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PRESERVAÇÃO DO REBORDO ALVEOLAR – ENSAIO CLÍNICO RANDOMIZADO E REVISÃO SISTEMÁTICA DA LITERATURA

ALVEOLAR RIDGE PRESERVATION - RANDOMIZED CLINICAL TRIAL AND A SYSTEMATIC REVIEW OF THE LITERATURE

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PORTO ALEGRE – RS

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Tese apresentada ao Programa de Pós-Graduação em Odontologia da Faculdade de Odontologia da Pontifícia Universidade Católica do Rio Grande do Sul como requisito final para obtenção do título de Doutor em Odontologia, na Área de Concentração de Prótese Dentária.

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“A alegria está na luta, na tentativa,

no sofrimento envolvido.

Não na vitória propriamente dita.”

Mahatma Gandhi

“No que diz respeito ao empenho, ao compromisso, ao esforço, à dedicação, não existe meio termo. Ou você faz uma coisa bem feita ou não faz.

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RESUMO

PRESERVAÇÃO DO REBORDO ALVEOLAR – ENSAIO CLÍNICO RANDOMIZADO E REVISÃO SISTEMÁTICA DA LITERATURA

RESUMO

Várias técnicas e materiais têm sido sugeridos para a preservação do rebordo alveolar (PRA) após a extração dentária e antes da colocação do implante. Este estudo, o qual é composto por dois manuscritos, buscou avaliar, através de um ensaio clínico randomizado, as alterações ósseas radiográficas após a PRA com dois diferentes biomateriais e, através de uma revisão sistemática da literatura, as evidências do efeito deste procedimento após a extração dentária e se ele permite a colocação do implante (com ou sem enxerto adicional). No primeiro capítulo, a preservação do rebordo alveolar foi realizada em 27 pacientes divididos em 2 grupos. Um substituto ósseo sintético (SOS) ou um xenoenxerto derivado de bovinos (XDB), ambos com uma membrana de colágeno como barreira (Bio-Gide®), foram utilizados nos grupos teste e controle, respectivamente. Radiografias periapicais padronizadas foram tiradas em intervalos regulares de tempo, do tempo inicial (TI) aos 8 meses (8M). Os níveis da crista óssea alveolar nos aspectos mesial (Mav), distal (Dav) e central (Cav) do alvéolo foram medidas em todos os intervalos de tempo e comparados às medições intra-cirúrgicas. Todas as radiografias obtidas foram subtraídas das imagens de acompanhamento. As áreas de ganho, de perda ou inalteradas em termos de níveis de cinza foram testadas para diferença significativa entre os dois grupos. No segundo capítulo, ambas pesquisas eletrônica e manual procuraram por referências que atenderam a critérios específicos de inclusão e exclusão. Dois revisores realizaram uma triagem calibrada e independente, enquanto que um terceiro revisor foi consultado em caso de discordâncias. Ensaios clínicos randomizados, ensaios clínicos controlados e estudos prospectivos com um mínimo de cinco pacientes e a cicatrização natural do alvéolo como controle foram incluídos. O estudo clínico experimental revelou que, entre TI-8M, a Mav e Dav mostraram diferenças médias de 0,9 ± 1,2 mm e 0,7 ± 1,8mm, e 0,4 ± 1,3 mm e 0,7 ± 1,3mm, nos grupos teste e controle, respectivamente ($P>0.05$). Ambos os tratamentos mostraram ganhos similares em níveis de cinza entre os intervalos de tempo. O SOS mostrou menos perda nos níveis de cinza entre TI-4M e TI-8M ($P<0.05$). A avaliação radiográfica subestimou as medições intra-cirúrgicas (mesial e distal) em 0,3mm na média (95% IC, 0,02-0,6). Muitas técnicas, materiais e metodologias diferentes foram apresentadas nas quatorze publicações revisadas, tornando as comparações diretas difíceis. Os achados radiográficos do ensaio clínico randomizado mostraram que ambos os tipos de enxerto ósseo foram eficientes na preservação das dimensões do rebordo alveolar após a extração dentária, porém nenhum deles mostrou superioridade em termos de alterações radiográficas do osso alveolar do tempo inicial aos 8 meses. Os resultados da revisão sistemática da literatura corroboraram alguns dos achados

preliminares do estudo clínico e mostraram que, apesar da heterogeneidade dos estudos, há evidência que os procedimentos de preservação do rebordo são eficazes na limitação da perda dimensional do rebordo pós-extração e são acompanhados por um grau diferente de regeneração óssea, com variadas quantidades de partículas residuais dos “materiais de enxerto”. Entretanto, a exposição de membranas nos procedimentos de regeneração óssea guiada pode comprometer os resultados. Não há evidência para sustentar a superioridade de uma técnica sobre a outra assim como a importância da preservação do rebordo em melhorar a possibilidade de colocar implantes, as taxas de sucesso/ sobrevivência dos implantes, estética, economia do tratamento, tempo de tratamento e satisfação do paciente.

Palavras Chave (termos *MeSH*): extração dentária; preservação do rebordo alveolar; preservação de alvéolos pós-extração; regeneração óssea guiada; implantes dentários; estética; revisão sistemática; ensaio clínico randomizado; radiografia.

Palavras Chave (DeCS): extração dentária; implantes dentários; estética; radiografia.

ABSTRACT

ALVEOLAR RIDGE PRESERVATION - RANDOMIZED CLINICAL TRIAL AND A SYSTEMATIC REVIEW OF THE LITERATURE

ABSTRACT

Several techniques and materials have been suggested for the preservation of the alveolar ridge (ARP) following tooth extraction and prior to implant placement. This study, which is composed by two manuscripts, aimed to evaluate, through a randomized clinical trial, the radiographical bone changes following ARP with two different biomaterials and, through a systematic review of the literature, the evidences of the effect of this procedure following tooth extraction and whether it allows implant placement (with or without further augmentation). In the first paper, alveolar ridge preservation was performed in 27 patients randomized in 2 groups. Synthetic bone substitute (SBS) or a bovine-derived xenograft (BDX), both with a collagen barrier membrane (Bio-Gide®), have been used in the test and control groups, respectively. Standardised periapical x-rays were taken at regular time intervals from baseline (BL) to 8 months (8M). The levels of the alveolar bone crest at the mesial (Mbh), distal (Dbh) and central aspects (Cbh) of the socket were measured at all time points and compared to intrasurgical measurements. All the obtained radiographs were subtracted from the follow-up images. The gain, loss and unchanged areas in terms of grey values were tested for significant difference between the two groups. In the second chapter, both electronic and hand search looked for references that met specific inclusion and exclusion criteria. Two reviewers performed calibrated and independent screening, whereas a third reviewer was consulted for any disagreement. Randomized clinical trials, controlled clinical trials and prospective studies with a minimum of five patients and an unassisted socket healing as a control were included. The experimental clinical study showed that, between BL-8M, the Mbh and Dbh showed mean differences of 0.9 ± 1.2 mm and 0.7 ± 1.8mm, and 0.4 ± 1.3 mm and 0.7 ± 1.3mm, in the test and control groups, respectively ($P>0.05$). Both treatments presented similar gain in grey values between the time intervals. The SBS presented less loss in grey values between BL-4M and BL-8M ($P<0.05$). Radiographic assessment underestimated the intrasurgical measurements (mesial and distal) of an average 0.3mm (95% CI, 0.02-0.6). Many different techniques, materials and methodologies were presented in the fourteen publications reviewed, making direct comparisons difficult. The radiographic findings of the randomized clinical trial showed that both types of bone grafts were efficient in preserving the dimensions of the alveolar ridge following tooth extraction, nevertheless any of them presented superiority in terms of radiographic alveolar bone changes from baseline to 8 months. The findings

of the systematic review of the literature corroborated some of the preliminary findings of the clinical study and showed that, despite the heterogeneity of the studies, there is evidence that ridge preservation procedures are effective in limiting post extraction ridge dimensional loss and are accompanied by a different degree of bone regeneration, with varying amounts of residual particles of the “grafting materials”. However, the exposure of membranes with GTR procedures may compromise the results. There is no evidence to support the superiority of one technique over the other as well as the importance of ridge preservation in improving the ability of placing implants, implant survival/ success rate, aesthetics, treatment economy, timing or patient satisfaction.

***Key Words* (*MeSH terms*):** *tooth extraction; alveolar ridge preservation; preservation of post-extraction sockets; guided bone regeneration; dental implants; aesthetics; systematic review; randomized clinical trial; radiography.*

Key Words (DeCS): *tooth extraction; dental implants; aesthetics; radiography.*

1. INTRODUÇÃO GERAL

Os implantes dentários têm sido empregados com sucesso na reabilitação de pacientes parcial e totalmente edêntulos por anos (FROUM *et al*., 2002). No entanto, o resultado da terapia com implantes não é mais medido pela sobrevivência do implante somente, mas sim pelo sucesso estético e funcional da reabilitação protética em longo prazo (BUSER *et al*., 2004; DARBY *et al*., 2009). Na última década, a crescente exigência por estética em Implantodontia deu uma maior ênfase ao plano de tratamento. A excelente restauração estética e funcional sobre um implante depende da sua colocação em uma ótima posição, a qual é influenciada pela altura, posição vestíbulo-lingual e dimensões do rebordo alveolar (IASELLA *et al*., 2003).

A reabsorção e o remodelamento do rebordo alveolar após a remoção do dente é um fenômeno natural da cicatrização, fisiologicamente indesejável e possivelmente inevitável que pode prejudicar a colocação do implante (ATWOOD, 1962; TALLGREN, 1972; LEKOVIC *et al*., 1998; YILMAZ *et al*., 1998; AIMETTI *et al*., 2009). Esta situação é particularmente importante na região anterior da maxila, onde uma posição proeminente da raiz é geralmente acompanhada por uma parede vestibular extremamente fina e frágil que pode ser danificada durante a extração dentária (GUARNIERI *et al*., 2004; NEVINS *et al*., 2006; AIMETTI *et al*., 2009; VAN DER WEIJDEN *et al.,* 2009). Assim, para atender os requisitos contemporâneos da colocação tridimensional proteticamente-guiada do implante, o rebordo alveolar remanescente deve ser restaurado em uma quantidade considerável de casos.

1.1. Importância da correta colocação tridimensional do implante

A colocação do implante deve ser baseada em um plano de tratamento orientado pela restauração para permitir ótimo suporte e estabilidade dos tecidos duros e moles circundantes (BUSER *et al*., 2004). O posicionamento tridimensional incorreto pode resultar em um alinhamento implante-restauração impróprio, o que por sua vez pode provocar resultados estéticos e biológicos ruins. Uma colocação mais vestibularizada do implante pode causar um risco significativo de recessão da mucosa marginal. Por outro lado, a colocação muito palatina pode resultar em um perfil de emergência ruim ou até sobrecontorno da restauração. Uma posição mésio-distal inapropriada pode afetar o tamanho e o formato da papila além de causar forma de embrasura ou perfil de emergência inadequados. Por último, o mal-posicionamento corono-apical pode provocar complicações biológicas se o implante for colocado muito profundamente ou complicações estéticas se o metal do ombro do implante ficar visível (DARBY *et al*., 2009).

Além de um correto posicionamento, o desfecho estético do implante inserido também pode ser influenciado pela quantidade de osso disponível no sítio do implante e sua relação com os tecidos moles. O contorno dos tecidos moles é dependente da anatomia óssea subjacente, uma vez que os tecidos moles possuem, em certa medida, dimensões constantes (KAN *et al*., 2003). Com relação ao volume ósseo, primeiramente, a perda do osso alveolar pode ocorrer antes da extração dentária devido a doença periodontal, patologia periapical e trauma nos dentes e no próprio osso (YILMAZ *et al*., 1998; SMUKLER *et al*., 1999; SCHROPP *et al*., 2003; VAN DER WEIJDEN *et al*., 2009). Em segundo lugar, a remoção traumática dos dentes pode causar

perda óssea e, por esta razão, deveria ser evitada (LAM, 1960; SMUKLER *et al*., 1999; SCHROPP *et al*., 2003). Por último, é bem documentado que o osso alveolar sofre atrofia após a extração do dente (PIETROKOVSKI & MASSLER, 1967; SIMION *et al*., 1994; SCHROPP *et al*., 2003). Desta forma, o entendimento do processo de cicatrização dos sítios pós-extração, incluindo alterações do contorno causadas pela reabsorção e remodelamento ósseo, é essencial para a obtenção de reconstruções protéticas funcionais e estéticas satisfatórias (LAM, 1960; SCHROPP *et al*., 2003; VAN DER WEIJDEN *et al*., 2009).

1.2. Aspectos histológicos da cicatrização não-assistida do alvéolo

O processo alveolar é um tecido dento-dependente e sua arquitetura é orientada pelo eixo de erupção, formato e eventual inclinação dos dentes (SCHROEDER, 1986; BARONE *et al*., 2008; VAN DER WEIJDEN *et al*., 2009). O dente, por sua vez, é ancorado ao maxilar através do osso fibroso no qual as fibras do ligamento periodontal se inserem. Este osso fibroso irá obviamente perder sua função e desaparecer após a remoção do dente, resultando em atrofia do processo alveolar (ARAÚJO & LINDHE, 2005; VAN DER WEIJDEN *et al*., 2009).

Investigações histológicas em animais (CLAFLIN, 1936; CARDAROPOLI *et al*., 2003; ARAÚJO & LINDHE, 2005) e humanos (AMLER *et al*., 1960; AMLER, 1969; BOYNE, 1966; EVIAN *et al*., 1982) têm descrito a cicatrização dos alvéolos pós-extração. Amler *et al*. (1960) e Amler (1969) descreveram pioneiramente a cicatrização histológica não-assistida de

alvéolos em humanos saudáveis. Quando o dente é removido, ocorre a formação de um coágulo, que é gradativamente substituído por tecido de granulação na base e na periferia do alvéolo. A neoformação óssea é evidente primeiramente após a primeira semana, com osteóide presente na base do alvéolo como espículas ósseas não-calcificadas. Este osteóide começa a mineralizar a partir da base do alvéolo em direção coronal e atinge dois terços do preenchimento do alvéolo em 38 dias. Neste estágio, o primeiro sinal de uma reabsorção progressiva da crista alveolar pode ser observado. Este processo é acompanhado de uma reepitelização continuada, a qual cobre completamente o alvéolo 6 semanas após a extração. O preenchimento adicional de osso acontece com uma densidade radiográfica máxima por volta do centésimo dia.

Estes resultados histológicos iniciais foram corroborados mais recentemente por outros estudos usando o modelo animal. Observou-se que as células do tecido de cicatrização de alvéolos dentários 4 semanas após a extração do dente são osteoblásticas por natureza, mostrando um comprometimento para formar tecido ósseo (PENTEADO *et al*., 2005). Além disso, Cardaropoli *et al*. (2003) e Penteado *et al*. (2005) mostraram que a formação óssea ocorre de forma centrípeta, isto é, ela inicia a partir do osso antigo das paredes lateral e apical do alvéolo em direção ao centro da ferida. Isto ocorre devido à maior proximidade em relação às fontes de vasos e células. Na área apical estas fontes estão mais próximas do que na área coronal. Por consequência, a síntese de matriz proteica extracelular encontra-se em um estágio mais avançado na região apical do que na região coronal (PENTEADO *et al*., 2005). Adicionalmente, Cardaropoli *et al*. (2003),

a partir do exame de secções mésio-distais de alvéolos pós-extração em cães, encontraram que: (i) o tecido ósseo preencheu o alvéolo pós-extração após um mês, (ii) um rebordo cortical incluindo tecido ósseo e lamelar formou-se após 3 meses, (iii) após o intervalo de 3 meses o tecido ósseo foi gradualmente substituído com osso lamelar e medular. Também, durante o processo de cicatrização, uma ponte de osso cortical formou-se, a qual "fechou" o alvéolo. Neste último estudo, todavia, as informações fornecidas restringiram-se às alterações internas dos alvéolos.

Araújo & Lindhe (2005) afirmaram que acentuadas alterações dimensionais com uma notável atividade osteoclástica ocorreram durante as 8 primeiras semanas após a extração do dente, resultando em reabsorção da região crestal de ambas paredes ósseas vestibular e lingual. Além disso, a reabsorção das paredes vestibular e lingual do sítio da extração ocorreu em duas fases sobrepostas. Na primeira fase, o osso fibroso foi reabsorvido e substituído com tecido ósseo. Uma vez que a crista da parede óssea vestibular é composta exclusivamente de osso fibroso, este remodelamento resultou em uma redução vertical substancial da crista vestibular. A segunda fase mostrou que a reabsorção ocorre a partir das paredes externas de ambas as paredes ósseas, resultando em uma reabsorção horizontal que pode induzir uma redução vertical adicional do osso vestibular.

1.3. Consequências anatômicas da cicatrização não-assistida do alvéolo

Embora ocorra um preenchimento do alvéolo com neoformação óssea, o defeito resultante será somente parcialmente restaurado mesmo com uma

cicatrização sem intercorrências (VAN DER WEIJDEN *et al*., 2009). A perda de espessura é maior do que a perda de altura do rebordo alveolar após a extração dentária, e ambas foram descritas como sendo mais pronunciada no aspecto vestibular do que no aspecto palatino dos maxilares (LAM, 1960; PIETROKOVSKI & MASSLER, 1967; JOHNSON, 1963; JOHNSON, 1969; LEKOVIC *et al*., 1997; LEKOVIC *et al*., 1998; IASELLA *et al*., 2003; BOTTICELLI *et al*., 2004; ARAÚJO & LINDHE, 2005; ARAÚJO *et al*., 2005; VAN DER WEIJDEN *et al*., 2009; PELEGRINE *et al*., 2010).

Em ambos os maxilares, os alvéolos mais largos (molares) mostram uma quantidade de reabsorção significativamente maior (PIETROKOVSKI & MASSLER, 1967; ARAÚJO *et al*., 2006) e requerem mais tempo para formar a ponte de tecido ósseo sobre o defeito do que alvéolos mais estreitos (incisivos e pré-molares) (SCHROPP *et al*., 2003). O nível até o qual a crista reabsorve após a extração é ditado pelo nível ósseo no sítio da extração, ao invés do nível ósseo dos dentes adjacentes. Os alvéolos de dentes com perda óssea horizontal cicatrizam mais rapidamente, uma vez que o nível reduzido do rebordo alveolar significa que menos preenchimento ósseo é necessário. Este processo de reabsorção resulta em um rebordo mais estreito e curto (PINHO *et al*., 2006) e o efeito deste padrão reabsortivo é o deslocamento do rebordo para uma posição mais palatina/ lingual (PIETROKOVSKI & MASSLER, 1967; ARAÚJO & LINDHE, 2005; VAN DER WEIJDEN *et al*., 2009). O rebordo deslocado faz com que seja mais difícil colocar o implante em uma posição restauradora ótima sem que ocorra uma deiscência vestibular no implante (IASELLA *et al*., 2003).

