. Local delivery of EGF-liposome mediated bone modeling in orthodontic tooth movement by increasing RANKL expression. Life Science; 4:693–9, 2009.
7. Arman E, Haffner-Krausz R, Gorivodsky M, Lonai P. Fgfr2 is required for limb outgrowth and lung-branching morphogenesis. Proceedings of the National Academy of Sciences of the United States of America 1999;96: 11895–99.
8. Atsuta I, Ayukawa Y, Kondo R, Oshiro W, Matsuura Y, Furuhashi A, Tsukiyama Y, Koyano K. Soft tissue sealing around dental implants based on histological interpretation. J Prosthodont Res. 2016 Jan;60(1):3-11. doi: 10.1016/j.jpor.2015.07.001. Epub 2015 Dec 23. Review.
9. Berglundh T, Lindhe J, Ericsson I, Marinello CP, Liljenberg B, Thomsen P. The soft tissue barrier at implants and teeth. Clin Oral Implants Res 1991; 2:81–90.

10. Berglundh T, Lindhe J. Dimension of the periimplant mucosa. Biological width revisited. J Clin Periodontal 1996; 23:971–973.

11. Bhardwaj G, Webster TJ. Reduced bacterial growth and increased osteoblast proliferation on titanium with a nanophase TiO2 surface treatment. Int J Nanomedicine. 2017 Jan 6;12:363-369. doi: 10.2147/IJN.S116105. eCollection 2017.

12. Bikfalvi A, Klein S, Pintucci G, Rifkin DB. Biological roles of fibroblast growth factor-2. Endocrine Reviews 1997;18:26–45.

13. Canavarro C, Teles RP, Capelli Júnior J. Matrix metalloproteinases -1, -2, -3, -7, -8, -12, and -13 in gingival crevicular fluid during orthodontic tooth movement: a longitudinal randomized split-mouth study. Eur J Orthod; 35(5):652-8, 2013.

14. Carmeliet P. Mechanisms of angiogenesis and arteriogenesis. Nat Med;6:389–95. 2000.

15. Carmeliet, P., et al. 2001. Synergism between vascular endothelial growth factor and placental growth factor contributes to angiogenesis and plasma extravasation in pathological conditions. *Nat. Med.***7**:575–583.

16. Chen HW, Su SF, Chien CT, Lin WH, Yu SL, Chou CC, Chen JJ, Yang PC. Titanium dioxide nanoparticles induce emphysema-like lung injury in mice. FASEB J. Nov;20(13):2393-5. Epub 2006 Oct 5.

17. Clines GA, Mohammad KS, Grunda JM et al. Regulation of postnatal trabecular bone formation by the osteoblast endothelin A receptor. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research, 26(10), 2523-2536, 2011.

18. Cocchetto R, Traini T, Caddeo F, Celletti R. Evaluation of hard tissue response around wider platform-switched implants. Int J Periodontics Restorative Dent. 30(2):163-71, 2010.

19. Collin-Osdoby P, Rothe L, Bekker S, Anderson F, Huang Y, Osdoby P. Development, and bone pit resorption in association with angiogenesis in vivo on the chick chorioallantoic membrane and activates isolated avian osteoclast resorption in vitro. Journal of Bone and Mineral Research 2002;17:1859–71.

20. Comut, A.A., Weber, H.P., Shortkroff, S., Cui, F.Z. & Spector, M. Connective tissue orientation around dental implants in a canine model. Clinical Oral Implants Research 12: 433–440, 2001.

21. Cooper L. A role for surface topography in creating and maintaining bone at titanium endosseous implants. J Prosthet Dent. 2000;84:522-534

22. Dai J, Rabie AB. Recombinant adeno-associated virus vector hybrids efficiently target different skeletal cells. Front Biosci;12:4280–4287, 2007.

23. Dawas K, Loizidou M, Shankar A, Ali H, Taylor I. Angiogenesis in cancer: the role of endothelin-1. Annals of the Royal College of Surgeons of England; 81(5):306, 1999.

24. Debiais F, Hott M, Graulet AM, Marie PJ. The effects of fibroblast growth factor-2 on human neonatal calvaria osteoblastic cells are differentiation stage specific. Journal of Bone and Mineral Research 1998;13:645–54.

25. Dolanmaz D, Saglam M, Inan O, Dundar N, Alniacık G, Gursoy Trak B, Kocak E, Hakki SS. Monitoring bone morphogenetic protein-2 and -7, soluble receptor activator of nuclear factor-κB ligand and osteoprotegerin levels in the peri-implant sulcular fluid during the osseointegration of hydrophilic-modified sandblasted acid-etched and sandblasted acid-etched surface dental implants. J Periodontal Res 2015;50(1):62– 7.

26. Dunbar SA, Jacobson JW. Quantitative, multiplexed detection of Salmonella and other pathogens by LuminexxMAP suspension array. Methods Mol Biol; 394:1-19, 2007.

27. Eloot AK, Vanobbergen JN, De Baets F, Martens LC. Oral health and habits in children with asthma related to severity and duration of condition. Eur J Paediatr Dent. Dec;5(4):210-5, 2004.

28. Ergul A, Jupin D, Johnson MH, Prisant LM. Elevated endothelin-1 levels are associated with decreased arterial elasticity in hypertensive patients. J Clin Hypertens (Greenwich) 2006;8:549-554. 24.

29. Frenkel SR, Simon J, Alexander H, Dennis M, Ricci JLOsseointegration on metallic implant surfaces: Effects of microgeometry and growth factor treatment. J Biomed Mater Res. 2002;63:706-713

30. Garcıa GV, Corral L, Bascones MA. Plasma Rico en Plaquetas y su utilizacion em implantologia dental. Avances en Perı´odoncia e Implantologia Oral; 16:81–92, 2004.

31. Gehrke SA, Neto UTS. Evaluation of the Surface Treatment on Bone Healing in a Transmucosal 1-mm Area of Implant Abutment: An Experimental Study in the Rabbit Tibia. Clinical Implant Dentistry and Related Research, Volume 18, Number 3, 2016

32. Georg-H. Nentwig . The Ankylos Implant System: Concept and Clinical Application. Journal of Oral Implantology: June, Vol. 30, No. 3, pp. 171-177, 2004.

33. Geurs N, Vassilopoulos PJ, Reddy MS. Histological evidence of connective tissue integration on laser microgrooved abutments in humans. Clin Adv Periodontics; 11: 29-33, 2011.

34. Ghiraldini B, Conte A, Casarin RC, Casati MZ, Pimentel SP, Cirano FR, R i b e i r o F V . Influence of glycemic control on peri-implant bone healing: 12-month outcomes of local release of bone-related factors and implant stabilization in type 2 diabetics. Clin Implant Dent Relat Res 2016;18(4):801–809.

35. Globus RK, Plouet J, Gospodarowicz D. Cultured bovine bone cells synthesize basic fibroblast growth factor and store it in their extracellular matrix. Endocrinology 1989;124:1539–47.

36. Gray, M.O., Long, C.S., Kalinyak, J.E., Li, H.T., Karliner, J.S. Angiotensin II stimulates cardiac myocyte hypertrophyvia paracrine release ofTGF-beta 1 and endothelin-1 from fibroblasts. Cardiovasc. Res., 1998 40, 352–363.

37. Guida L, Annunziata M, Rocci A, Contaldo M, Rullo R, Oliva A. Biological response of human bone marrow mesenchymal stem cells to fluoride-modified titanium surfaces. Clin Oral Implants Res.; 21(11):1234–1241, 2010.

38. Hanada K, Dennis JE, Caplan AI. Stimulatory effects of basic fibroblast growth factor and bone morphogenetic protein-2 on osteogenic differentiation of rat bone marrow-derived mesenchymal stem cells. Journal of Bone and Mineral Research 1997;12:1606–14.