1.4. Cronologia da cicatrização do alvéolo

Os contornos dos processos alveolares mudam continuamente após as extrações dentárias, porque ocorre reabsorção óssea e subsequente rearranjo estrutural (LAM, 1960). Este remodelamento acontece em duas fases. A reabsorção inicial é parte do processo de cicatrização e acontece mais rapidamente nos 3 primeiros meses (AMLER *et al*., 1960; LAM, 1960; JOHNSON, 1969; SCHROPP *et al*., 2003; AIMETTI *et al*., 2009; PELEGRINE *et al*., 2010). Neste período, a neoformação óssea e quase a inteira perda de altura da crista alveolar acontecem simultaneamente com uma redução de aproximadamente dois terços da espessura do rebordo (JOHNSON, 1969; SCHROPP *et al*., 2003; ARAÚJO & LINDHE, 2005; VAN DER WEIJDEN *et al*., 2009). O processo continua nos 3 meses seguintes e, entre 6 e 12 meses, parte deste osso neoformado sofre remodelamento e aproximadamente 50% da redução em espessura do rebordo alveolar ocorre (SCHROPP *et al*., 2003). A segunda fase é contínua e mais lenta, ocorrendo ao longo da vida do indivíduo (LAM, 1960; VAN DER WEIJDEN *et al*., 2009).

1.5. Desvantagens do aumento do rebordo alveolar após a reabsorção óssea e antes da colocação do implante

Van der Weijden *et al*. (2009), em uma revisão sistemática da literatura, encontraram que, durante o período de cicatrização pós-extração, as médias ponderadas das mudanças mostraram a perda clínica em espessura (3,87 mm) como sendo maior do que a perda em altura, avaliada tanto clinicamente (1,67–2,03 mm) como radiograficamente (1,53 mm). Visto que um rebordo de

8 mm de espessura é preferível para a colocação de um implante (IASELLA *et al*., 2003), a reabsorção que acontece após a extração de um dente pode conduzir para um rebordo de aproximadamente 4,1mm de espessura, o qual não é adequado, e irá mostrar uma deiscência quando um implante de 4 mm de diâmetro for colocado (LEKOVIC *et al*., 1998). Assim, um aumento do osso alveolar existente faz-se necessário para a colocação do implante em uma posição proteticamente favorável (FROUM *et al*., 2002; BARONE *et al*., 2008; AIMETTI *et al*., 2009).

Os implantes colocados em um sítio onde o osso foi regenerado são previsíveis e bem sucedidos (FIORELLINI & NEVINS, 2003), e suas taxas de sucesso são comparáveis às taxas de sucesso de implantes colocados em osso nativo (NEVINS *et al*., 1998; FUGAZOTTO *et al.*, 1997; BUSER *et al.*, 1996; JOVANOVIC *et al*., 2003; NEVINS *et al*., 2006; DE COSTER *et al*., 2009). Buser *et al*. (1995) demonstraram em estudos pré-clínicos que os implantes colocados em osso regenerado associados ao uso de membranas osseointegraram com sucesso e que a maturação do osso continuou após a colocação do implante. A colocação de implante em sítios pós-extração geralmente pode ser controlada com procedimentos de enxerto ósseo com alta previsibilidade, desde que pelo menos duas paredes ósseas intactas remanesçam. Entretanto, à medida que o tempo da extração até a colocação do implante aumenta, a reabsorção progressiva do rebordo pode resultar em uma perda de volume ósseo a um nível que o aumento ósseo simultâneo torna-se menos previsível (ZITZMAN *et al*., 1999).

1.6. Vantagens da prevenção da reabsorção em detrimento à reconstrução tardia do rebordo

Visto que as dimensões do rebordo são tão cruciais, seria vantajoso preservar a dimensão do rebordo pós-extração em vez de reconstruí-lo depois, assegurando assim a manutenção das suas dimensões vertical e horizontal ideais e diminuindo a morbidade para o paciente (IASELLA *et al*., 2003; NEVINS *et al*., 2006). Desta forma, métodos que asseguram a preservação, o aumento ou a reconstrução da altura, espessura e qualidade do rebordo alveolar imediatamente após a extração dentária com procedimentos de regeneração óssea ou em conjunto com a colocação de implantes endósseos parecem ser essenciais para manter as suas dimensões verticais e horizontais. Isto reduziria de fato a necessidade de um enxerto tardio, simplificando e otimizando o sucesso da colocação do implante em termos de estética e função (HOWELL *et al*., 1997; LEKOVIC *et al*., 1997; LEKOVIC *et al.*, 1998; CAMARGO *et al*., 2000; SCHROPP *et al*., 2003; STVRTECKY *et al*., 2003; BARONE *et al*., 2008; AIMETTI *et al*., 2009; DARBY *et al*., 2009).

Tem havido um grande interesse em estudos sobre preservação do osso alveolar na região anterior estética (PELEGRINE *et al*., 2010). Vários métodos têm sido sugeridos para facilitar a formação óssea em alvéolos de extração frescos, minimizando desta forma a perda de altura óssea e espessura vestíbulo-lingual. Estes incluem regeneração óssea guiada, seguindo os princípios propostos por Nyman *et al*. (1982), com ou sem material de enxerto (BECKER *et al*., 1994; LEKOVIC *et al*., 1997; LEKOVIC *et al*., 1998; VANCE *et al*., 2004; NEVINS *et al*., 2006; BARONE *et al*., 2008),

enxertos com substitutos ósseos (CAMARGO *et al*., 2000; IASELLA *et al*., 2003; GUARNIERI *et al*., 2004; AIMETTI *et* al., 2009; DE COSTER *et al*., 2009), materiais osteogênicos como medula óssea autógena (PELEGRINE *et al*., 2010) e plasma rico em fatores de crescimento (PRFC) (ANITUA, 1999), e outros biomateriais (SERINO *et al*., 2003; SERINO *et al.*, 2008; FIORELLINI *et al*., 2005). Os materiais de enxerto usados como preenchedores de espaço após a extração dentária são capazes de fornecer um suporte mecânico e prevenir o colapso de ambas as paredes ósseas vestibular e lingual, servindo assim para retardar a reabsorção do rebordo residual (YILMAZ *et al*., 1998) e permanecer no local até que suficiente cicatrização (neoformação óssea) ocorra (SERINO *et al.*, 2008). Em outras palavras, os materiais substitutos ósseos ideais devem ser osteoindutores e osteocondutores, estimulando e servindo como um arcabouço para o crescimento ósseo.

Todavia, o uso de materiais de enxerto em alvéolos pós-extração frescos tem sido questionado porque eles parecem interferir com o processo normal de cicatrização (SERINO *et al*., 2003; NEVINS *et al*., 2006; SERINO *et al*., 2008; DE COSTER *et al*., 2009) e partículas residuais do material enxertado podem ser encontradas envoltas em tecido conjuntivo ou tecido ósseo no interior dos alvéolos até 6-9 meses após sua inserção (PINHOLT *et al*., 1991; BECKER *et al*., 1994; BECKER *et al*., 1996; BUSER *et al*., 1998; NEVINS *et al*., 2006). Esta interferência é relacionada ao processo de reabsorção destes materiais enxertados nos sítios dos implantes, o qual envolve uma resposta de células gigantes a um corpo estranho com a ativação em um estágio posterior de um processo osteoclástico (SERINO *et al*., 2008). De acordo com Norton & Wilson (2002), a neoformação óssea

dentro do alvéolo enxertado não pode ser demonstrada histologicamente em humanos antes de 6 meses de cicatrização. A demonstração de profundidades de sondagem de bolsa reduzidas e a imagem radiográfica dos materiais de enxerto têm extrapolado os achados histológicos de animais e podem levar a uma conclusão, talvez errônea, que o enxerto foi osseoincorporado (NORTON & WILSON, 2002).

A colocação imediata de implantes em alvéolos frescos pós-extração também tem sido sugerida, porém com resultados controversos (LANG *et al*., 1994; ARTZI *et al*., 1998; BECKER *et al*., 2000; PAOLANTONIO *et al.,* 2001; SCHROPP *et al*., 2003; BOTTICELLI *et al*., 2004; BOTTICELLI *et al*., 2008; ARAÚJO *et al*., 2006). Esta técnica pode ser afetada negativamente pela falta de fechamento de tecido mole, presença de infecção e defeitos entre o osso e os implantes (FERRUS *et al*., 2010; PELEGRINE *et al*., 2010). Recentemente foi demonstrado em estudos clínicos (BOTTICELLI *et al*., 2004) e pré-clínicos (ARAÚJO *et al*., 2005; ARAÚJO *et al*., 2006) que implantes colocados em alvéolos pós-extração falharam em prevenir a remodelação que ocorre nas paredes do alvéolo, especialmente no aspecto vestibular, o que resulta em uma perda marginal de osseointegração.

Apesar de o material substituto ósseo utilizado ser relevante, outros aspectos como a morfologia do alvéolo, a altura óssea interproximal e a presença e espessura das paredes corticais vestibular e lingual influenciam as alterações dimensionais no osso após a extração dentária e a previsibilidade de procedimentos de regeneração óssea guiada. Conquanto os alvéolos pós-extração com paredes ósseas intactas sejam capazes de alcançar a regeneração óssea por si mesmos (LEKOVIC *et al*., 1997;

AIMETTI *et al*., 2009), o osso não regenera a um nível coronal em relação ao nível horizontal da crista óssea dos dentes vizinhos, isto é, um preenchimento de 100% do alvéolo nunca ocorre (SCHROPP *et al*., 2003).

Fickl *et al*. (2008) demonstraram, em cães, que a elevação de um retalho resultou em uma perda mais acentuada da dimensão do rebordo comparada à não-elevação de um retalho. Esta reabsorção e perda de altura do osso alveolar ocorre supostamente em virtude da separação do periósteo e a ruptura de sua inserção de tecido conjuntivo na superfície óssea. A consequente redução do aporte sangüíneo pode provocar a morte dos osteócitos e a necrose do tecido mineralizado circundante das paredes ósseas. Este osso necrótico é assim gradualmente eliminado através da reabsorção superficial orquestrada pelos osteoclastos no periósteo (HOWELL *et al*., 1997; ARAÚJO & LINDHE, 2005; AIMETTI *et al*., 2009).

Além do mais, o levantamento de um retalho durante procedimentos de enxerto ósseo pode prejudicar a estética do rebordo e da papila (CAMARGO *et al*., 2000; IASELLA *et al*., 2003), por promover uma alteração da posição da linha mucogengival em direção coronal (CAMARGO *et al*., 2000). Esta situação é particularmente relevante quando do emprego da técnica de preservação do alvéolo com o uso de membranas como barreiras oclusivas, pois 3 grandes desvantagens supostamente são associadas com esta técnica: (1) a elevação de retalhos vestibulares e linguais em combinação com a extração dentária é necessária para a colocação das membranas; (2) a técnica e as barreiras precisam de um avanço do retalho vestibular para alcançar fechamento primário da ferida além de uma segunda cirurgia para a remoção da membrana, quando esta for não-absorvível; e (3)

a exposição de membranas não-absorvíveis ao meio bucal no curso da cicatrização resulta em risco aumentado de infecção bacteriana (SIMION *et al*., 1994) e limitada preservação do osso alveolar, com resultados semelhantes à da cicatrização não-assistida do alvéolo (LEKOVIC *et al*., 1997). Em virtude disso, CAMARGO *et al.* (2000) não recomendam a utilização de procedimentos regenerativos com retalho e membranas.

Enquanto o fechamento por primeira intenção da ferida cirúrgica tem sido sugerido como sendo capaz de melhorar a estabilidade da ferida (DE COSTER *et al*., 2009) e de oferecer uma melhor proteção aos materiais de enxerto (SCHEPERS *et al*., 1993; AIMETTI *et al*., 2009), Penteado *et al*. (2005), em contrapartida, afirmaram que o crescimento de tecido conjuntivo para dentro de um defeito ósseo pode perturbar ou prevenir totalmente a osteogênese na área. Em outras palavras, o contato direto entre o tecido conjuntivo gengival com a área do alvéolo como observado quando os retalhos são avançados favoreceriam a reabsorção do osso alveolar. Quando os tecidos gengivais são mantidos afastados da área do alvéolo durante as fases iniciais da cicatrização deixando a abertura do alvéolo exposta, acontece uma menor reabsorção do osso alveolar (CAMARGO *et al*., 2000).

1.7. Ausência de estudos clínicos prospectivos com o alvéolo vazio como controle

Embora o interesse em estudos sobre a preservação de alvéolos avaliando diferentes técnicas/ biomateriais tenha aumentado significativamente nos últimos anos, ainda há muito poucas evidências baseadas em estudos clínicos prospectivos controlados. A maioria das

publicações com humanos são relatos de casos, séries de casos ou estudos que não incluem a cicatrização não-assistida do alvéolo como controle. Além do mais, muitas variáveis, incluindo o tipo e o tamanho dos defeitos, o descolamento ou não de um retalho, o fechamento ou não da ferida por primeira intenção, o tipo de enxerto utilizado e a ausência de pontos de referência para medições confiáveis fazem a comparação direta entre os estudos difícil (NEVINS *et al*., 2006). Em uma revisão recentemente publicada, Darby *et al*. (2009) mostraram que as técnicas de preservação do alvéolo são efetivas em limitar as alterações horizontal e vertical do rebordo em sítios pós-extração e são acompanhadas por diferentes graus de formação óssea e materiais de enxerto residuais no alvéolo da extração. Porém, estudos retrospectivos e prospectivos não-controlados assim como estudos com animais foram incluídos nesta revisão. Consequentemente, isto pode ter levado a conclusões equivocadas devido à ampla heterogeneidade dos desenhos de estudos selecionados, tornando difícil a transposição para a realidade clínica.

Para a elaboração de uma revisão sistemática, o primeiro passo é a definição de uma pergunta focada, cujo estreitamento do foco produz uma pergunta de pesquisa passível de resposta. Caso contrário, a pergunta poderá ser tão ampla para ter qualquer chance de ser respondida ou poderia de fato ser uma série de perguntas. O estreitamento do alcance em uma revisão sistemática constitui-se em uma força para a tomada de decisão clínica uma vez que ela ajuda a assegurar que a revisão irá produzir um resumo tão conclusivo quanto os dados permitirem (NEEDLEMAN, 2002).

O propósito deste estudo foi avaliar, clinicamente e sistematicamente

na literatura, a eficácia da técnica de preservação do rebordo alveolar em alvéolos pós-extração. Primeiramente, este estudo buscou comparar radiograficamente, através de um ensaio clínico randomizado, a eficácia de um substituto ósseo sintético (Straumann® Bone Ceramic) com a de um xenoenxerto bovino (BioOss®) na limitação das alterações dimensionais do alvéolo pós-extração. Radiografias periapicais estandardizadas foram tiradas em intervalos de tempo regulares e os níveis da crista óssea alveolar foram medidos nos aspectos mesial, distal e central do alvéolo. Além disso, as imagens radiográficas foram subtraídas umas das outras e as áreas inalteradas, de ganho ou de perda foram avaliadas em termos de níveis de cinza. Por último, foi realizada uma comparação com as medições obtidas intra-cirurgicamente.

Em um segundo momento, uma revisão sistemática da literatura foi realizada nas mais importantes bases de dados científicas existentes atualmente. A estratégia de busca teve foco na procura por estudos prospectivos clínicos, radiográficos e histológicos em humanos, onde diferentes biomateriais foram utilizados e com um número mínimo de 5 pacientes por grupo. Outro critério a ser considerado foi a inclusão de um grupo controle, representado pela cicatrização natural do alvéolo pós-extração. Uma pesquisa manual adicional foi realizada e os dados obtidos a partir dos artigos que atenderam a todos os critérios de inclusão foram computados e comparados. A revisão buscou evidências da técnica executada previamente à colocação de implantes dentários e se ela permite a colocação bem sucedida do implante, com ou sem aumento ósseo adicional.

2. CAPÍTULOS

2.1 CAPÍTULO 1

Artigo 1 – aceito pelo periódico Clinical Oral Implants Research, qualis A2 e fator de impacto 2.756

Radiographic alveolar bone changes following ridge preservation with two different biomaterials

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Keywords: Alveolar ridge preservation, guided bone regeneration, radiography.

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Abstract

Objectives: The aim of this randomized controlled trial was to evaluate radiographical bone changes following alveolar ridge preservation with a synthetic bone substitute or a bovine xenograft.

Methods: Alveolar ridge preservation was performed in 27 patients randomized in 2 groups. In the test group (n=14), the extraction socket was treated with Straumann Bone Ceramic (SBC) and a collagen barrier membrane (Bio-Gide®), whereas, in the control group (n=13) with deproteinized bovine bone mineral (DBBM) and the same barrier. Standardised periapical x-rays were taken at 4 time points, BL: after tooth extraction, GR: immediately after socket grafting, 4M: 16 weeks, 8M: 32 weeks post-op. The levels of the alveolar bone crest at the mesial (Mh), and distal (Dh) and central aspects of the socket were measured at all time points. All the obtained radiographs were subtracted from the follow-up images. The gain, loss and unchanged areas in terms of grey values were tested for significant difference between the two groups.

Results: In the test group, the Mh and Dh showed a mean difference (+/- standard deviation) of 0.9 ±1.2 mm and 0.7 ± 1.8mm respectively between BL-8M. In the control group, the Mh and Dh showed a mean difference of 0.4 ±1.3 mm and 0.7 ± 1.3mm respectively ($P>0.05$). Both treatments presented similar gain in grey values between BL-GR, BL-4M and BL-8M. The SBC presented less loss in grey values between BL-4M and BL-8M ($P<0.05$). Radiographic assessment underestimated the intrasurgical measurements (mesial and distal) of an average 0.3mm (95% CI, 0.02-0.6).

Conclusion: Both types of bone grafts presented similar radiographic

alveolar bone changes when used for alveolar ridge preservation.

Keywords: Alveolar ridge preservation, guided bone regeneration, radiography.

Introduction

Following tooth extraction, a significant alteration of the alveolar ridge contour takes place due to extended osseous resorption and remodelling (Amler 1969, Cardaropoli et al. 2003, Araujo et al 2005). As a result of these processes, post-extraction site dimensions are inferior to the dimensions of the alveolar bone prior to tooth extraction (Pietrokovski and Massler 1967, Johnson 1969). In a recent study, Schropp et al. (2003) evaluated bone formation in the alveolar socket and quantified contour changes of the alveolar ridge following extraction of single teeth using study casts and standardised periapical radiographs. The authors reported a 5-7 mm reduction in the width of the alveolar ridge (a 50% of the pre extraction alveolar ridge dimensions) that usually took place during the first three post extraction months.