39. Hänggi MP, Hänggi DC, Schoolfield JD, Meyer J,Cochran DL, Hermann JS. Crestal bone changes around titanium implants. Part I: A retrospective radiographic evaluation in humans comparing two non-submerged implant designs with different machined collar lengths. J Periodontol. May;76(5):791-802, 2005.

40. Hermann JS, Buser D, Schenk RK, Higginbottom FL, Cochran DL. Biologic width around titan ium implants. A physiologically formed and stable dimension over time. Clin Oral Implants Res 2000; 11:1–11.

41. Hermann JS, Cochran DL, Nummikoski PV, Buser D. Crestal bone changes around titanium implants. A radio- graphic evaluation of unloaded nonsubmerged and sub-merged implants in the canine mandible. J Periodontal 1997; 68:1117–1130.

42. Hermann JS, Schoolfield JD, Nummikoski PV, Buser D, Schenk RK, Cochran DL. Crestal bone changes around tita- nium implants: a methodologic study comparing linear radiographic with histometric measurements. Int J Oral Maxillofac Implants 2001; 16:475–485.

43. Hermann JS, Schoolfield JD, Nummikoski PV, Buser D, Schenk RK, Cochran DL. Crestal bone changes around titanium implants: a methodologic study comparing linear radiographic with histometric measurements. Int J Oral Maxillofac Implants. Jul-Aug;16(4):475-85, 2001.

44. Hoorstmeyer A, Licht C, Scherr G, Eckes B, Krieg T. Signalling and regulation of collagen I synthesis by ET-1 and TGF-beta1. FEBS J 2005;272:6297- 6309. 25.

45. Iglarz M, Silvestre JS, Duriez M, Henrion D, Levy BI. Chronic blockade of endothelin receptors improves ischemia-induced angiogenesis in rat hindlimbs through activation of vascular endothelial growth factor-NO pathway. Arterioscler Thromb Vasc Biol 2001; 21:1598–603.

46. Jacobsen KA, Al-Aql ZS, Wan C, et al. Bone formation during distraction osteogenesis is dependent on both VEGFR1 and VEGFR2 signaling. J Bone Miner Res 2008;23:596–609.

47. Jones AA, Cochran DL. Consequencesofimplant design. Dent Clin North Am. 2006 Jul;50(3):339-60, v.

48. Jones S, Faulkner G, Raboud D, Fyfe K, Wolfaardt J. Simulation of impact test for determining "health" of percutaneous bone anchored implants. J Biomech Eng. 2006 Oct;128(5):647-53

49. Khan ZA, Farhangkhoee H, Mahon JL, et al. Endothelins: Regulators of extracellular matrix protein production in diabetes. Exp Biol Med (Maywood) 2006; 231:1022-1029

50. Kitano Y, Kurihara H, Kurihara Y, Maemura K, Ryo Y, Yazaki Y, et al. Gene expression of bone matrix proteins and endothelin receptors in endothelin- 1-deficient mice revealed by in situ hybridization. Journal of Bone and Mineral Research 1998;13:237–44.

51. Klagsbrun M. The fibroblast growth factor family: structural and biological properties. Progress in Growth Factor Research 1989;1:207–35.

52. Kloss, F.R., Steinmuller-Nethl, D., Stigler, R.G., Ennemoser, T., Rasse, M. & Hachl, O. (2011) In vivo investigation on connective tissue healing to polished surfaces with different surface wettability. Clinical Oral Implants Research 22: 699–705.

53. Kolbe MF, Ribeiro FV, Luchesi VH, Casarin RC, Sallum EA, Nociti FH Jr, Ambrosano GM, Cirano FR, Pimentel SP, Casati MZ. Photodynamic therapy during supportive periodontal care: clinical, microbiologic, immunoinflammatory, and patient-centered performance in a split-mouth randomized clinical trial. J Periodontol. 2014 Aug;85(8):e277-86.