Modern aesthetic implant or tooth-supported prostheses, especially in the anterior region, require a complete ridge contour reconstruction in order to achieve an aesthetically pleasing immergence profile in the area of missing teeth. In order to preserve the original ridge dimensions following tooth extraction and promote bone regeneration of the residual alveolar socket, various bone grafts and substitutes used in combination or not with barriers for guided tissue regeneration (GTR) have been suggested (Becker et al.

1994, 1996, Gross 1995, Brugnami et al. 1996, Artzi et al. 2000, Feuille et al. 2003, Iasella et al. 2003, Serino et al. 2003, Froum et al. 2002, Barone et al. 2008). Among these grafting materials, deproteinized bovine bone mineral xenografts (DBBM) were able to promote bone regeneration and preserve the pre extraction alveolar ridge dimensions when grafted in immediate extraction sockets, especially when combined with barriers for guided tissue regeneration (Artzi et al. 2000, Carmagnola et al. 2003). Furthermore, a randomised controlled clinical radiographic trial demonstrated that the post extraction alveolar ridge resorption was significantly reduced when the extraction sockets were grafted with a deproteinized bovine bone in comparison to the sockets that left to heal without any grafting (Nevins et al. 2006). According to the authors, the form of the residual alveolar ridge as evaluated in sagittal CT images was more favourable for subsequent implant placement when a socket preservation procedure took place. However, in another randomized controlled clinical trial comparing ridge dimensions and histologic characteristics following socket preservation with two different techniques, the combination of deproteinized bovine bone and a collagen membrane was found inferior in terms of new bone formation to a combination of allograft “putty” combined with a calcium sulphate barrier (Vance 2004) indicating that further research is necessary in order to identify the ideal grafting material for alveolar ridge preservation.

Straumann Bone Ceramic® (SBC) is a fully synthetic bone graft substitute of medical grade purity in particulate form composed of biphasic calcium phosphate - a mixture of 60% hydroxyapatite (HA), which is 100% crystalline, and of 40% of the beta form of tricalcium phosphate (beta-TCP).

The two mineral phases are mixed at an early stage of synthesis delivering blocks of a homogenous distribution of the two mineral phases and 90% porosity. The objective of combining the insoluble HA with the soluble β-TCP is that HA would maintain the space (scaffolding function) while the β-TCP resorbs promoting at the same time bone regeneration. The biocompatibility and osteoconductivity of the calcium phosphates has been demonstrated in recent human controlled trials where SBC has been found to produce similar amounts of newly formed bone when compared to a bovine xenograft for grafting of the maxillary sinus (Cordaro et al. 2008, Froum et al. 2008) or for periodontal regeneration (Zafiropoulos et al. 2007). In a randomized control clinical trial from our group (Mardas et al. 2010), these two biomaterials were tested clinically and histologically for alveolar ridge preservation in combination with collagen membranes for GTR. It was reported that following grafting of the socket with either SBC or DBBM, an equal preservation of the alveolar ridge dimensions was achieved and the same amount of bone regeneration was observed in the post extraction sockets at 8 months following the ridge preservation surgery.

The aim of this study was to evaluate the radiographical bone changes following alveolar ridge preservation with a synthetic bone substitute or a bovine xenograft.

Materials and Methods

Study population

Thirty patients participated in this randomized, controlled, single-blind,

clinical trial that took place in UCL Eastman Dental Institute, Clinical Investigation Center during the period March 2006- July 2009. The study was conducted in accordance with ethical principles founded in the Declaration of Helsinki and the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP), awarded an ISO 14155 and approved by the relevant independent committee on the Ethics of Human Research of University College London.

The patients were evaluated for initial study eligibility based on the following inclusion criteria: age between 18 and 75 years old; good general health; presence of a hopeless tooth in mandibular or maxillary incisor, canine or pre molar region requiring extraction; the tooth to be extracted has at least one neighbour tooth.

In addition, patients were excluded from the studying in case of: pregnancy or lactating period; any known diseases (not including controlled diabetes mellitus) and the related medication, infections or recent surgical procedures within one month of baseline visit known to affect oral status or contraindicate surgical treatment; anticoagulant therapy; HIV or Hepatitis; administration of any other investigational drug within 30 days of study initiation; limited mental capacity or language skills or suffering from a known psychological disorder; heavy smoking (> 10 cigarettes per day); uncontrolled or untreated periodontal disease; full mouth plaque level >30% at the enrollment visit; severe bruxism; acute endodontic lesion in the test tooth or in the neighbouring areas; major part of the buccal or palatal osseous wall damaged or lost following tooth extraction.

The subjects were randomly assigned to the test or control group by a

computer-generated table. A balanced random permuted block approach was used to prepare the randomization tables in order to avoid unequal balance between the two treatments.

Surgical treatment and postoperative care.

The surgical protocol has been described in details elsewhere (Mardas et al. 2010). In summary, following the performance of minimally extended full thickness mucoperiosteal flaps, the tooth was atraumatically extracted by means of periotomes, attempting to preserve as much as possible from the surrounding osseous walls. Following tooth extraction, the following intrasurgical measurements of residual ridges dimensions were taken using a UNC-15 probe:

•Bucco-lingual/ palatal width of the alveolar ridge at its most central part (B-L/P).

•Width of the buccal (Bbw) and lingual /palatal (L/Pbw) bone plate at its most central part.

•Distance of the alveolar bone crest at the mesial-central (Mbh) and distal-central (Dbh) aspects of the socket to the relative cementum-enamel junction or restoration margin of the neighbouring teeth.

In the randomly assigned test group the extraction socket was loosely filled with 0.40-1.00 in diameter SBC particles (Straumann Bone Ceramic®; Straumann AG, Basel, Switzerland) while in the control group the extraction socket was filled with 0.25-1.00 mm in diameter DBBM particles (Bio-Oss®; Geistlich Biomaterials, Wollhusen, Switzerland). In both groups a bi-layer

collagen barrier (Bio-Gide®, Geistlich, Switzerland) was used to cover the grafting material. The flaps were coronally replaced and secured by vertical mattress and horizontal cross mattress sutures (Gore Tex®, Gore & Associates, Inc. Flagstaff, Arizona, USA) in order to cover as much as possible of the biomaterials without however being able to achieve their complete coverage.

Systemic antibiotics (Amoxicillin 500mg and Metronidazole 400 mg) were administered 3 times per day for the 1st postoperative week and Paracetamol 500mg was subscribed upon patient discretion for post-operative pain control. All the patients refrained from tooth brushing in the operated area and rinse with 0.2% chlorhexidine-digluconate mouthwash for the first two postoperative weeks. Any removable temporary prosthesis was not worn for the first 2-3 weeks and subsequently was adjusted to relieve any pressure elicited to the wound area. The sutures were removed after 14 days and wound healing assessment together with prophylaxis were provided at regular intervals following operation.

Radiographic method

Standardized intraoral periapical radiographs were taken at the following observation periods:

- *At baseline (BL): immediately after tooth extraction.*
- *At Grafting (GR): immediately after socket augmentation.*
- *At 4months (4M): 16 weeks after tooth extraction visit.*
- *At 8months (8M): 32 weeks after tooth extraction just before dental implant*

placement.

The periapical radiographs were produced as previously described by Sewerin (1990), using the paralleling technique with an occlusal bite index, prepared from a silicone material and attached to the cone of the x-ray unit. The same bite index was used in all the visits (BL, GR, 4M and 8M). All the periapical radiographs were developed using the same type of film (DETAILS) and X-ray (DETAILS) and were developed with the same automatic x-ray developer under standardized conditions. The radiographs were digitized using a slide scanner (SprintScan® 35, CS-2700, Polaroid Scanner, Cambridge, MA, USA) after selecting constant scanning settings, 600 d.p.i. resolution, and 256 grey levels. The images were coded to preserve blinding of the recordings and stored in JPEG File Format without compression.

Linear radiographic measurements

Linear measurements on the digitized radiographs were performed by means of a digital image analysis computer program for radiographic linear measurements (X-PoseIt®, version 3.1.17, Image Interpreter System, Lystrup, Denmark). The distance from the alveolar bone crest at the mesial (MbhR), distal (DbhR) and central (CbhR) aspects of the socket to the cementum-enamel junction or restoration margin of the neighbouring to the extraction teeth were measured during all above mentioned observation periods (BL, GR, 4M and 8M). For assessment of the bone levels changes at the extraction site, a reference line connecting the cementum-enamel junction or restoration margin of the neighbouring to the extraction teeth was drawn in all the radiographs. The vertical distances from this reference line to the alveolar

bone crest at the mesial (Mh), distal (Dh) and central (Ch) aspects of the socket were measured by a single calibrated examiner, other than the surgeon who was also not aware of the treatment assignment (test or control). The reproducibility of the examiner was previously tested in duplicated measurements taken within a week interval in 15 randomly selected digitized radiographs.

Subtraction radiography

Quantitative digital subtraction radiography was performed using the same digital analysis software (X-PoseIt®, version 3.01). A region of interest (ROI) that corresponded to the alveolus of the extracted tooth and a region of control (ROC) that corresponded to an area expected not to be involved in bone changes were outlined in all the baseline radiographs immediately after the extraction (BL). The radiographs at the baseline were subtracted from the follow-up images taken at GR, 4M an 8M observation periods resulting in the subtraction images: BL-GR BL-4M, BL-8M, 4M-8M. Following the alignment and superimposition of digitized images (using 10 reference points drawn on both images) taken at two different time points (BL, GR, 4M and 8M) both ROI and ROC transferred automatically in the resulting superimposition image and the grey shade pixel value within the ROI of each image was subtracted from the corresponding pixel-value of the other image, resulting in the "subtraction image" that represented the differences in grey shades within the ROI between the two radiographs. Hard mineralised tissue was defined as pixels with a grey level more than 128 that appear bright in the subtraction image. Respectively, non mineralised tissue was defined as pixels with a grey level

less than 128 that appear dark in the image. Pixels with a grey scale within a conservative interval mean ± 3 X SD for the region of control were defined as unchanged. Pixel values above this level were defined as hard tissue gain and values below as hard tissue loss. The mean grey values and the size of the gain, loss and unchanged areas were tested for significant difference between the two groups at the various observation periods.

Statistical analysis

All data were entered in a computer database, proofed for entry errors and imported into SPSS® (version 17). Differences between and within the two treatment groups were assessed at each time interval (BL-GR BL-4M, BL-8M, 4M-8M) by using independent samples t-tests for differences in means between groups when the data was normally distributed and Mann-Whitney U test for differences in medians when the data was non-normally distributed. The differences between the repeated measures at each follow-up visit were evaluated with a non-parametric Friedman test for repeated measures. Post hoc comparisons between study groups at each visit were computed with Wilcoxon Signed-Rank Tests and Bonferroni corrections. Non-parametric linear correlation analysis (Spearman) was performed between clinical (B-L/P, Bbw, L/Pbw, Mbh and Dbh) and radiographic linear measurements (MbhR and DbhR) (combining the mesial and distal measures at both visits) and intraclass correlation coefficient reported. The difference between intrasurgical measurements and radiographic assessment were computed (normal distribution) and multiple linear regression models were created to

ascertain the impact of additional intrasurgical measurements (bucco-palatal and mesio-distal widths) on the validity of radiographic measurements. Significance level was set to be at $p<0.05$.

Results

Twenty seven out of the thirty patients that have been initially enrolled participated in the radiographic part of the study. Two patients were excluded before randomization due to complete loss of the buccal osseous plate following extraction. One patient quit the study before randomization. One patient that had been assigned in the test (SBC) group quit the study before implant placement. In this patient only the radiographs corresponding to BL, GR and 4M were included in the analysis. The distribution of the treated sites is presented in table 1.

The level of agreement between the duplicated radiographic linear measurements (Mh, Dh, Ch) performed by the single calibrated examiner is presented in table 2. For the mesial linear measurements (Mh) both measurements were anticipated to fall within a +/- 0.192mm range on 95% of occasions (CR). Similarly the CR for the distal measurements (Dh) was +/- 0.164mm and for the central measurements (Ch) was +/-0.388mm.

Linear radiographic measurements

A comparison of the linear radiographic measurements was performed: a) between treatment groups and b) within treatment groups.

a) Between treatment groups

The mean values of the three different linear radiographic measurements (Mh, Ch , Dh) during all the observation periods (BL, GR, 4M and 8M) is presented in Tables 3, 4 and 5. At all observation periods, the Mh measurements were statistically higher in the SBC group ($P<0.05$) (Table 3). At GR and 4M observation periods the Ch measurements were statistically significant higher ($P>0.05$) in the SBC group (Table 4).

The changes of radiographic hard tissue levels between different time intervals (BL-GR BL-4M, BL-8M, GR-4M, GR-8M) are presented in tables 6, 7 and 8. The linear radiographic measurements in the mesial site of the socket (Mh) increased by approximately 0.9mm in the SBC group for the period between BL and 8M, whereas in the DBBM group increased by 0.4mm (Table 6). No statistical significant difference was observed between the 2 groups at any time interval ($P>0.05$) (Table 6).

The linear radiographic measurements in the central site of the socket (Ch) have been reduced by approximately 16 mm in SBC group and 18.6 mm in DBBM group for the period between BL and 8M (Table 7). No statistical significant difference was observed between the 2 groups at any time interval ($P>0.05$) (Table 7).

The linear radiographic measurements in the distal site (Dh) of the socket increased by 0.36mm and 0.05mm in the SBC and DBBM group respectively (Table 8). The difference between the groups was not statistically significant at any time interval ($P>0.05$) (Table 8).

b) Within treatment groups

The radiographic linear measurements changes within each group during the 8 month observation period are shown in figures 1, 2 and 3.

In the SBC group, the Mh was increased by 0. 92 mm (Fig 1) and the Dh by 1.03 mm (Fig 3) between GR and 8M, while the Ch decreased by 16.05 mm between BL and 8 months (Fig 2). The Mh and Dh values immediately after grafting of the socket GR were statistically significant lower than the relevant values at 8M indicating some progressive hard tissue loss in these sites treated with SBC ($P=0.03$ and $P=0.04$ respectively) (Fig 1, 3). The Ch values immediately after extraction and prior to grafting (BL) were statistically significant higher than those values at 8M indicating radiographic socket fill in these sites treated with SBC ($P<0.0001$) (Fig 2).

In the DBBM group, the Mh was increased by 0. 58 mm ($P=0.08$) (Fig 1) and the Dh by 1.00 mm ($P<0.05$) (Fig 3) between GR and 8M, while the Ch decreased by 18.6 mm between BL and 8 months (Fig 3). The Dh values at GR were statistically significant lower ($P<0.05$) than those values at 8M indicating some progressive hard tissue loss in the distal sites treated with DBBM. In the mesial sites although there was a trend for bone loss it was not statistical significant ($P>0.05$). The Ch values immediately after extraction and prior to grafting (BL) were statistically significant higher ($P<0.0001$) than the Ch values at 8M indicating radiographic socket fill in these sites treated with DBBM.

Subtraction radiographic measurements

Seventeen radiographs from different observation periods were not

available for subtraction radiography evaluation due to inadequate standardization or poor quality of the x-rays.

The grey shade pixel value within the ROI corresponding to hard tissue gain, loss or unchanged areas is presented in table 9. No statistical significant differences in grey shade pixel values corresponding to hard tissue gain were observed between the two groups at any of the observation periods (BL-GR, BL-4M, BL-8M) ($P>0.05$). The sites treated with SBC presented with statistically significant lower ($P<0.05$) mean gray shade pixel values corresponding to loss of hard tissue than the sites treated with DBBM at the observation period between BL and 8M. The unchanged areas were not different between study groups at each visit comparison ($P>0.05$).

Comparison between radiographic and clinical measurements

A positive albeit moderate linear association between clinical (Mbh and Dbh) and radiographic measures (MbhR and DbhR) was noted (Fig 4). Both correlation coefficient ($R= 0.40$, $p<0.0001$) and intraclass correlation coefficient (0.40, $p<0.0001$) were statistically significant. No differences were noted if correlation analyses were performed at separate visits (4 months and 8 months) (data not shown). The mean difference between the intrasurgical measurement and radiographic assessment was of 0.3mm (95% CI, 0.02-0.6). Multivariate analysis of this difference resulted in Bbw ($p=0.004$) and L/Pbw ($p=0.04$) widths as the only influential factors (Linear Regression Model $F=4.948$, $p=0.009$, Adjusted R square=0.78).

Discussion

The present investigation indicated that alveolar ridge preservation with either SBC or DBBM resulted in similar radiographic bone level changes. This is in agreement with the clinical results obtained in the study where the two biomaterials presented similar ability in preserving a significant portion of the pre-extraction clinical dimensions of the alveolar ridge and supporting bone formation (Mardas et al. 2010). In this first clinical study, the distance of the alveolar bone crest at the mesial and distal aspects of the socket to the relative cementum-enamel junction or restoration margin of the neighbouring teeth were measured intrasurgically at baseline and at 8 months following tooth extraction and alveolar ridge preservation. The mean differences between the two groups were not statistically significant. In addition, within each group, the mean values taken at baseline were not statistical different to the values taken at 8M indicating that interproximal bone could be fully preserved following ridge preservation with both biomaterials. In the present investigation, the radiographic analysis on the same patients showed a small decrease in the interproximal radiographic bone levels at 4 months and 8 months following operation in both groups. In the SBC group, the changes in Mh and Dh, representing possible radiographic hard tissue loss at the mesial and distal site, were 0.9 ± 1.2 mm and 0.7 ± 1.8 mm respectively at 8 months following tooth extraction (BL-8M). For the same period (BL-8M), in the DBBM group the Mh and Dh showed a mean difference of 0.4 ± 1.3 mm and 0.7 ± 1.3 mm respectively indicating a mild interproximal bone loss of similar extend to that observed in the SBC group**.** On the other hand caution should be taken in interpreting data on bone level changes between different observation

periods. Due to the high number of statistical comparisons computed in this study it may be possible that some of the results could be the result of statistical chance. In addition to that, it is questionable whether or not radiographic hard tissue changes at interproximal sites, of less than 1.0 mm present any significant clinical relevance.