54. Kozawa O, Kawamura H, Hatakeyama D, Matsuno H, Uematsu T. Endothelin-1 induces vascular endothelial growth factor synthesis in osteoblasts: involvement of p38 mitogen-activated protein kinase. Cell Signalling 2000;12:375–80.

55. Krebs M, Schmenger K, Neumann K, Weigl P, Moser W, Nentwig GH. Long-term evaluation of ANKYLOS® dental implants, part i: 20-year life table analysis of a longitudinal study of more than 12,500 implants. Clin Implant Dent Relat Res. 2015 Jan;17 Suppl 1:e275-86.

56. Kurihara Y, Kurihara H, Suzuki H et al. Elevated blood pressure and craniofacial abnormalities in mice deficient in endothelin-1. Nature, 368(6473), 703-710 (1994). 5.

57. Landlinger C, Preuner S, Willinger B, Haberpursch B, Racil Z, Mayer J, Lion T. Species-specific identification of a wide range of clinically relevant fungal pathogens by use of LuminexxMAP technology. J ClinMicrobiol. 2009 Apr;47(4):1063-73.

58. Lang NP, Salvi GE, Huynh-Ba G, Ivanovski S, Donos N, Bosshardt DD. Early osseointegration to hydrophilic and hydrophobic implant surfaces in humans. Clin Oral Implants Res. 2011 Apr;22(4):349-56.

59. Lazzara RJ, Porter SS. Platform switching: a new concept in implant dentistry for controlling postrestorative crestal bone levels. Int J Periodontics Restorative Dent. 2006 Feb;26(1):9-17.

60. Li R, Stewart DJ, von Schroeder HP, et al. Effect of cell-based VEGF gene therapy on healing of a segmental bone defect. J Orthop Res 2009;27:8–14.

61. Lindquist LW, Carlsson GE, Jemt T. A prospective 15-year follow-up study of mandibular fixed prostheses supported by osseointegrated implants.Clinical results and marginal bone loss. Clin Oral Implants Res. 1996 Dec;7(4):329-36.

62. Luginbuehl V, Meinel L, Merkle HP, Gander B. Localized delivery of growth factors for bone repair. European Journal of Pharmaceutics and Biopharmaceutics 2004;58:197–208 Biological Chemistry 2001;276:36770–8.

63. Luther G, Wagner ER, Zhu G, Kang Q, Luo Q, Lamplot J, et al. BMP-9 induced osteogenic differentiation of mesenchymal stem cells: molecular mechanism and therapeutic potential. Curr Gene Ther 2011;11:229–240.

64. Manz MC.Factors associated with radiographic vertical bone loss around implants placed in a clinical study. Ann Periodontol. 2000 Dec;5(1):137-51.

65. Mardas N, Schwarz F, Petrie A, Hakimi AR, Donos N. The effect of SLActive surface in guided bone formation in osteoporotic-like conditions. Clin Oral Implants Res. 2011 Apr;22(4):406-15.

66. Marie P, Debiais F, Cohen-Solal M, de Vernejoul MC. New factors controlling bone remodeling. Joint Bone Spine 2000;67:150–6.

67. Masaki T, Miwa S, Sawamura T, Ninomiya H, Okamoto Y. Subcellular mechanisms of endothelin action in vascular system. Eur J Pharmacol 1999;375:133-138. 23.

68. Mason IJ. The ins and outs of fibroblast growth factors. Cell 1994;78:547–52.

69. Michalakis KX, Calvani P, Hirayama H. Biomechanical considerations on tooth-implant supported fixed partial dentures. J Dent Biomech , 2012; (3): 1-16.

70. Mombelli A, Gmür R, Gobbi C, Lang NP. Actinobacillusactinomycetemcomitans in adult periodontitis. I. Topographic distribution before and after treatment. J Periodontol. 1994 Sep;65(9):820-6.