Another interesting observation of this study was that the baseline linear measurements before grafting at mesial sites were found to be significantly different between the two groups. It was not possible to explain this discrepancy with any obvious biological or methodological reasons. The use of a strict randomization methodology and the masking of the examiner who performed the measurements have limited the possibility of introducing a systematic error able to create such a discrepancy in the baseline measurements. Therefore, we have to attribute this difference to an accidental fact.

Intraoral radiographic examination to assess bone levels following tooth extraction (Schropp et al. 2003, Munhoz 2006, Aimetti et al 2007), or to detect changes in infrabony defects after regenerative treatment, has been used at previous clinical studies (Zybutz et al. 2000, Stavropoulos et al. 2003, Liñares et al. 2006). However, such type of analysis has specific limitations as an assessment tool, starting from the fact that periapical radiographs provide only 2 dimensional images of 3 dimensional structures. Furthermore, the radiographic image of interproximal bone loss may change with changing projection geometry. Therefore, it is important that the images are taken under standardized conditions (film type, time of exposure, film processing) at a

standardized projection geometry (Wenzel and Sewerin 1991). In the present study film type, time of exposure, film processing and radiographic equipment were fully standardised for all the radiographs taken. In addition standardized projection geometry has been accomplished by using a customised bite index and the cone parallel technique. On the other hand, it should be emphasized that some degree of magnification is inevitable despite the fact that the intraoral radiographs were standardized. This magnification could be attributed to the contraction of the acrylic material, possible tooth migration or occlusal changes that in some cases have made difficult an accurate and reproducible placement of the bite-index or in some other occasions, the angulation of the cone and the bite index that may have slightly differed between the study visits. It is questionable however whether the utilization of other periapical film-positioning technique would have facilitated the repositioning of the films at the different observation periods and reduces this source of noise in the subtracted images (Ludlow and Peleaux 1994).

Besides standardization, the identification of anatomical landmarks in x-rays and the measurements of the distances between them represent a significant bias factor in all studies utilizing conventional radiography for evaluation of hard tissue changes. Both conventional methods (direct measurements on x-rays using magnifying means) and the use of computer assisted digital image analysis systems underestimate the true linear distances between reference anatomical landmarks such as cementum-enamel junction (CEJ) or the bone crest (BC) to a varying degree when compared to the gold standard of intrasurgical measurements (Shrout 1993, Eickholz 1998). The mean difference of assessments of the CEJ-BC distance

by means of computer assisted radiographic analysis and direct surgical measurements, was reported to be between 0.3mm and 1.4mm (Eickholz et al 1999, Zybutz 2000). In the present study a direct correlation between radiographic linear measurements (MbhR and DbhR) and the intrasurgical measurements (Mbh and Dbh) between the CEJ-BC was performed to evaluate the validity of our linear radiographic measurements. Our findings are consistent with those previously reported with an average difference in radiographic measurements compared to the gold standard (intrasurgical) of 0.3mm. Similarly a moderate linear association between radiographic and intrasurgical measurements was found. Furthermore, the multivariate models suggested that the buccal and palatal widths of the alveolar crest (Bbw and L/Pbw) as measured intrasurgically, were the most influential factors in affecting the validity of radiographic assessment compared to gold standard. In particular, greater buccal and smaller palatal widths were associated with an overestimation and underestimation of the radiographic assessment of linear alveolar crestal bone heights respectively.

The reproducibility of radiographic linear measurements may also be influenced by different factors. Wolf and co-workers (2001) tested the reproducibility of the radiographic linear measurements of interproximal bone loss at infrabony defects inter- and intra-examiner and reported that the radiographic measurements tended to overestimate the amount of bone loss as assessed by intrasurgical measurements and the reproducibility of the measurements found to be significantly influenced by the examiner. In the present study, one single, previously calibrated examiner, other than the surgeon who was also not aware of the treatment assignment (test or control)

performed all the measurements. The reproducibility of the measurements obtained by this examiner anticipated to fall within less than +/- 0.2mm in 95 % of the measurements and was comparable to previous reports (Wolf et al. 2001).

In addition to linear radiographic measurements, the present study evaluated hard tissue changes using subtraction radiography where the grey shade pixel value within the ROI corresponding to hard tissue gain, and unchanged areas were compared between the two groups. The analysis showed that grey shade pixel values corresponding to hard tissue loss were significantly lower in the SBC group. However, changes in grey shade pixel values may not necessarily depict the 'real' healing events that take place into the socket at the different observation periods. This is due to the fact that subtraction radiography is not able to distinguish between changes in the mineralized connective tissue and the presence of residual radiopaque biomaterial. In our study, grey shade pixel values within the ROI corresponding to hard tissue gain may be explained by the addition of a radiopaque biomaterial into an empty socket but also by an ongoing bone formation process during the healing period. In a similar way the difference in grey shade pixel values corresponding to hard tissue loss observed between the two groups could be explained by either an increased bone resorption process in the sockets grafted by DBBM or an increased resorption rate of the DBBM material or a combination of these biological processes resulting in all cases in reduced radiopacity. An initial correlation of subtraction radiographic data with the qualitatitive histological analysis performed in the first part of this study (Mardas et al. al 2010) supports the assumption that part of the

radiographic hard tissue gain observed in the subtraction images taken can be attributed to ongoing new bone formation especially at the base of the socket. However, the amount and location of bone formation or bone resorption cannot be estimated with the methodology applied in this study.

Conclusions

Taking into consideration the limitations of this study, alveolar ridge preservation with either a synthetic bone substitute, or a bovine-derived xenograft, both in combination with a collagen barrier will equally preserve radiographic bone levels up to 8 months following the grafting of the sockets.

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Legends

Table 1: Tooth extraction distribution between the two groups.

Table 2: Reproducibility of the radiographic linear measurements.

Table 3: Mesial height (Mh) in mm (mean ± standard deviation, N= number of X- rays evaluated). *P-values (statistically significant at the level of P<0.05 with the t-test for the difference in Mh between SBC and DBMM groups.

Table 4: Central height (Ch) in mm (mean ± standard deviation, N= number of X- rays evaluated). *P-values (statistically significant at the level of P<0.05 with the t-test for the difference in Ch between SBC and DBMM groups.

Table 5: Distal height (Dh) in mm (mean (median) ± standard deviation, N= number of X- rays evaluated). *P-values (statistically significant at the level of P<0.05 with the Mann–Whitney Utest for the difference in Dh between SBC and DBMM groups.

Table 6: Change in mesial height in mm (mean ± standard deviation) at different time intervals. *P-values (statistically significant at the level of P<0.05 with the t-test for the difference in change in Mh between SBC and DBMM groups at different time intervals).

Table 7: Change in central height in mm (mean ± standard deviation) at

different time intervals. *P-values (statistically significant at the level of P<0.05 with the t-test for the difference in change in Mh between SBC and DBMM groups at different time intervals).

Table 8: Change in distal height in mm (mean (median) ± standard deviation) at different time intervals. *P-values (statistically significant at the level of P<0.05 with the Mann-Whitney U test for the difference in change in Dh between SBC and DBMM groups at different time intervals).

Table 9: Grey shade pixel value within the ROI corresponding to hard tissue gain, loss or unchanged areas. * P-values (statistically significant at the level of P<0.05 for multiple comparisons between the groups (Tukey corrections).

Figure 1: Changes Mh (yellow arrow) in SBC and DBBM group during the 8 months observation period together with the relevant standardized periapical X- rays from the SBC group.

Figure 2: Changes Ch (yellow arrow) in SBC and DBBM group during the 8 months observation period together with the relevant standardized periapical X- rays from the SBC group.

Figure 3: Changes Dh (yellow arrow) in SBC and DBBM group during the 8 months observation period together with the relevant standardized periapical X- rays from the SBC group.

Figure 4: Scatter plot for the correlation between radiographic assessment and intrasurgical measurements.

	Central incisor	*Lateral incisor*	*Canine*	*Premolars*	*Total*
Maxilla SBC	6	1	1	1	**9**
Maxilla DBBM	7			5	**12**
Mandible SBC	1			3	**4**
Mandible DBBM				1	**1**
Total	**14**	**1**	**1**	**10**	**26**

Table 1: Tooth extraction distribution between the two groups.

Parameter	Lin's Correlation Coefficient	**Bland and Altman's approach**				
		Systematic error		**Random error**		**Limits of agreement**
		Mean difference	***P-*** (paired *t*-test)	***Standard Deviation***	***Coefficient of Repeatability*** **CR**	
Mh	0.99	0.02	0.382	0.096	0.192	-0.166, 0.210
Ch	0.99	-0.01	0.838	0.194	0.388	-0.390, 0.369
Dh	0.99	-0.01	0.470	0.082	0.164	-0.176, 0.145

Table 2: Reproducibility of the radiographic linear measurements.

Mesial height	**SBC**	**DBBM**	***p-value***
BL	4.0±2.2 (N=13)	2.1±1.5(N=12)	0.018*
GR	3.5±1.4(N=12)	1.9±1.5(N=13)	0.009*
4 M	4.2±1.5(N=12)	2.5±1.8(N=12)	0.015*
8 M	4.5±1.8(N=12)	2.8±1.6(12)	0.022*

Table 3: Mesial height (Mh) in mm (mean ± standard deviation, N= number of X- rays evaluated). *P-values (statistically significant at the level of P<0.05 with the t-test for the difference in Mh between SBC and DBMM groups.

Central height	SBC	DBBM	*p-value*
BL	22.1±5.7(N=13)	21.83±4.43(N=11)	0.895
GR	3.9±1.8(N=12)	2.49±1.09(N=11)	0.041*
4 M	5.0±2.3(N=12)	3.0±1.7(N=11)	0.025*
8 M	4.8±2.4(N=11)	3.4±1.5(N=11)	0.123

Table 4: Central height (Ch) in mm (mean ± standard deviation, N= number of X- rays evaluated). *P-values (statistically significant at the level of P<0.05 with the t-test for the difference in Ch between SBC and DBMM groups.

Distal height	SBC	DBBM	*p-value*
BL (N)	3.9 (2.8) ±3.3 (N=13)	1.9 (2.1) ±1.33(N=11)	0.224
GR(N)	3.5(1.7) ±3.0 (N=12)	1.7 (2.0) ±1.3 (N=12)	0.623
4 M (N)	4.3(3.1)±3.4 (N=12)	2.5 (2.7)±1.3 (N=12)	0.194
8 M (N)	4.7 (3.8) ±3.8(N=12)	2.9 (3.2) ±1.1 (N=11)	0.538

Table 5: Distal height (Dh) in mm (mean (median) ± standard deviation, N= number of X- rays evaluated). *P-values (statistically significant at the level of P<0.05 with the Mann–Whitney U-test for the difference in Dh between SBC and DBMM groups.

Change in Mh	SBC	DBBM	*p-value*
BL-GR	0.0±0.5	0.0±0.4	0.959
BL-4M	0.7±1.0	0.4±1.3	0.508
BL-8M	0.9±1.2	0.4±1.3	0.357
GR-4M	0.7±1.0	0.6±1.0	0.770
GR-8M	0.9±1.2	0.6±1.0	0.476

Table 6: Change in mesial height in mm (mean ± standard deviation) at different time intervals. *P-values (statistically significant at the level of P<0.05 with the t-test for the difference in change in Mh between SBC and DBMM groups at different time intervals).

Change in Ch	SBC	DBBM	*p-value*
BL-GR	-17.3±4.2	-19.3±4.3	0.281
BL-4M	-16.2±4.1	-18.8±4.2	0.156
BL-8M	-16.0±4.3	-18.6±4.2	0.182
GR-4M	1.1±1.2	0.5±1.4	0.235
GR-8M	1.0±1.0	0.9±1.5	0.894

Table 7: Change in central height in mm (mean ± standard deviation) at different time intervals. *P-values (statistically significant at the level of P<0.05 with the t-test for the difference in change in Ch between SBC and DBMM groups at different time intervals).

Change in Dh	SBC	DBBM	*p-value*
BL-GR	0.3 (0.0)±1.1	0.1 (0.1)±0.5	0.954
BL-4M	0.5 (0.5)±1.6	0.5 (0.7)±0.8	0.839
BL-8M	0.7 (0.5)±1.8	0.7(0.8)±1.3	0.974
GR-4M	0.8(0.7)±1.1	0.8(0.7)±1.2	0.999
GR-8M	1.0 (1.3)±1.4	1.0 (1.2)±1.3	0.878

Table 8: Change in distal height in mm (mean ± standard deviation) at different time intervals. *P-values (statistically significant at the level of P<0.05 with the Mann-Whitney U test for the difference in change in Dh between SBC and DBMM groups at different time intervals).

Tx	G BL-GR	G BL-4M	G BL-8M	L BL-GR	L BL-4M	L BL-8M	U BL-GR	U BL-4M	U BL-8M
SBC	168.4±22.4	130.7±73.1	110.0±74.1	26.7±46.5	48.6±47.1*	32.5±37.7*	129.5±13.3	134.1±17.9	128.0±16.3
DBBM	150.2±71.0	172.5±24.3	140.3±68.6	56.1±54.9	60.0±40.2*	65.4±39.4*	134.8±18.3	132.0±24.2	134.0±21.9

Table 9: Grey shade pixel value within the ROI corresponding to hard tissue gain (G), loss (L) or unchanged areas (U). * Statistically significant at the level of P<0.05 for multiple comparisons between the groups with Tukey corrections).

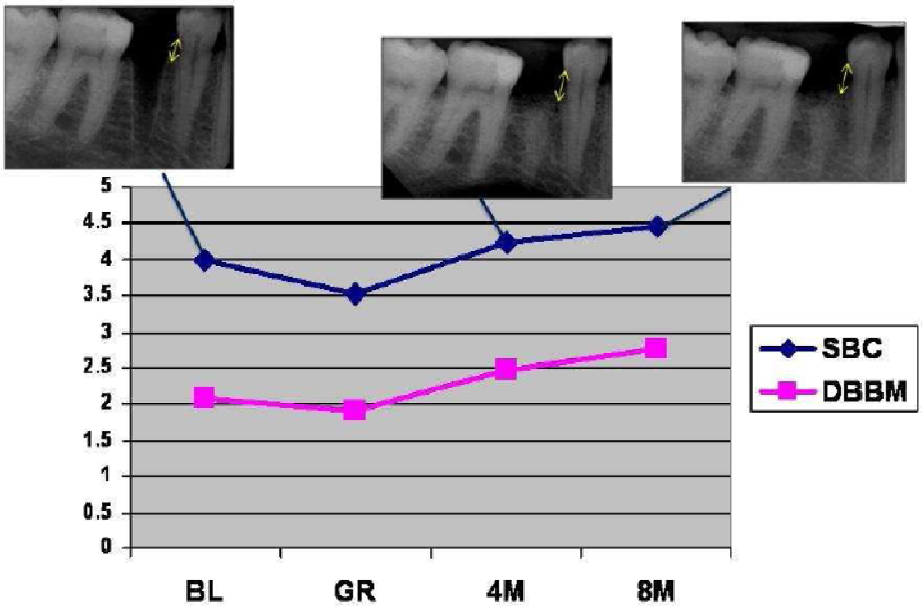

Figure 1: Changes Mh (yellow arrow) in SBC and DBBM group during the 8 months observation period together with the relevant standardized periapical X- rays from the SBC group.
254x190mm (96 x 96 DPI)

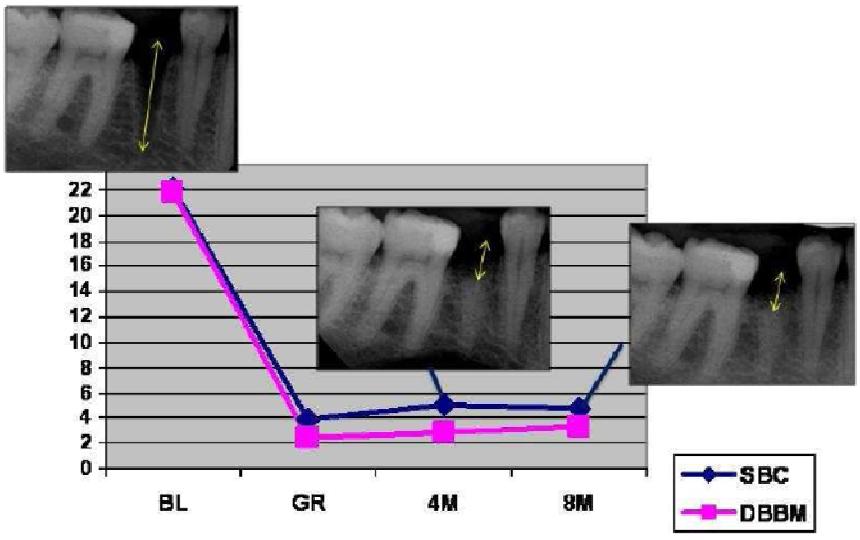

Figure 2: Changes Ch (yellow arrow) in SBC and DBBM group during the 8 months observation period together with the relevant standardized periapical X- rays from the SBC group.
254x190mm (96 x 96 DPI)

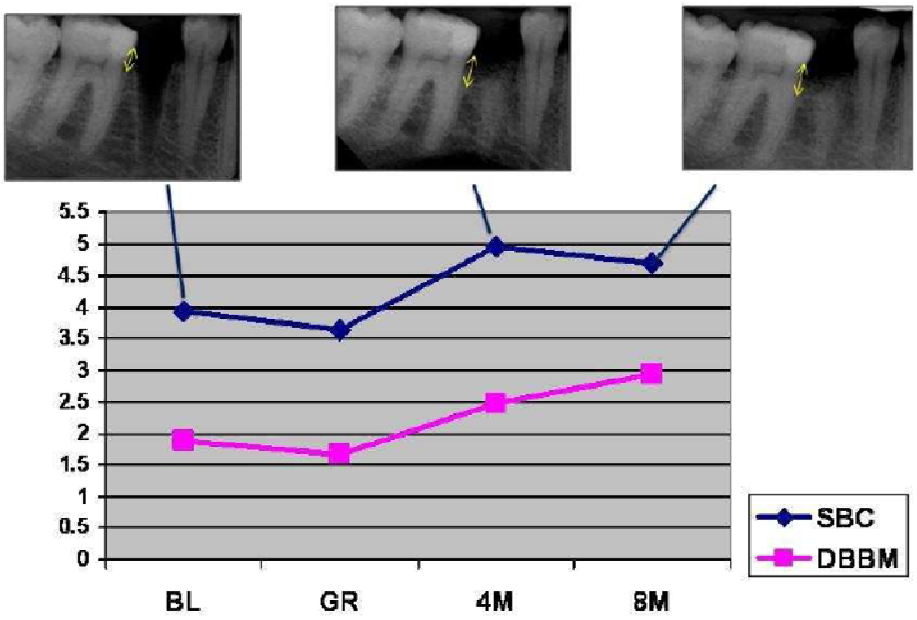

Figure3: Changes Dh (yellow arrow) in SBC and DBBM group during the 8 months observation period together with the relevant standardized periapical X- rays from the SBC group.
254x190mm (96 x 96 DPI)

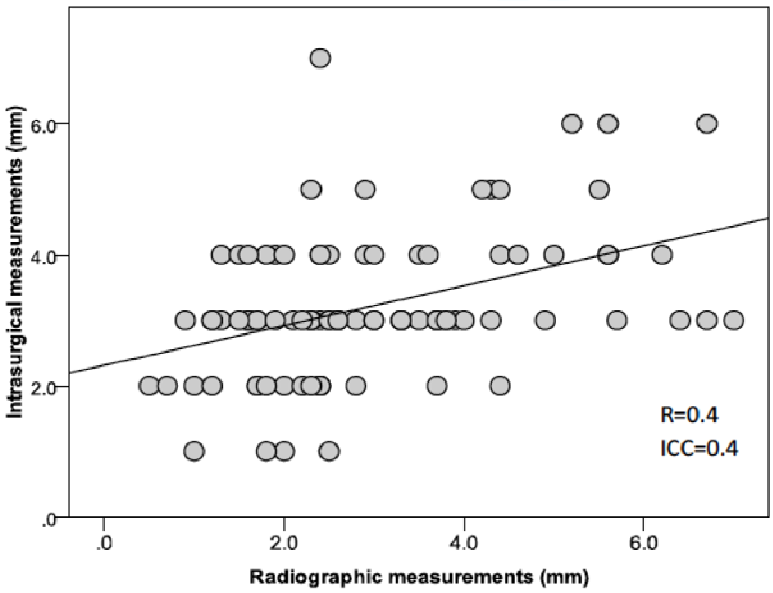

Figure 4: Scatter plot for the correlation between radiographic assessment and intrasurgical measurements.

2.2 CAPÍTULO 2

Artigo 2 – em processo de submissão ao periódico Clinical Oral Implants Research, qualis A2 e fator de impacto 2.756

ALVEOLAR RIDGE PRESERVATION - A SYSTEMATIC REVIEW

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Alveolar ridge preservation - a systematic review of the literature

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Key words: Tooth extraction, tooth socket, bone resorption, socket preservation, bone substitutes, bone regeneration, systematic review.

Abstract

Objectives: To evaluate the effect of alveolar ridge preservation following tooth extraction and whether it allows implant placement, with or without further augmentation. **Methods:** An electronic search within four databases (Medline, Embase, Cochrane Central Register of Controlled Trials and LILACS) up to 29th of June 2009 looked at references that met strict inclusion/exclusion criteria. Additionally, a hand search within 12 journals was conducted up to May 2010. Screening was performed by two independent and calibrated reviewers, whereas a third reviewer was consulted for any disagreement. RCTs, CCTs and prospective studies with a minimum of five patients and an unassisted socket healing as a control were included. **Results:** Out of 6,216 publications, 45 full-texts were screened and 11 fullfilled the inclusion/ exclusion criteria. Hand search yielded 3 more papers, leading to 14 human studies for data retrieval. Many different techniques, materials and methodologies were presented in the publications reviewed, making direct comparisons difficult. **Conclusions:** Despite the heterogeneity of the studies, there is evidence that ridge preservation procedures are effective in limiting post extraction ridge dimensional loss and are accompanied by a different degree of bone regeneration, with varying amounts of residual particles of the “grafting materials”. The exposure of membranes with GTR procedures may compromise the results. There is no evidence to support a clinical superiority of one technique over the other. There is not enough evidence supporting the importance of ridge preservation in improving the ability of placing implants, implant survival/ success rate, aesthetics, treatment economy, timing or patient satisfaction.

Introduction

Long-term aesthetic and functional success dictates the outcome of implant therapy, which is no longer measured by implant survival alone (Buser et al. 2004). Excellent functional and aesthetic restoration of an implant depends on its placement in an optimum location, which is influenced by the height, buccal/ lingual position and dimensions of the alveolar ridge (Iasella et al. 2003). The resorption of the alveolar ridge following tooth extraction, especially in the anterior region (Van der Weijden et al. 2009), has led to the necessity for the restoration of the remaining alveolar ridge in a relative amount of cases in order to meet the contemporaneous requirement of the three-dimensional prosthetically driven implant placement.

An inaccurate 3D positioning of an implant may result in an improper restoration-implant alignment, which in turn can cause poor aesthetic and biological results (Darby et al. 2009). Besides a correct position, the aesthetic outcome of the inserted implant can also be affected by the amount of bone available at the site and its relationship with the soft tissues. Soft tissue contour is dependent of the underlying bone anatomy, since peri-implant soft tissues have to a certain extent constant dimensions (Kan et al. 2003). The height and thickness of the facial bone wall as well as the height of the alveolar bone at interproximal aspects are also of great relevance (Darby et al. 2009). Many reasons can lead to loss of bone volume prior to tooth extraction, such as periodontal disease, periapical pathology and trauma (Lam 1960; Schropp et al. 2003; Van der Weijden et al. 2009). Moreover, it is well documented that alveolar bone undergoes atrophy after tooth extraction and the understanding of the healing process of post-extraction sites is

essential to obtain best possible functional and aesthetic prosthetic reconstructions (Lam 1960; Schropp et al. 2003; Van der Weijden et al. 2009).

The alveolar process is a tooth-dependent tissue and its architecture is orientated by teeth eruption (Schroeder 1986). The bundle bone, into which the periodontal ligament fibres invest, anchors the tooth to the jaws and will obviously lose its function and disappear following tooth removal, resulting in a significant resorption of the alveolar ridge (Amler 1969; Cardaropoli et al. 2003; Araújo et al. 2005; Araújo & Lindhe 2005; Van der Weijden et al. 2009). The reduction of alveolar ridge width is greater than the reduction of height after tooth extraction, and both have been described to be more pronounced at the buccal aspect than at the palatal aspect of the jaws (Lam 1960; Johnson 1963, 1969; Pietrokovski & Massler 1967; Lekovic et al. 1997; Iasella et al. 2003; Boticelli et al. 2004; Araújo & Lindhe 2005; Van der Weijden et al. 2009; Pelegrine et al. 2010). The amount of tissue resorption has been shown to be significantly greater in the edentulous molar region than in the incisor and premolar regions of both jaws (Pietrokovski & Massler 1967; Schropp et al. 2003). Also, the level to which the bone crest resorbs after extraction is dictated by the bone level at the extraction site, rather than the bone level of the adjacent teeth (Schropp et al. 2003). As a consequence of this resorptive process, the alveolar ridge becomes narrower and shorter, with a clear shifting to a more palatal/ lingual position (Pietrokovski & Massler 1967; Araújo & Lindhe 2005).

Histologic investigations in animals (Claflin 1936; Cardaropoli et al. 2003; Araújo & Lindhe 2005) and humans (Amler 1960, 1969; Boyne 1966; Evian 1982) have shown that socket healing is initiated immediately after

extraction. It begins with the formation of a blood clot that is replaced by the infiltration of granulation tissue at the base and periphery of the socket. New bone formation is firstly evident after the first week, with osteoid present at the base of the socket. This osteoid begins to mineralize from the base of the socket coronally and reaches two thirds of the entire socket fill in 38 days. At this point, the first signal of a progressive resorption of the alveolar crest can be observed. This mineralization is accompanied by continued re-epithelialization, which completely covers the socket by 6 weeks post-extraction. However, the resulting ridge will only become partially restored even with uneventful healing (Van der Weijden et al. 2009). Araújo & Lindhe (2005) claimed that marked dimensional alterations with a noticeable osteoclastic activity occurred during the first 8 weeks following the extraction, resulting in resorption of the crestal region of both the buccal and the lingual bone walls. Moreover, the resorption of the buccal/lingual walls of the extraction site comprised resorption and replacement of the bundle bone with woven bone and, in a later stage, included resorption that occurred from the outer surfaces of both bone walls.

Regarding the timing of the healing process, the early and majority resorption takes place within the first 3-month period after tooth extraction. Bone formation in the alveoli and almost the entire loss of height of the alveolar bone crest take place simultaneously with a reduction of approximately two thirds of the ridge width (Johnson 1969; Schropp et al. 2003; Araújo & Lindhe, 2005; Van der Weijden et al. 2009) and continues during the subsequent 3 months (Schropp et al. 2003). From 6 to 12 months, some of this new bone undergoes remodelling (Schropp et al. 2003) and

approximately 50% of alveolar ridge reduction in thickness occurs. The bone resorption in the residual ridge still continues throughout life, at a slower rate (Lam 1960; Van der Weijden et al. 2009), and may lead to a ridge of approximately 4.1mm wide. As long as a 8-mm wide ridge is preferable (Iasella et al. 2003) when a 4-mm implant is placed, the likelihood of a dehiscence taking place is high.

Therefore, because post extraction ridge dimensions are so crucial, it would be advantageous to preserve it rather than reconstruct thereafter, ensuring the maintenance of its ideal vertical and horizontal dimensions (Iasella et al. 2003, Schropp et al. 2003). It would, in turn, reduce the need for further augmentation/ surgical procedures and simplify implant surgery at a later time (Darby et al. 2009), minimizing morbidity and patient discomfort.

Several methods have been suggested for alveolar ridge preservation in fresh extraction sockets in the aesthetic anterior region, with different degrees of success. These include guided bone regeneration, with or without grafting material (Lekovic et al. 1997,1998; Nevins et al. 2006; Barone et al. 2008), bone graft substitutes (Camargo et al. 2000; Iasella et al. 2003; Aimetti et al. 2009; De Coster et al. 2009; Mardas et al. 2010), osteogenic materials such as autologous bone (Becker et al. 1994), autologous bone marrow (Pelegrine et al. 2010) and plasma rich in growth factors (Anitua et al. 1999), and other biomaterials (Fiorellini et al. 2005). Immediate implant placement in fresh extraction sockets has also been suggested with controversial results (Artzi et al. 1998; Paolantonio et al. 2001; Schropp et al. 2003; Boticelli et al. 2004, 2008; Araújo et al. 2006) and may be adversely affected by the lack of soft tissue closure, presence of infection and defects between the bone and

the implants (Ferrus et al. 2010; Pelegrine et al. 2010). Recently, implants placed in extraction sockets were demonstrated not to preserve the dimension of the ridge, especially on the buccal aspect, and this resulted in some marginal loss of osseointegration (Araújo et al. 2006). Most recently, it has also been suggested that the elevation of a mucoperiostal flap resulted in a more marked loss of ridge dimension compared to no flap elevation (Fickl et al. 2008).

Although the interest in studies aiming at evaluating different ridge preservation techniques/biomaterials has increased significantly in the last years, there are still very few evidences of their outcome based on prospective controlled human studies. Most of the publications on humans are case reports, case series, retrospective studies or studies that do no include unassisted socket healing as a control. Thus, the rationale of the present review was to systematically evaluate the evidences of the effect of various materials and techniques aimed at preservation of alveolar ridge dimensions following tooth extraction and whether they allow successful implant placement, with or without further augmentation.

Methods

Prior to commencement of the study a detailed protocol was developed and agreed upon by the authors based on the Cochrane guidelines and previous reviews published by our group (Donos et al. 2008, Needleman et al. 2002, 2005, 2006).

Focused question

“In humans, following tooth/root extraction, what is the effect of ridge preservation on residual alveolar ridge dimensions and on histological characteristics, compared to unassisted socket healing?”

Types of studies

In order to increase the power of the present review, the following types of prospective studies were considered to be relevant: randomised controlled trials (RCTs), controlled clinical trials (CCTs) and cohort studies with control group. In addition, single arms (subgroups) of trials that fulfilled the inclusion criteria were also included.

Populations of studies

Those healthy individuals, without any age limit, who underwent any type of ridge preservation following permanent tooth extraction, were included. Smokers and patients with history of periodontal disease were also included. The cut off line of the minimum number of subject per group was drawn at five. However, no limit was set up for study duration or follow-up period.

Types of Interventions

Studies reporting on any of the following types of interventions were included: socket grafting (autograft, allograft, xenograft, alloplastic materials); socket sealing (soft tissue grafts); guided bone regeneration (GBR) (resorbable/non-resorbable barriers); biological active materials (growth factors) and the combination of the above techniques/materials.

Outcome variables

Change in oro-facial (horizontal) and apico-coronal (vertical) alveolar ridge dimension was considered as *primary outcome. Secondary outcomes* were the followings: (i) change in buccal plate thickness; (ii) bone volume alteration following extraction; (iii) complications; (iv) site eligibility for placement of an adequate size dental implant with or without further augmentation; (v) histological healing characteristics. We also attempted to evaluate *Patient-centred outcomes*, like complaints, satisfaction, economics, preference and quality of life.

Quality assessment

In order to evaluate the strength of the reported results of the individual studies, based on the Consolidated Standards Of Reporting Trials (CONSORT) statement of Cochrane Collaboration and on previous reviews from our group (Donos et al. 2008, Needleman et al. 2005, 2006, Ong et al. 2008), the following parameters were assessed and taken into consideration in the final analysis: sample size calculation, statement of eligibility criteria, ethics approval, informed consent, baseline homogeneity, randomization method, allocation concealment, masking, calibration, follow up, protocol violation, statistic method, unit of analysis, CONSORT implementation, (International Standard Randomised Controlled Trial Number Register) ISRCTN and funding disclosure. Based on the above, we attempted to categorize the possible risk of bias as low, moderate or high, albeit this classification was not based on undisputed criteria. Low risk referred to studies with adequate randomisation method, sequence concealment and

masking of examiner. Trial was generally classified as moderate, or high risk of bias if one, or many of the above key categories were missing, respectively.

Inclusion criteria

The following *inclusion criteria* were then established:

- Prospective RCT, CCT and cohort studies where one of the above mentioned types of interventions were carried out in the test group, whereas unassisted socket healing served as control;
- healthy individuals, without any age limit, who underwent ARP following tooth extraction;
- minimum five patients per group;
- clinical or 3D radiographical evaluation on hard tissue level or histological assessment.

Exclusion criteria

- Case reports, case series with less than 5 patients per group and retrospective analyses;
- lack of control group comprising unassisted socket healing
- subjects with contributing medical history that may have an effect on outcome
- immediate placement of dental implant;
- extraction of third molars and deciduous teeth;
- ridge dimensions evaluated on soft tissue level;
- two dimensional radiographic measurements.

Search strategy

The search strategy incorporated both electronic and hand search. The following electronic databases were utilized: (i) MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE 1950 to present via Ovid interface; (ii) EMBASE Classic + EMBASE 1947 to present via Ovid interface; (iii) The Cochrane Central Register of Controlled Trials (CENTRAL); (iv) LILACS.

The comprehensive search strategy adopted the guidelines of the Cochrane Collaboration and resulted in the following combination of key words and *MeSH terms:*

(“tooth extraction” OR “tooth removal” OR “socket” OR “alveol$” OR “ridge” OR “crest” OR *“tooth socket”* OR *“alveolar bone loss”* OR *“bone resorption”* OR *“bone remodeling”*) AND (“preserv$” OR “reconstruct$” OR “augment$” OR “fill$” OR “seal$” OR “graft$” OR “repair$” OR “*alveolar ridge augmentation*” OR “*bone regeneration”* OR *“bone substitutes”* OR *“transplantation”*)

The number of retrieved titles has been further reduced by the application of Cochrane filter for RCTs, CCTs and cohort trials on humans only.

In order to identify all relevant articles, an extensive hand search was accomplished encompassing the bibliography of the included papers and review articles. Furthermore the following journals were meticulously screened: *Clinical Oral Implant Research, Clinical Implant Dentistry and Related Research, European Journal of Oral Implantology, Implant Dentistry, International Journal of Oral and Maxillofacial Implants, International Journal*

of Periodontics and Restorative Dentistry, Journal of Clinical Periodontology, Journal of Dental Research, Journal of Oral and Maxillofacial Surgery, Journal of Periodontology, Oral Surgery, Oral Medicine, Oral Radiology, Oral Pathology and Endodontics, Periodontology 2000.

Aiming to maximize the pool of relevant papers, neither language nor publishing year restrictions were applied. Translations were carried out by two reviewers (AH, LAM).

The extracted data were copied into Reference Manager® 10 software (Thomson Reuters, New York, NY, USA). Thus the further steps of screening were performed on this interface. A three-stage selection of the resulted hits was performed independently and in duplicate by two reviewers (AH and LAM). In order to increase accuracy, a calibration exercise was performed with the first 500 titles, resulting in 96.4% agreement. In case of disagreement at the title selection stage, the trial was included in the abstract stage. At the abstract and full text selection any disagreements between the above reviewers were attempted to iron out by discussion. Should it remained unresolved, a third reviewer (NM) was involved to take the decision. The reasons for exclusion were recorded either in the Reference Manager (abstract stage) or in a specific data extraction form (full text stage). Accordingly, the level of agreement was determined by Kappa score calculation.

Results

Search sequence

The final electronic search was carried out on 29th June 2009. In order to

uncover any possible relevant recent data, the electronic search was updated in April 2010. Figure 1 summarizes the flow chart of the screening process. The electronic search yielded 6,216 relevant hits after removal of duplicates. Subsequently, 157 titles were selected for the abstract stage. Following investigation of the abstracts and resolving the three disagreements by involvement of the third reviewer, 42 articles qualified for full text evaluation. Three extra papers were then added to the list as a result of hand search. The meticulous assessment of these articles resulted in the following 14 publications, which met the inclusion criteria: Aimetti et al. 2009 (aim), Anitua 1999 (ani), Barone et al. 2008 (bar), Camargo et al. 2000 (cam), Fiorellini et al. 2005 (fio), Froum et al. 2002 (fro), Guarnieri et al. 2004 (gua), Iasella et al. 2003 (ias), Lekovic et al. 1997 (lek7), Lekovic et al. 1998 (lek8), Nevins et al. 2006 (nev), Pelegrine et al. 2010 (pel), Serino et al. 2003 (ser3) and Serino et al. 2008 (ser8).

The excluded full text papers along the reasons for exclusion are listed in table 1. The most typical reasons for exclusion were case report, lack of control group with unassisted socket healing, retrospective analysis, assessment of two dimensional radiographs, surgical removal of impacted third molars, measurements on soft tissue level.

Agreement between the reviewers (AH, LAM) resulted in 0.96 and 0.90 Kappa score at the abstract and full text selection level, respectively (Table 2). Both values indicate good level of agreement (Landis & Koch 1977).

Quality assessment

Considerable heterogeneity was discerned among and even within the

studies in terms of quality of methodology.