71. Montero A, Okada Y, Tomita M, Ito M, Tsurukami H, Nakamura T, et al. Disruption of the fibroblast growth factor-2 gene results in decreased bone mass and bone formation. Journal of Clinical Investigation 2000;105:1085–93.

72. Murlas, C.G., Gulati, A., Singh, G., Najmabadi, F. Endothelin-1 stimulates proliferation of normal airway epithelial cells. Biochem. Biophys. Res. Commun.1995, 212,953–959.

73. Naert I, Koutsikakis G, Duyck J, Quirynen M, Jacobs R, van Steenberghe D. Biologic outcome of single-implant restorations as tooth replacements: a long-term follow-up study. Clin Implant Dent Relat Res. 2000;2(4):209-18.

74. Nevins, M., Kim, D.M., Jun, S.H., Guze, K., Schupbach, P. & Nevins, M.L. (2010) Histologic evidence of a connective tissue attachment to laser microgrooved abutments: a canine study. International Journal of Periodontics and Restorative Dentistry 30: 245–255.

75. Nevins, M., Nevins, M.L., Camelo, M., Boyesen, J.L. & Kim, D.M. (2008) Human histologic evidence of a connective tissue attachment to a dental implant. International Journal of Periodontics and Restorative Dentistry 28: 111–121.

76. Ohuchi N , Koike K, Sano M, Kusama T, Kizawa Y, Hayashi K, Taniguchi Y, Ohsawa M, Iwamoto K, Murakami H. Proliferative effects of angiotensin II and endothelin-1 on guinea pig gingival fibroblast cells in culture. Comparative Biochemistry and Physiology Part C 132 (2002) 451–460

77. Otomo H, Sakai A, Uchida S, Tanaka S, Watanuki M, Moriwaki S, Niida S, Nakamura T. Flt-1 tyrosine kinase-deficient homozygous mice result in decreased trabecular bone volume with reduced osteogenic potential. Bone 2007;40:1494–1501.

78. Ozawa CR, Banfi A, Glazer NL, Thurston G, Springer ML, Kraft PE, McDonald DM, Blau HM. Microenvironmental VEGF concentration, not total dose, determines a threshold between normal and aberrant angiogenesis. J Clin Invest;113:516–27, 2004.

79. Peng Y, Kang Q, Cheng H, Li X, Sun MH, Jiang W, Luu HH, Luo J, Szatkowski JP, Vanichakarn P,Park JY, Li Y, Haydon RC, He TC. Transcriptional characterization of bone morphogenetic proteins (BMPs)-mediated osteogenic signaling. J Cell Biochem 2003;90:1149–1165

80. Peng Y, Kang Q, Luo Q, Jiang W, Si W, Liu BA, Luu HH, Park JK, Li X, Luo J,Montag AG, Haydon RC, He TC. Inhibitor of DNA binding/differentiation helix-loop-helix proteins mediate bone morphogenetic protein-induced osteoblast differentiation of mesenchymal stem cells. J Biol Chem 2004;279:32941–32949.

81. Piacentini, L., Gray, M., Honbo, N.Y., Chentoufi, J., Bergman, M., Karliner, J.S. Endothelin-1 stimulates cardiac fibroblast proliferation through activation of protein kinase, C. J. Mol. Cell Cardiol., 2000, 32, 565–576.

82. Pitaru S, Kotev-Emeth S, Noff D, Kaffuler S, Savion N. Effect of basic fibroblast growth factor on the growth and differentiation of adult stromal bone marrow cells: enhanced development of mineralized bone-like tissue in culture. Journal of Bone and Mineral Research 1993;8:919–29.

83. Pourabbas R, Kashefimehr A, Rahmanpour N, Babaloo Z, Kishen A, Tenenbaum HC, Azarpazhooh A. Effects of photodynamic therapy on clinical and gingival crevicular fluid inflammatory biomarkers in chronic periodontitis: a split-mouth randomized clinical trial.) J Periodontol. 2014 Sep;85(9):1222-9.