Among the 14 included controlled studies 8 were accepted as randomised trial (aim, bar, fio, fro, ias, lek8, nev, pel), however merely 4 reported on adequate sequence generation (bar, fro, ias, lek8). Moreover none of the papers disclosed allocation concealment. Masking of the examiner was reported at clinical level in 2 out of 8 (ias, lek8), at radiological level in 1 out of 2 (fio) and at histological level in 4 out of 11(aim, ani, bar, fro) studies. Examiner calibration was declared by three authors (aim, fio, ias), whilst inclusion and exclusion criteria were defined in seven publications (aim, ani, bar, fro, ias, nev, pel). Apart from three studies (ani, bar, nev) all the other declared the approval of the ethical committee. Three studies were funded by industry (cam, fio, fro), two studies by academic institution (gua, ser8) and the remaining nine did not report on source of funding. Nine trials implemented patient-based analysis (aim, bar, cam, fio, ias, lek7, lek8, pel, ser8), whilst the extraction site served as unit of analysis in the rest five investigations (ani, fro, gua, nev, ser3). Sample size calculation was carried out merely in three experiments (aim, fio, ias), moreover statistical analysis appeared to be appropriately described in only one study (pel). None of the studies were either registered with ISRCTN or implementing CONSORT guidelines (Table 3).

Risk of bias

Based on the above described assessment method and due to the existing potential risk factors, no study qualified for the low risk level. Three studies were classified in the moderate (ias, fro, lek8) while the rest, in the

high risk of bias category (Table 3).

Study characteristics

Among the fourteen included articles three of them investigated ridge preservation techniques merely on clinical level (cam, lek7, lek8); four of them analyzed solely the histological characteristics (ani, fro, gua, ser8); another five studies examined both clinical and histological parameters (aim, bar, ias, pel, ser3) and two studies looked into three dimensional radiography and histology (fio, nev). In regard to the type of studies eight of them qualified for RCT, whereas six of them were CCTs (Table 3).

The year of publication were distributed between 1997 and 2010, thus encompassed 14 years. Apart from a multicentre study (fio) eight of them were reported as a single centre trial (aim, anit, bar, fro, lek8, pel, ser3, ser8) and five did not declare (cam, gua, ias, lek7, nev). In regard to the setting of the trials nine, out of fourteen were conducted in academic institution (aim, cam, fio, fro, lek7, lek8, pel, ser3, ser8); a single one in hospital (bar), another one in a private practice (ani) and the setting in three studies remained unclear (gua, ias, nev).

The following sections refer to baseline or general characteristics of the trials. Merely three studies reported on achieved baseline homogeneity between the groups (bar, ias, ser8).

Population characteristics and confounding factors

Slightly more female than male subjects were included in the studies and the age varied between 26 and 77 years. The number of subjects varied

between 5 and 26 in the test and between 5 and 20 in the control groups (Table 4).

It was attempted to identify confounding factors, such as periodontitis, smoking, systemic disease, medication and irradiation. Limited data were reported on these factors in the included studies. Smokers were included in ani, bar (≤10 cig/day) and ias studies. Patients with some forms of periodontitis in their dental history were also enrolled in seven studies (ani, bar, gua, lek8, nev, ser3, ser8). The others did not include (pel) or did not declare (aim, cam, fio, fro, ias, lek7) these factors (Table 4).

Site distribution and defect morphology

The most challenging sites, namely maxillary anteriors were selected by aim, nev and pel groups, whereas cam and fio included maxillary premolars too. Bar, gua, ias, lek7, lek8 and ser8 expanded their inclusion criteria on mandibular teeth as well. There was no site selection in ani, fro and ser3 papers, although no molar site was selected in the control group of ser3.

The remaining local bone volume around the investigated socket, especially the presence and width of the buccal plate were reported as follows. In fio's study all included sites had loss of buccal wall ≥50%. On the contrary, in gua's study sites presenting with severe alveolar ridge resorption (≥50%) were excluded. Fro has also excluded sites where the remaining buccal plate loss was found to be greater than or equal to two millimetres. In ser3 study buccal bone wall could be either totally or partially lost. Nev included prominent roots only, subsequently buccal plate was compromised. In aim and bar studies the selected sites presented with 4-wall-configuration.

Defect morphology remained unclear in ani, cam, ias, lek7, lek8 reports (Table 4).

Intervention characteristics

Guided Bone Regeneration (GBR)

GBR technique was applied in two studies using a non-resorbable membrane (expanded polytetrafluoroethylene (ePTFE)) by lek7 or resorbable polyglycolide/polylactide (PGPL) membrane by lek8.

Bone replacements

In nine out of the fourteen included studies various bone replacement materials were utilised as an attempt to maintain the ridge dimension. Autologous bone marrow graft was used by pel and plasma rich in growth factors (PRGF) with or without autologous bone transplant by ani. Demineralised freeze-dried bone allograft (DFDBA) by fro and xenograft (deproteinized bovine bone mineral, DBBM) by nev were investigated respectively. Alloplastic materials were placed in the extraction sockets in six studies. PGPL sponge was reported in ser3 and ser8, calcium sulphate hemihydrate in aim and gua, bioactive glass in fro and bioactive glass covered by calcium sulphate in cam.

Biological active materials

Collagen sponges from bovine origin were soaked in different concentration of type 2 recombinant human bone morphogenic protein (rhBMP-2) by fio.

Combination

Two studies reported on combination of graft with GBR. Corticocancellous porcine bone and a collagen membrane by bar, whereas freeze-dried bone allograft (FDBA) and a collagen membrane was employed by ias.

No publication reporting on socket sealing technique has fulfilled the inclusion criteria.

Flap management

Full thickness mucoperiosteal flaps were used in all studies, but two (aim, nev). Aim reported on flapless technique, whilst nev prepared split thickness flap. Primary closure of the flaps were achieved in nine studies (ani, bar, fio, fro, gua, lek7, lek8, nev, pel), eventually in five studies this was not initially intended (aim, cam, ias, ser3, ser8).

Postoperative care

Various type, amount and duration of penicillin-type beta-lactam antibiotics were administered in eight studies (aim, ani, bar, cam, fio, gua, lek7, lek8), while doxycycline were prescribed in two studies (fro, ias). No use of any systemic antibiotics was reported in two studies (ser3, ser8) and no data were found on this in further two studies (nev, pel). Subjects were requested to rinse with chlorhexidine (0.12% or 0.2%) after extraction from two to four weeks in 11 studies (aim, bar, cam, fio, fro, gua, ias, lek7, lek8, ser3, ser8) while three studies did not report on any aspects of postoperative care (ani, nev, pel).

Outcome characteristics

Healing period

The investigated period of healing of the individual studies showed the following wide variation (in months): 1-3 (nev), 2.5-4 (ani), 3 (aim, gua, ser8), 4 (fio), 4 or 6 (ias), 6 (cam, lek7, lek8, pel, ser3), 6-8 (fro) and 7-9 (bar).

Clinical outcomes

8 out of the 14 included studies reported on clinical changes of the alveolar ridge dimension (aim, bar, cam, ias, lek7, lek8, pel, ser3). In a total of 216 sockets of 188 patients were evaluated in the test, compared to 157 sockets of 131 patients in the control groups.

Horizontal dimension

7 studies assessed horizontal (bucco-lngual) changes of the alveolar ridge (aim, bar, cam, ias, lek7, lek8, pel) (Table 4). 5 of them reported significant smaller reduction in the test compared to the control group (aim, bar, lek7, lek8, pel). The mean change in ridge width from baseline to re-entry varied between -1.2±0.9 mm and -3.5±2.7 mm in the test, and between -2.6±2.3 mm and -4.6±0.3 mm in the control groups of the individual studies. This reduction found to be statistically significant in all trials at the control sockets and all trials but one (lek7) at the experimental groups. In this study ePTFE was employed. Merely lek7 reported no significant difference in horizontal changes between baseline and re-entry in the treatment group. Cam reported greater reduction in test (bioactive glass) than in the control group; this difference was not significant, though.

Vertical dimension

Changes in apico-coronal dimension (*ridge height*) were measured in one or more of the following sites of interest: mid-buccal, mesial and distal. Data were captured on internal vertical change (*socket fill*) as well.

Eight studies investigated the mean change in ridge height at the *mid-buccal* aspect (aim, bar, cam, ias, lek7, lek8, pel, ser3). The difference in reduction of mid-buccal resorption found to be statistically significant in favour of the test group, in all but two studies (cam, ser3). Both of the latter two studies employed alloplastic materials. Interestingly, in these two studies, no significant difference between baseline and re-entry was reported as a result of unassisted socket healing either. The height change varied from baseline to re-entry between +1.3±2.0 mm and -0.7±1.4 mm in the test, and between -0.8±1.6 mm and -3.6±1.5 mm in the control groups. The height reduction in the test group between baseline and re-entry was not significant in four studies (cam, ias, lek7, lek8). Moreover two studies reported on height increment instead of loss in the test group following ARP (ias, ser3).

Vertical dimension changes at *mesial* and *distal* aspects were measured in four studies (aim, bar, ias, ser3). Less resorption took place in the ARP group in contrast to the unassisted socket healing in all the four studies. However, the mean difference between test and control reached statistical significance in a single study only (ias). They measured -0.1±0.7 mm vs. -1.0±0.8 mm mesial and -0.1±0.7 mm vs. -0.8±0.8 mm distal to the extraction socket at the test vs. control groups respectively.

Five studies captured data on the *socket fill* (aim, cam, lek7, lek8, pel). The difference in internal fill reported to be statistically significant in favour of

the test over the control in three articles (cam, lek7, lek8) (Table 4)

No data were found on initial *buccal plate thickness*. However, a single study investigated the vestibular thickness loss (pel). The median change in the test groups measured as 0.75 mm compared to the 1.75 mm in the control group. The difference was statistically significant.

Radiographic measurements

Two studies, reporting on three dimensional radiographic assessment, met the inclusion criteria (fio, nev). The results on the cross section CT scans must be evaluated in light of the experimental materials, which were radiolucent in one study (fio), but radiopaque in the other (nev).

Xenograft (DBBM) was utilized in the test group of the study of Nev. The height of the ridge was calculated between the floor of the nasal cavity, serving as a defined anatomic landmark, and the most coronal line, where the ridge width hit the 6 mm benchmark. This aimed to correspond to the eligible minimum horizontal dimension for implant placement. The difference in height loss in the test group (-2.42±2.58 mm) comparing to the control (-5.24±3.72 mm) observed to be significant in favour of the test.

Biological active material, namely collagen sponge soaked in rhBMP-2 in various concentrations was tested in the multicenter study of fio. The investigators included merely those sites, where at least 50% buccal bone loss was apparent. The mean change in width of the remaining palatal ridge at the most coronal part of the ridge height (coronal 1/4 of extraction socket length) was measured 0.57±2.56 mm, 0.82±1.40 mm, 1.76±1.67 mm and 3.27±2.53 mm in the control, collagen sponge, 0.75 mg/ml rhBMP-2 and 1.5

mg/ml rhBMP-2 groups, respectively. The difference found to be statistically significant contrasting the 1.5 mg/ml rhBMP-2 group to the control, collagen sponge or 0.75 mg/ml groups. These figures also indicate that instead of ridge width reduction, an increase was measured not only the treatment, but also in the control group. The mean change in ridge height was found as -1.17±1.23 mm, -1.00±1.40 mm, -0.62±1.39 and -0.02±1.20 in the above groups, respectively. Moreover, the differences between the 1.5 mg/ml rhBMP-2 and control group appeared to be significant in all investigated parameters. In addition, no significant difference was found in vertical changes when compared to the control, collagen sponge and 0.75 mg/ml rhBMP-2 groups. (Table 4)

No data were identified on *bone volume alterations* following ridge preservation.

Histological results

Seven studies evaluated the histological pattern of the healing beside the clinical or radiographic results (aim, bar, fio, ias, nev, pel, ser3), and four trials focused on histology only (ani, fro, gua, ser8). Only 3 out of the 11 studies reported statistical significant differences between the test and the control in favour of the test (aim, bar, fro) (Table 5)

Seven studies evaluated the application of some type of *grafts* or *bone substitutes*. Ani employed PRGF with or without *autologous bone*. Compact mature bone was found by 8/10 biopsies in the test group, while connective tissue filled in the defects in the controls. *Xenograft* was used by nev. DBBM particles were present after 6 months embedded either in bone or in soft

tissue. In the control specimens new bone formation was observed.

Allograft and *alloplast* were employed in the study of fro. Reossifying areas were observed to varying extent in close proximity of the demineralized FDBA, meanwhile the bioactive glass was encompassed by new bone. More vital bone and less connective tissue were observed in the tests compared to the control biopsies. The same alloplastic material (MGCSH) was used by aim and gua. The implant appeared to be resorbable, alongside new bone formation in all specimens in the test group. Newly formed bone was found in the both control groups as well, however in a smaller extent than in the test group as reported by gua. Aim found more mature bone in the test compared to the control biopsies. The effect of PGPL sponge was investigated in both study of ser in 3 or 6 months after implantation in the socket. No residual PGPL was found even after 3 months. Mineralised bone was found in both studies either in the test, or in the control groups, although in a greater amount in the test specimens according to the histomorphometric analysis.

Biological active material was employed by fio. rhBMP-2 soaked by collagen sponge appeared to be completely resorbable after 4 months regardless the concentration of the growth factor. Mineralised tissue was found and trabecular bone formation was noticed in 2/3 of the samples.

Combination of *GBR and bone substitute* was employed in two studies. Bar investigated the effect of porcine bone covered by collagen membrane. Newly formed bone was observed in the test as well as in the control groups. Histomorphometry revealed significant differences between the two groups in terms of total bone volume and connective tissue in favour of the test. Residual graft material was present. Tetracycline hydrated FDBA and

collagen membrane was used by ias. Similar amount of total bone and trabecular spaces was found in controls as in the tests. Total bone volume was divided into vital and non-vital (graft) parts in the test, resulted in more newly formed bone in the control group.

Due to the relatively small histological sample sizes, the statistical results should be handled with care.

Adverse events, complications

Postoperative healing was uneventful in 9 out of the 14 studies (aim, ani, bar, cam, fro, lek8, pel, ser3, ser8). In the multicenter study with 80 subjects employing rhBMP-2 (fio) 250 adverse events were reported. The vast majority of them were expected after tooth extraction and were considered as minor e.g. edema, pain and erythema. However, more edema and erythema were observed in test groups than among the controls. In another trial (lek7), the employed ePTFE barrier became prematurely exposed in the ARP group, thus had to be removed at the half time of the investigation period. In three trials no reports on adverse event were found (gua, ias, nev).

Feasibility of implant placement

Merely three studies reported on the ultimate clinical importance of the ridge preservation procedure, namely the needlessness of further or second augmentation at the stage of implant placement. All of them favoured the ridge preservation group over the controls.

Autologous bone marrow was utilized by pel. In five cases bone augmentation/expansion had to be performed alongside implant insertion. All

of them belonged to the control group, meanwhile no further augmentation was necessary in any of the ARP sites.

Biological active material was employed by fio. According to their data significantly more implants could be placed without secondary augmentation in the 1.5 mg/ml rhBMP-2 group (86%), compared to the 0.75 mg/ml rhBMP-2 (55%) or to the control groups (45%).

GBR with xenograft was carried out by bar. At the time of re-entry, implants could be placed in both test and control groups, although some fixtures presented with dehiscence. Consequently GBR had to be carried out simultaneously. This happened at the controls only.

Seven studies (aim, fro, gua, ias, nev, se3, ser8) reported that the placements of the implants were successful, but no differences between the two groups were revealed, whatsoever. Merely re-entry without implantation were performed in three trials (cam, lek7, lek8), and the placement of implants remained unclear in a single article (ani).

We failed to identify a single trial investigating *patient based analysis* or *patient's preference.* None of the included studies revealed the *economic* aspects of the treatment in light of cost/benefit ratio.

Meta-analysis

Due to the broad variety of inclusion criteria, applied methods, materials and follow-up periods, it was not feasible to carry out a cumulative meta-analysis.

Discussion

Key findings

The aim of the present review was to systematically evaluate the effect of ARP following tooth extraction. In the current literature several studies have addressed this subject, nevertheless the majority of them have been considered as stand alone case reports or case series (i.e. comparison of the experimental treatment to the natural healing of an untreated, control socket has not been carried out). Another cluster of publications appeared to be retrospectively designed. In order to obtain the highest possible level of evidence, as well as retrieve sufficient number of studies, we decided to include randomised controlled trials, controlled clinical trials and prospective cohort studies with a control group of empty sockets. In order to estimate the potential risks of bias, a high value was set on the meticulous assessment of the research methodology of the included experiments.

Over the last decades, several publications reported on placement of dental implant in extraction socket as an attempt to maintain the alveolar ridge dimensions. Although the recent evidence failed to support this hypothesis (Araújo et al. 2006), the reason for excluding this type of intervention from our review was that the dental implant is not a device aimed primary at preserving ridge dimension, but a long term replacement of the lost dentition. Other clinical trials, evaluating the efficacy of ARP following removal of third molars were also not included, due to their unique anatomy and dissimilar healing characteristics. Moreover, implant placement in the site of a third molar is not being considered as a quintessential daily surgical intervention. With respect to assessment measures, studies evaluating the three dimensional ridge

alterations on two dimensional radiographs were not included. Studies measuring volumetric changes on study casts were also excluded. An impression models the gingival soft tissue above the investigated alveolar ridge as well, therefore this evaluating technique is not suitable to track dimensional changes at bone level.

Alongside quantitative assessment, evaluation of the quality of the newly formed tissue following ARP possess a paramount importance as well. The remodelling of woven bone into lamellar bone with trabecular and marrow characteristic - the mineralization and maturation of the novel tissue in the extraction socket, in other words, takes place from the second week up to several months (Amler 1969; Cardaropoli et al. 2003; Schropp et al. 2003). The clinician often encounters the challenge to place an implant in a site of recent extraction, where the ridge dimension seems to be maintained, but the tissue of the implant bed appears to be immature, when preparing the osteotomy. This may even be accompanied by a “mushy” bone replacement material that was placed in the socket by the time of extraction.

A few review articles addressing ARP were published in the last decade. (Fiorellini & Nevins 2003; Fugazotto 2005; John et al. 2007; Darby et al. 2008; Darby et al. 2009). Nevertheless, to the best of our knowledge no review has evaluated the histological aspect of ARP or the risk of bias of the included studies. Furthermore, none of the previous reviews included exclusively controlled trials with unassisted socket healing.

As a result of this notion, the present systematic review produced 14 publications, out of the initial 6,216 relevant hits.

Main findings

I. Clinical dimensional alterations

It is well established in the literature that tooth extraction has a detrimental impact on both the horizontal and the vertical dimensions of the remaining alveolar ridge. The remodeling takes place up to 12 months and may result in 50% resorption in alveolar ridge width (Schropp et al. 2003). Since sufficient ridge width and height have been considered as one of the key requirements of successful implant therapy (Albrektsson et al. 1981; Buser et al. 2000; Ong et al. 2008), the alteration in oro-facial (horizontal) and apico-coronal (vertical) alveolar ridge dimensions were selected as the primary outcomes of the present review.

Several preclinical and clinical experiments demonstrated that the bone loss at the buccal side of the alveolar process was more pronounced than the lingual side (Araújo & Lindhe 2005, 2009; Fickl et al. 2008; Matarasso et al. 2009). Moreover, the lingual bone plate appeared to be markedly wider than its buccal counterpart prior to and ensuing tooth extraction (Araújo & Lindhe 2005, 2009). Consequently, in the present review the vertical changes were evaluated at the mid-buccal, the mesio-buccal and the disto-buccal area. The horizontal component, where applicable, was measured at the mid portion of the extraction site in the included articles.

For the interpretation of the results we attempted to cluster the experiments in respect to the type of intervention.

GBR

Promoting regeneration by preclusion of undesirable epithelial cells

with a mechanical barrier membrane, thus allocating sufficient space and time for new periodontal tissue and/or bone formation, has been described as the principle of guided tissue and bone regeneration (Gottlow et al. 1984; Dahlin et al. 1988; Seibert & Nyman 1990; Buser et al. 1993). This conception was applied on alveolar socket healing by several clinical experiments. Two of them met the inclusion criteria of the present review (lek7, lek8). The extraction socket was either covered by an e-PTFE barrier (lek7) or by a PG/PL membrane (lek8). The treatment resulted in statistically significant difference between test and control in all the investigated parameters, regardless of the type of membrane. It has to be emphasized, though that 3 out of 10 cases, the exposed non-resorbable ePTFE barrier had to be prematurely removed at half time of the healing. The results of these three cases resembled to the control ones. However, in case the healing was uncompromised, an imposing difference could be measured after six months in width changes between the mean results of test and control in favour of the test, i.e., 2.72 mm when using ePTFE and 3.25 mm with the PG/PL. The contrast in ridge height changes appeared to be more moderate, but still significantly different between test and control, namely 0.72 mm employing ePTFE and 1.12 mm with the PG/PL. Nevertheless the reduction in ridge height is usually smaller than in ridge width ensuing unassisted socket healing.

Bone replacements

Effectual grafting procedures have been associated with the

osteoconductive, osteoinductive or osteogenetic properties of the bone replacement material. Bone grafts and substitutes were successfully employed for periodontal reconstructions as well as alveolar ridge augmentation procedures (Dragoo & Sullivan 1973; Yukna 1993; Mellonig 2000; Zitzmann et al. 2001). Nevertheless, the biologic mechanisms and reasons are not yet entirely understood. Recent studies investigated the impact of a xenograft for ARP on dog models. The outcome failed to demonstrate an unambiguous advantage of the material (Araújo et al. 2008, 2009; Fickl et al. 2008; Araújo & Lindhe 2009). Grafting procedures have been carried out in numerous human studies, although the vast majority has been considered as case series with no comparison to empty socket. Hence 9 studies met the inclusion criteria of the present review.

Two studies utilized *autografts* i.e. iliac bone marrow by pel and PRGF with or without autologous bone by ani. Pelegrine's experiment demonstrated significant difference between the test and the control groups both in median ridge width and ridge height i.e. 1.5 mm and 0.5 mm respectively. Ani presented merely histological results.

Allograft (DFDBA) was placed in the fresh extraction socket in the histological study of fro, however no clinical measurement were in this study performed.

Xenograft (DBBM) without a membrane was utilized in nev study investigating the results at radiographic and histological level.

Various *alloplastic* materials were inserted in the extraction socket in six studies. Medical-grade calcium sulphate was implanted by aim and gua. Significant difference was measured in favour of the test in aim study both in

width (1.2 mm) and in height changes (0.7 mm), while gua presented histological results only. Bioactive glass covered by calcium sulphate failed to show significant difference between test and control sites in cam experiment, moreover the shrinkage of the alveolar width appeared to be greater in the test group compared to the control (-0.42 mm). Fro evaluated the histological characteristics of the socket healing only following implantation of bio glass. Finally, PG/PL sponge was applied by the group of Serino in a histological (ser8) and a clinical-histological (ser3) study. The dimensional changes in the investigated ridge height failed to reach statistical significance due to the broad standard deviation.

Biological active materials

The benefit of biological active molecules were proven in periodontal and bone regeneration through fostering the proliferation and differentiation of different mesenchymal cells in various preclinical models (Wikesjö et al. 2003, 2004). The safety and feasibility of rhBMP-2 on human ARP or ridge augmentation was evaluated and proven to be safe in a bi-centre clinical study (Howell et al. 1997). A randomised control trial was carried out by the same group thereafter, investigating the effect of rhBMP-2 soaked collagen sponge on ARP (fio). Since the dimensional changes of the alveolar ridge in this multicenter trial were measured on CT scans, we discuss them under the radiological section in details.

Combination

In order to prevent the collapse of the membrane as well as to provide a

scaffold for bone formation in the membrane-secluded area, GTR and GBR are efficiently combined with various bone replacement materials (Simion et al. 1994; Buser et al. 1996; Hämmerle 1999; Donos et al. 2002, 2004; Tonetti et al. 2004; Hämmerle et al. 2008). Combination of GBR and xenograft was tested for ARP in a dog model with less convincing results (Fickl et al. 2008, 2009). Two human experiments met the inclusion criteria of the present systematic review. Bar adapted a resorbable collagen membrane over the cortico-cancellous porcine bone filler. The dimensional alteration of the ridge measured to be significantly different between the test and the control (1.2 mm in width and 0.7 mm in height) in favour of the test. In ias experiment tetracycline hydrated FDBA was covered by collagen membrane. Despite the insignificant difference between the two groups in alveolar width, the changes in height reached statistical significance not only at the mid-buccal, but also at the mesial as well as at the distal sites. Moreover, a mean 1.3 mm increase at the mid-buccal part was measured in the test compared to the 0.9 mm decrease in the control group.

Sufficient volume of buccal bone is one of the prerequisites for long term success of the implant. Providing a sound osseous foundation to the covering keratinised mucosa appears to be even more essential in the aesthetic zone, where the buccal plate is more delicate. A recent systematic review by Van der Weijden and co-workers (2009) provided evidence to support the clinical observation, that the reduction in ridge width seemed to be more substantial (3.87 mm), than the reduction in ridge height (1.67 mm). In respect to the final figures of our systematic review only, the horizontal ridge contraction was most successfully limited in the two studies applying solely a barrier

membrane over the socket (lek7, lek8). Whereas the vertical shrinkage was most efficiently limited by employing GBR with additional bone graft (bar, ias). Consequently, one could come to a conclusion that the GBR technique might be the 'panacea' for ARP. To draw such a lesson would be delusive, though.

One shall bear in mind that it is tempting to dichotomize studies into the previous treatment categories and draw conclusions merely upon the material of intervention. However, the different site location, socket morphology, flap management, healing time, antimicrobial regime and confounding factors mean that such a dichotomy would be misleading.

In case we illuminate the results from a different perspective, we may arrive at more delicate conclusions. In other words, *'Which of the above factors may play pivotal role to determine the success of the ridge preservation procedure?'*

It can be postulated that the statistically significant difference that favours the test over the control treatment, can be accepted as a kind of measure of success of ARP. Generally, five versus two studies presented with significant difference favouring the test over the controls in reducing the bone loss in horizontal dimension (aim, bar, lek7, lek8, pel vs. cam, ias), while six versus two favoured the test group for changes in vertical mid-buccal dimension (aim, bar, ias, lek7, lek8, pel vs. cam, ser3). Hence, we can create and compare these two virtual groups; one for the studies presented with significant difference between test and control *(signif)* and another one for the studies presented with non significant differences *(non signif).*

Site location

Maxillary and mandibular anteriors and premolars seemed to be equally distributed in studies both in the signif and in the non signif group regarding ridge width as well as ridge height alteration. One study in the non signif group included any type of teeth (ser3). Thus the available data of the review do not endorse a difference on outcome with regard to the predisposing site location.

Socket morphology

Following the same guiding principle on the socket morphology, 3 studies in the signif group reported 'intact' socket walls either as 4-wall configuration (aim, bar) or by the exclusion of severe bone loss (pel) in scope of ridge with. The result was similar in ridge height, in addition, a single study reported on buccal dehiscence in the non signif group (ser3). None of the remaining trials reported data on socket morphology. The present finding supports the clinical observation that the less intact is the osseous wall following extraction, the less success of ARP can be anticipated. Hence the socket morphology may play a crucial role in the outcome of ARP.

Flap management

The outcome of the studies appeared to be even more straightforward in light of flap approximation. In respect of ridge width, all experiments in the signif group achieved primary flap closure, apart from one (aim). Aim did not detached the periosteum aiming to preserve blood supply of the underlying residual ridge. On the other hand, in the non signif group no primary closure

was achieved in both trials. The results pertaining to ridge height appeared to be similar. Not only achieving, but also maintaining the epithelial seal above the socket seems to be decisive. In case the ePTFE barrier was prematurely exposed, the result occurred to be similar to the ones in the control group. It may be concluded therefore, that the primary flap closure seems to have an impact on the success of ARP.

Healing time

The modelling and remodelling of the bone in the socket is a dynamic process, which is not being completed in the first few months following extraction (Cardaropoli et al. 2003; Schropp et al. 2003). During the time of healing, the volume of the alveolar ridge is gradually decreasing, while the quality of the newly formed tissue is gradually increasing in case of unassisted healing. Consequently, the clinician encounters with the challenge to determine the optimal timing of re-entry. Hence, the implant shall be inserted as early as possible, but as late as necessary in order to maintain the ridge dimension, but also to reach complete epithelial seal and some extent of osseous fill. The healing time in the signif group varied between 3 and 9 months, which is comparable to the 4 and 6 months in non signif group. The distribution was fairly similar regarding horizontal and vertical dimensions in both groups of outcome. It has to be emphasized that at the most of the trials the healing period was reasonably long (6 months) and none of the studies investigated shorter than 3 months healing.

As a conclusion, both less and more successful results can be achieved by shorter or longer time of healing.

Antimicrobials

Clinical parameters tend to improve when regular chlorhexidine rinsing regime is prescribed following tooth extraction (Lang et al. 1994). Subjects of the included trials in the present review in both the signif and the non signif groups were prescribed various types of antibiotics and instructed to rinse with 0.12% or 0.2% chlorhexidine for 2 to 3 weeks. Antibiotics were not prescribed in a single trial (ser3) in the non signif group. Another study in the signif group (pel) did not report on the application of antimicrobials. Based on limited data, the present review failed to detect decisive evidence on the substantial benefit of employment of antibiotics following ARP.

Confounding factors

It is well established in the periodontal and implant literature that heavy smoking and untreated periodontal disease are associated with limited success of regenerative procedures (Tonetti et al. 1995). However, light or social smoking and treated periodontal disease may not adversely influence these procedures. Some evidence exists on ridge preservation that smoking may lead to increased reduction of the residual alveolar ridge and defer postextraction socket healing (Saldanha et al. 2006). Two of the investigated trials in this review (one in signif and one in non signif group) included smokers (ias, bar). Moreover, the half of the studies did not report on smoking, thus no conclusion can be drawn. None of the studies have included subjects with untreated periodontal disease. Albeit one study in the non signif (ser3) and two studies in the signif group (bar, lek8) have included patients whose periodontal treatment was carried out prior to the ARP experiment.

This indicates that treated periodontal environment may not hinder the success of ARP.

II. Radiographical dimensional alterations

Two studies evaluated dimensional changes on CT scan (fio, nev). Fio compared the treatment groups of rhBMP-2 on a collagen sponge carrier in the concentrations of 1.5 mg/ml (T1), 0.75 mg/ml (T2) and 0.0 mg/ml (T3) to each other and to the test group of empty socket (C). Only maxillary sockets of anteriors and premolars with at least 50% buccal bone loss were considered for inclusion in this multicentre study. Primary closure was achieved following full thickness flap elevation. The difference between the T1 versus all the other groups found to be statistical significant in terms of change in horizontal dimensions, measured at the coronal 25% on the CT scan. However, dense tissue gain was reported instead of loss in this study not only in the test but also in the control group. Regarding the vertical dimensions the difference between T1 and C was also significant. Moreover, no significant difference was measured in the T1 group between baseline and at 4 months.

In summary, this study showed that, despite the heterogeneity of the studies, there is evidence that ridge preservation procedures are effective in limiting post extraction ridge dimensional loss and are accompanied by a different degree of bone regeneration, with varying amounts of residual particles of the “grafting materials”. However, the exposure of membranes with GTR procedures may compromise the results. There is no evidence to support any relevant clinical superiority of one technique over the other as

well as the importance of ridge preservation in improving the ability of placing implants, implant survival/ success rate, aesthetics, treatment economy, timing or patient satisfaction.

Recommendations for further research

- Role and fate of the buccal plate.
- Consequent investigation period. Ideally to resemble to the implant insertion protocols e.g. 6 weeks (delayed immediate), 3 months (early) or 6 months (late).
- Necessity of re-augmentation at implant placement.
- Quality of life, patient's preference.
- Cost-benefit, economics.

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FIGURES LEGEND

Figure 1. Flow of studies through the review.

TABLES LEGEND

Table 1. Reasons for exclusion of full-text articles.

Table 2. Kappa score at the abstract and full text selection level.

Table 3. Quality Assessment.

Table 4. Clinical and Radiographic Assessment.

Table 5. Histological Assessment.

Figure 1.

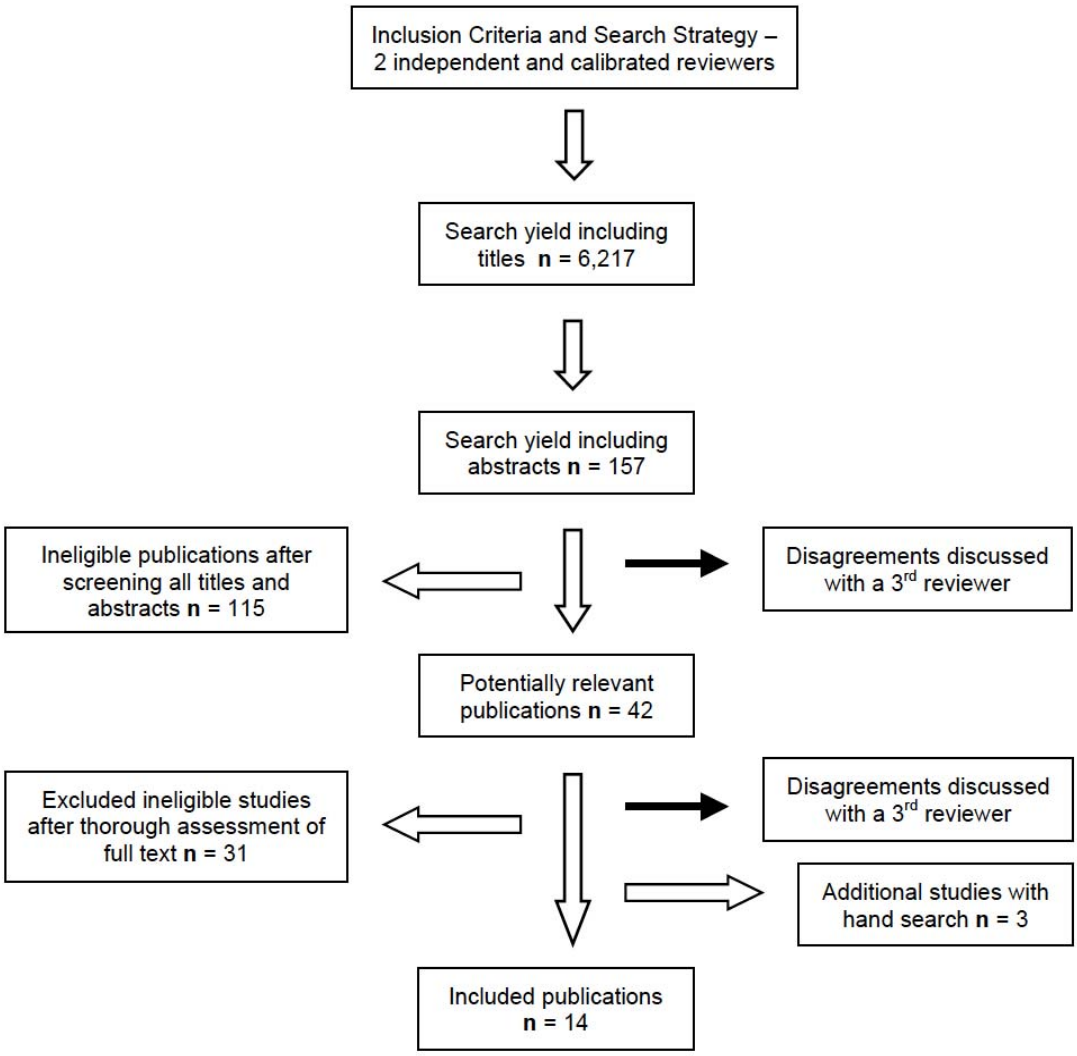
Inclusion Criteria and Search Strategy – 2 independent and calibrated reviewers
Search yield including titles n = 6,217
Search yield including abstracts n = 157
Ineligible publications after screening all titles and abstracts n = 115
Disagreements discussed with a 3rd reviewer
Potentially relevant publications n = 42
Excluded ineligible studies after thorough assessment of full text n = 31
Disagreements discussed with a 3rd reviewer
Additional studies with hand search n = 3
Included publications n = 14

Table 1.