84. Rabie ABM, Dai J, Xu R. Recombinant AAV-mediated VEGF gene therapy induces mandibular condylar growth. Gene Ther 2007;14:972–980.

85. Ramanujan S, Koenig GC, Padera TP, Stoll BR, Jain RK. Local imbalance of proangiogenic and antiangiogenic factors: a potential mechanism of focal necrosis and dormancy in tumors. Cancer Res 2000;60:1442–8.

86. Rupp F, Scheideler L, Eichler M, Geis-Gerstorfer J. Wetting behavior of dental implants. Int J Oral Maxillofac Implants. 2011 Nov-Dec;26(6):1256-66.

87. Sato Y, Shimada T, Takaki R. Autocrinological role of basic fibroblast growth factor on tube formation of vascular endothelial cells in vitro. Biochemical and Biophysical Research Communications 1991;180:1098–102.

88. Savani RC, Cao G, Pooler PM, Zaman A, Zhou Z, DeLisser HM. Differential involvement of the hyaluronan (HA) receptors CD44 and receptor for HAmediated motility in endothelial cell function and angiogenesis. Journal of Biological Chemistry 2001;276:36770–8.

89. Schierano G, Pejrone G, Brusco P, Trombetta A, Martinasso G, Preti G, Canuto RA. TNF-alpha TGF-beta2 and IL-1beta levels in gingival and peri-implant crevicular fluid before and after de novo plaque accumulation. J ClinPeriodontol. 2008 Jun;35(6):532-8.

90. Schwarz F, Ferrari D, Herten M, Mihatovic I, Wieland M, Sager M, Becker J. Effects of surface hydrophilicity and microtopography on early stages of soft and hard tissue integration at non-submerged titanium implants: an immunohistochemical study in dogs. J Periodontol. 2007 Nov;78(11):2171-84

91. Schwarz F, Herten M, Sager M, Wieland M, Dard M, Becker J. Histological and immunohistochemical analysis of initial and early osseous integration at chemically modified and conventional SLA titanium implants: preliminary results of a pilot study in dogs. Clin Oral Implants Res. 2007 Aug;18(4):481-8.

92. Schwarz F, Sager M, Ferrari D, Herten M, Wieland M, Becker J. Bone regeneration in dehiscence-type defects at non-submerged and submerged chemically modified (SLActive) and conventional SLA titanium implants: an immunohistochemical study in dogs. J Clin Periodontol. 2008 Jan;35(1):64-75.

93. Schwarz, F., Herten, M., Sager, M., Wieland, M., Dard, M. & Becker, J. Histological and immunohistochemical analysis of initial and early subepithelial connective tissue attachment at chemically modified and conventional SLA titanium implants. A pilot study in dogs. Clinical Oral Investigations. 2007b11: 245–255.

94. Schweda F, Blumberg FC, Schweda A, Nabel C, Holmer SR, Riegger GA, Pfeifer M, Kramer BK. Effects of chronic hypoxia on renal PDGF-A, PDGF-B, and VEGF gene expression in rats. Nephron 2000;86:161–6.

95. Sezer O, Niemo¨ ller K, Jakob C, Zavrski I, Heider U, Eucker J, Kaufmann O, Possinger K. Relationship between bone marrow angiogenesis and plasma cell infiltration and serum beta2-microglobulin levels in patients with multiple myeloma. Annals of Hematology 2001;80:598–601.

96. Shapoff CA, Lahey B, Wasserlauf PA, Kim DM. Radiographic analysis of crestal bone levels around Laser-Lok collar dental implants. Int J Periodontics Restorative Dent. 2010 Apr;30(2):129-37.

97. Shichiri M, Hirata Y, Nakajima T, Ando K, Imai T, Yanagisawa M, Masaki T, Marumo F. Endothelin-1 is an autocrine/paracrine growth factor for human cancer cell lines. Journal of Clinical Investigation. 1991;87(5):1867.

98. Socransky SS, Smith C, Haffajee AD. Subgingival microbial profiles in refractory periodontal disease. J ClinPeriodontol. 2002 Mar;29(3):260-8.

99. Tete, S., Mastrangelo, F., Bianchi, A., Zizzari, V. & Scarano, A. Collagen fiber orientation around machined titanium and zirconia dental implant necks: an animal study. International Journal of Oral and Maxillofacial Implants. 2009:24, 52–58.

100. Tsai T-L, Wang B, Squire MW, Guo L-W, Li W-J. Endothelial cells direct human mesenchymal stem cells for osteo-and chondro-lineage differentiation through endothelin-1 and AKT signaling. Stem cell research & therapy. 2015;6(1):1-14.

101. Üstün K, Erciyas K, Sezer U, Şenyurt SZ, Gündoğar H, Üstün Ö, Öztuzcu S. Clinical and biochemical effects of 810 nm diode laser as an adjunct to periodontal therapy: a randomized split-mouth clinical trial. Photomed Laser Surg. 2014 Feb;32(2):61-6.

102. Veillette CJH, von Schroeder HP. Endothelin-1 down-regulates the expression of vascular endothelial growth factor-A associated with osteoprogenitor proliferation and differentiation. Bone, 34(2), 288-296 (2004).

103. Vela-Nebot X, Rodríguez-Ciurana X, Rodado-Alonso C, Segalà-Torres M. Benefits of an implant platform modification technique to reduce crestal bone resorption. Implant Dent. 2006 Sep;15(3):313-20.

104. Villarreal, F.J., Kim, N.N., Ungab, G.D., Printz, M.P., Dillmann, W.H. Identification of functional angiotensin II receptors on rat cardiac fibroblasts. Circulation, 1993. 88,2849–2861.

105. Von Schroeder HP, Veillette CJ, Payandeh J, Qureshi A, Heersche JNM. Endothelin-1 promotes osteoprogenitor proliferation and differentiation in fetal rat calvarial cell cultures. Bone, 33(4), 673-684 (2003).

106. Wang X, Lu T, Wen J, Xu L, Zeng D, Wu Q, Cao L, Lin S, Liu X, Jiang X. Selective responses of human gingival fibroblasts and bacteria on carbon fiber reinforced polyetheretherketone with multilevel nanostructured TiO2. Biomaterials. 2016 Mar;83:207-18. doi: 10.1016/j.biomaterials.2016.01.001. Epub 2016 Jan 4.

107. Weiner S, Simon J, Ehrenberg OS, Zweig B, Ricci JL. The effects of laser microtextured collars upon crestal bone levels of dental implants. Implant Dent 2008; 17:217–228.

108. Wennerberg A, Svanborg LM, Berner S, Andersson M. Spontaneously formed nanostructures on titanium surfaces. Clin Oral Implants Res. 2013 Feb;24(2):203-9.

109. Yamamoto E, Awano S, Koseki T. Expression of endothelin-1 in gingival epithelial cells. J Periodontal Res 2003;38:417-424

110. Yin JJ, Mohammad KS, Käkönen SM, Harris S, Wu-Wong JR, Wessale JL. A causal role for endothelin-1 in the pathogenesis of osteoblastic bone metastases. Proceedings of the National Academy of Sciences. 2003;100(19):10954-9.

111. Zarb GA, Schmitt A. Terminal dentition in elderly patients and implant therapy alternatives. IntDentJ. 1990 Apr;40(2):67-73

112. Zelzer E, McLean W, Ng YS, Fukai N, Reginato AM, Lovejoy S, D'Amore PA, Olsen BR. Skeletal defects in VEGF(120/120) mice reveal multiple roles for VEGF in skeletogenesis. Development 2002;129:1893–904

113. Zhao G, Schwartz Z, Wieland M, Rupp F, Geis-Gerstorfer J, Cochran DL, Boyan BD. High surface energy enhances cell response to titanium substrate microstructure. J Biomed Mater Res A. 2005 Jul 1;74(1):49-58.