First author (year)	Journal	Reasons for Inclusion/ Exclusion
Bianchi (2004)	Int J Periodont Rest Dent	• Retrospective analysis; • Single-arm of the study from Fiorellini et al. (2005).
Bolouri (2001)	Comp Cont Educ Dent	• Results reported as optical density on two-dimensional radiographies only; • High drop-out rates.
Brawn (2007)	Impl Dent	• Case report; • No control group.
Brkovic (2008)	J Can Dent Assoc	• Case Report.
Carmagnola (2003)	Clin Oral Impl Res	• Lack of realistic control group (seemed to be a retrospective analysis of patients who were not intended to participate into the study initially); • Follow-up period for the control group differed from the test groups (T1: 4 months; T2: 7 months; C: 1-15 y, mean: 7.8 years).
Cranin (1988)	J Biomed Mat Res	• Case series without control group.
De Coster (2009)	Clin Impl Dent Relat Res	• Retrospective study as stated by the authors themselves in the discussion section; • Healing period btw 1.5 months-1.5years; • Case series without clear results; • No histomorphometry nor clinical nor radiographic measurements reported in the results; • Does not answer the focused question.
Graziani (2008)	J Cranofac Surg	• Fully-impacted third molar sockets; • Linear measurements on OPGs only.
Gulaldi (1998)	Oral Surg Oral Med Oral Pat Oral Rad End	• Fully-impacted third molar sockets; • Linear measurements on OPGs and scintigraphy only; • Primary outcome was to analyze bone metabolism.
Heberer (2008)	Clin Oral Impl Res	• Case series without control group.
Hoad-Reddick (1994)	Eur J Prosth Rest Dent	• Two-dimensional linear measurements obtained from OPGs and cephalometries only; • Lack of defined landmarks; • Surgical procedure has not been described; • Method for obtaining of the radiographies is not clear.
Hoad-Reddick (1999)	Eur J Prosth Rest Dent	• Description of a method for measurements on casts; • Describes neither the socket preservation procedure nor the results, but merely the soft tissue punch technique.
Howell (1997)	Int J Periodont Rest Dent	• Case series without control group.
Jung (2004)	Int J Periodont Rest Dent	• Case series without control group; • Primary outcome is socket sealing.
Kangvonkit (1986)	Int J Oral Maxillofac Surg	• Based on OPG and lat cephalograms only. Evaluation method remains unclear; • Clinical findings do not report dimensional alterations of the ridge; therefore, does not answer the focused question; • Focused on checking the biocompatibility of HA cones.

Karapataki (2000)	J Clin Periodontol	• Fully-impacted third molar sockets; • Primary outcome was to assess the periodontal status of second molars after extraction of third molars.
Kerr (2008)	J Periodontol	• No biomaterials have been used to preserve the ridge dimensions; therefore, does not answer the focused question.
Kwon (1986)	J Oral Maxillofac Surg	• Based on OPG and lat cephalograms only. Evaluation method remains unclear; • Radiographies not standardized; therefore, deviation in the angulations may have caused doubtful results; • Lack of description of the measurement methods.
Molly (2008)	J Periodontol	• Control group is covered by an e-PTFE membrane; thus unassisted socket healing is missing. Excellent study otherwise.
Munhoz (2006)	Dento Maxillofac Radiol	• Impacted third molars sockets; • Two-dimensional radiographical evaluation of periapicals.
Norton (2002)	Int J Oral Maxillofac Impl	• Case series without control group; • Resembling a retrospective design (healing period ranged from 3 to 11 months).
Page (1987)	J Oral Maxillofac Surg	• Case Report.
Pape (1988)	Deutsche Zahnarztliche Zeitschrift	• Augmentation of a resorbed ridge; • Case series without control group.
Penteado (2005)	Braz J Oral Sci	• Immunohystochemical analysis; • Does not address the focused question.
Quinn (1985)	J Am Dent Assoc	• Seems to be a retrospective analysis; • Measurement and evaluation methods have not been clearly described; • Clinical measurements performed at soft tissue level only based on tattoo points. Thus, failed to address the focused question.
Schepers (1993)	Impl Dent	• Retrospective case series without control group.
Simon (2004)	Ind J Dent Res	• Fully-impacted third molars sockets; • Evaluated soft tissue healing and radiographic analysis based on the two-dimensional periapicals.
Simion (1994)	Int J Periodont Rest Dent	• Titanium implants placed simultaneously; • No control group; • Focused on microbiological analysis only.
Smukler (1999)	Int J Oral Maxillofac Impl	• No empty socket as control, but healed edentulous ridge; • No compatibility of the follow-up periods for the different groups.
Svrtecky (2003)	J Prosth Dent	• Case Report.
Throndson (2002)	Oral Surg Oral Med Oral Pat Oral Rad End	• Fully-impacted third molar sockets; • Radiographic measurements based on two-dimensional periapicals only.
Yilmaz (1998)	J Clin Periodontol	• Soft tissue level measurements has been evaluated on study casts only.

Table 2.

Kappa statistics for comparison of reviewer agreement following abstract screening			
Reviewer 1	**Reviewer 2**		
	Accept	**Reject**	**Total**
Accept	39	2	41
Reject	1	115	116
Total	40	117	**157**
Simple Kappa Coefficient = 0.96 Observed percentage of agreement = 98%.			
Kappa statistics for comparison of reviewer agreement following full-text screening			
Reviewer 1	**Reviewer 2**		
	Accept	**Reject**	**Total**
Accept	11	1	12
Reject	1	29	30
Total	12	30	**42**
Simple Kappa Coefficient = 0.90 Observed percentage of agreement = 95%.			

Table 3.

Study *First author* *Year of publication* *Type*	Quality Criteria *Randomisation* **1. Randomised** **2. Adequate sequence generation** **3. Allocation concealment** **4. Concealment adequate**	*Masking* **1. Therapist** **2. Patient** **3. Examiner** **4. Statistician**	*Calibration* **1. Intra-examiner** **2. Inter-examiner**	*Eligibility Criteria* **1. Inclusion criteria defined** **2. Exclusion criteria defined**	*Follow up* **1. Percentage of completed follow ups** **2. Adequate correction**	*Ethical considerations* **1. Ethics approval** **2. Informed consent**	*Funding* **Source of Funding**	*Statistical analysis* **1. Sample size calculation and power** **2. Unit of analysis** **3. Appropriate statistics applied**	*Miscellaneous* **1. Comparable experimental groups** **2. CONSORT implemented** **3. ISRCTN registered** **4. Other comments**	Estimated Risk of Bias
Aimetti ***2009*** ***RCT***	1. Yes 2. N/R 3. N/R 4. N/A	1. N/R 2. N/R 3. Yes (histo), N/R (clin) 4. N/R	1. Yes (histo), N/R (clin) 2. N/A	1. Yes 2. Yes	1. N/R 2. N/A	1. Yes 2. Yes	N/R	1. Yes 2. Patient 3. Insufficient data to determine	1. Yes 2. N/R 3. N/R	**High**
Anitua ***1999*** ***CCT***	1. Yes (btw T-C) No (within T) 2. N/A 3. N/R 4. N/A	1. N/R 2. N/R 3. Yes 4. N/R	1. N/R 2. N/A	1. Yes 2. Yes	1. 100% 2. Yes	1. N/R 2. Yes	N/R	1. N/R 2. Patient + site 3. No statistical analysis was carried out	1. N/R 2. N/R 3. N/R 4. At severe defects autogenous bone was added to PRGF. Different healing periods.	**High**
Barone ***2008*** ***RCT***	1. Yes 2. Yes (computer-generated list) 3. N/R 4. N/A	1. N/R 2. N/R 3. Yes (histo), N/R (clin) 4. N/R	1. N/R 2. N/A	1. Yes 2. Yes	1. 100% 2. Yes	1. N/R 2. Yes	N/R, declared no conflict of interest	1. N/R 2. Patient 3. No	1. Yes 2. N/R 3. N/R 4. Different healing periods.	**High**
Camargo 2000 ***CCT***	1. N/R 2. N/A 3. N/R 4. N/A	1. N/R 2. N/R 3. N/R 4. N/R	1. N/R 2. N/A	1. Yes 2. Yes	1. 100% 2. Yes	1. Yes 2. Yes	Company	1. N/R 2. Patient 3. Insufficient data to determine	1. N/R 2. N/R 3. N/R	**High**
Fiorellini ***2005*** ***RCT***	1. Yes 2. N/R 3. N/R 4. N/A	1. N/R 2. N/R 3. Yes (CT scans) 4. N/R	1. N/R 2. Yes	1. Yes 2. No	1. 100% 2. Unclear	1. Yes 2. Yes	Company	1. Yes 2. Patient 3. No	1. N/R 2. N/R 3. N/R 4. Standardisation of CT scans N/R. Final number of sockets, patients remain unclear.	**High**
Froum ***2002***	1. Yes 2. Yes 3. N/R 4. N/A	1. N/R 2. N/R 3. Yes 4. N/R	1. N/R 2. N/A	1. Yes 2. Yes	1. 100% 2. Unclear	1. Yes 2. Yes	Company	1. N/R 2. Site 3. No	1. N/R 2. N/R 3. N/R 4. Different healing	**High**

RCT									periods. Enrolment of sites of subjects inconsistent.	
Guarnieri 2004 ***CCT***	1. N/R 2. N/A 3. N/R 4. N/A	1. N/R 2. N/R 3. N/R 4. N/R	1. N/R 2. N/A	1. Yes 2. No	1. N/R 2. N/A	1. Yes 2. Yes	Governme nt; institution	1. N/R 2. Site 3. No	1. N/R 2. N/R 3. N/R	**High**
Iasella 2003 ***RCT***	1. Yes 2. Yes 3. N/R 4. N/A	1. N/R 2. N/R 3. Yes 4. N/R	1. Yes 2. N/A	1. Yes 2. Yes	1. 100% 2. Yes	1. Yes 2. Yes	N/R	1. Yes 2. Patient 3. Insufficient data to determine	1. Yes 2. N/R 3. N/R	**Moderate**
Lekovic 1997 ***CCT***	1. N/R 2. N/A 3. N/R 4. N/A	1. N/R 2. N/R 3. N/R 4. N/R	1. N/R 2. N/A	1. No 2. No	1. 70% (premature exposure of ePTFE barrier in 3/10) 2. Yes	1. Yes 2. N/R	N/R	1. N/R 2. Patient 3. Insufficient data to determine	1. Yes 2. N/R 3. N/R	**High**
Lekovic 1998 ***RCT***	1. Yes 2. Yes 3. N/R 4. N/A	1. N/R 2. N/R 3. Yes 4. Yes	1. N/R 2. N/A	1. No 2. No	1. 100% 2. Yes	1. Yes 2. Yes	N/R	1. N/R 2. Patient 3. Insufficient data to determine	1. Yes 2. N/R 3. N/R	**Moderate**
Nevins 2006 ***RCT***	1. Yes 2. N/R 3. N/R 4. N/A	1. N/R 2. N/R 3. N/R 4. N/R	1. N/R 2. N/A	1. Yes 2. Yes	1. 100% 2. Yes	1. N/R 2. N/R	N/R	1. N/R 2. Site 3. No	1. Yes 2. N/R 3. N/R 4. Standardisation of CT scans N/R. Test material radiopaque. Different healing periods.	**High**
Pelegrine 2010 ***RCT***	1. Yes 2. N/R 3. N/R 4. N/A	1. N/R 2. N/R 3. N/R 4. N/R	1. N/R 2. N/A	1. Yes 2. Yes	1. 100% 2. Yes	1. Yes 2. Yes	Institution	1. N/R 2. Patient 3. Yes	1. N/R 2. N/R 3. N/R	**High**
Serino 2003 ***CCT***	1. N/R 2. N/A 3. N/R 4. N/A	1. N/R 2. N/R 3. N/R 4. N/R	1. N/R 2. N/A	1. Yes 2. No	1. 80% 2. Unclear	1. Yes 2. Yes	N/R	1. N/R 2. Site 3. No	1. N/R 2. N/R 3. N/R 4. Molars only in T.	**High**
Serino 2008 ***CCT***	1. N/R 2. N/A 3. N/R 4. N/A	1. N/R 2. N/R 3. N/R 4. N/R	1. N/R 2. N/A	1. Yes 2. No	1. 80% 2. Unclear	1. Yes 2. Yes	Governme nt; institution	1. N/R 2. Patient 3. Insufficient data to determine	1. N/R 2. N/R 3. N/R	**High**

N/A = not applicable; N/R = not reported, T = test; C = control; RCT = randomised controlled trial; CCT = controlled clinical trial; PRGF = platelet-rich growth factor; M = month(s)

Table 4.

First author *Year of publication* *Type* *Design* *Methodology*	*Trial characteristics* **1. Country** **2. Number of centres** **3. Setting**	*Population characteristics* **1. Age range (mean) in years** **2. Number of patients (sockets)**	*Confounding factors* **1. Smoking** **2. Periodontitis**	*Defect characteristics* **1. Socket location** **2. Defect morphology**	*Test material (number of sockets/ subjects)*	*Control (number of sockets/ subjects)*	*Surgical management* **1. Type of flap** **2. Soft tissue closure** **3. Postoperative antimicrobials**	*Follow-up* **1. Healing period** **2. Number of drop-outs** **3. Adverse events**	*Alveolar ridge dimension changes in horizontal width Mean/median mm (reference point)*	*Alveolar ridge dimension changes in vertical height Mean/median mm* **1. Mid-buccal** **2. Mesial** **3. Distal** **4. Socket Fill**	*Implant* **1. Feasibility of implant placement** **2. Necessity of simultaneous augmentation**
Aimetti 2009 RCT Parallel Clin + Histo	1. Italy 2. 1 3. University	1. 36-68 (51.27 ±8.4) 2. 40 (40)	1. No 2. N/R	1. Maxillary anterior 2. 4-wall configuration	Calcium sulphate (22/22)	Empty (18/18)	1. Flapless 2. No primary closure 3. Amoxicillin 2g/day for 5 days, Chlorexidine 0.12% for 2 weeks	1. 3 months 2. N/R 3. Uneventful healing	**T: -2.0 ± 1.1**** **C: -3.2 ± 1.8**** ‡	1. **T: -0.5±1.1*** **C: -1.2±0.6**** ‡ 2. T: -0.2±0.6 C: -0.5±0.9 3. T: -0.4±0.9 C: -0.5±1.1 4. T: 11.3±2.8** C: 10.0±2.3** (Acrylic stent)	1. Yes. 2. N/R
Anitua 1999 CCT Parallel + Split-mouth Histo	1. Spain 2. 1 3. Private practice	1. T: 35-55 (41) C: 38-54 (42) 2. 23 (26)	1. Yes 2. Yes	1. Any 2. Variable	T1: PRGF (5+3/5+3) T2: PRGF+Autologous bone (5/5)	Empty (10+3/10 +3)	1. Full-thickness 2. Primary closure 3. Amoxicillin 1.5g/day for 5 days	1. 2.5 – 4 months 2. 0 3. N/R	N/A	N/A	1. N/R 2. N/R
Barone 2008 RCT Parallel Clin + Histo	1. Italy 2. 1 3. Hospital	1. 26-69 2. 40 (40)	1. <10/day 2. Yes (treated)	1. Non-molars 2. 4-wall configuration	Corticocancellous porcine bone+ collagen membrane (20/20)	Empty (20/20)	1. Full-thickness 2. Primary closure 3. Amoxicillin 2g/day for 4 days + Chlorexidine 0.12% for 3 weeks	1. 7-9 months 2. 0 3. Uneventful healing (pain, swelling)	**T: -2.5 ± 1.2*** **C: -4.5 ± 0.8*** ‡	1. **T: -0.7±1.4*** **C: -3.6±1.5*** ‡ 2. T: -0.2±0.8 C: -0.4±1.2 3. T: -0.4±0.8 C: -0.5±1.0 4. N/R (Acrylic stent)	1. 'Implants were inserted in both groups' 2. Some GBR needed due to buccal dehiscence in the control group
Camargo 2000 CCT Split-mouth Clin	1. USA, Yugoslavia 2. N/R 3. University	1. 28-60 (44±15.9) 2. 16 (32)	1. N/R 2. N/R	1. Maxillary anterior, premolars 2. N/R	Bioactive glass +covered by calcium sulphate layer (16/8)	Empty (16/8)	1. Full-thickness with 4 vertical releasing incisions 2. No primary closure 3. Penicillin 1.5g/day for 7 days + Chlorexidine 0.12% for 2 weeks	1. 6 months 2. N/R 3. Uneventful healing	T: -3.48±2.68** C: -3.06±2.41**	1. T: -0.38±3.18 C: -1.00±2.25 2. N/R 3. N/R 4. **T: -6.43±2.78**** **C: -4.00±2.33**** ‡ (titanium tack)	1. Reentry only 2. N/A
Fiorellini 2005 RCT Parallel Radiogr + Histo	1. USA 2. 8 centres 3. University	1. 47.4 2. 80 (95)	1. N/R 2. N/R	1. Maxillary anterior, premolars 2. ≥50% buccal bone loss	T1: 1.5mg/ml rhBMP-2 (?/21?) T2: 0.75mg/ml rhBMP-2 (?/22?) T3: Collagen	Empty (?/20?)	1. Full-thickness with vertical incisions 2. Primary closure 3. Penicillin (?mg) for 7-10 days + Chlorexidine 0.12%	1. 4 months 2. No drop-outs reported. (3 patients incorrectly randomized, 1 patient received different graft) 3. 250 (T>C)	Coronal: T1: +3.27±2.53* T2: +1.76±1.67* T3: +0.82±1.40 C: +0.57±2.56 **‡ (T1 vs T2/T3/C)**	1. T1: -0.02 ± 1.2 **T2: -0.62±1.39*** **T3: -1.00±1.40*** **C: -1.17± 1.23*** **‡ (T1 vs C)** 2. N/R 3. N/R 4. N/R	1. N/R 2. T1: 14% T2: 45% T3: 41% C: 55% **(T1 vs T2/C) ‡**

					sponge (?/17?)						
Froum 2002 RCT Split mouth Histo	1. USA 2. Single centre 3. University	1. 35-77 (54.9±11.9) 2. 19 (30)	1. No 2. N/R	1. Any 2. 4-wall configuration, ≤2mm buccal plate loss	T1: Bioactive glass (10/8) T2: DFDBA (10/8)	Empty (10/10)	1. Full-thickness without vertical incisions 2. Primary closure 3. Doxycycline 100mg/day for 13 days + Chlorexidine 0.12% for 30 days	1. 6-8 months 2. 0 3. Uneventful healing	N/A	N/A	1. 'An implant of appropriate size was placed in the healed sockets.' 2. N/R
Guarnieri 2004 CCT Parallel + Split mouth Histo	1. Italy 2. N/R 3. N/R	1. 35-58 2. 10 (25)	1. N/R 2. Yes	1. Maxillary, mandibular anteriors, premolars 2. socket with ridge resorption ≥50% were excluded	Calcium sulphate (10/10)	Empty (5/5)	1. Full-thickness without vertical incisions 2. Primary closure 3. Amoxicillin (?mg) for 1 week + Chlorexidine 0.2% for 2 weeks	1. 3 months 2. N/R 3. N/R	N/A	N/A	1. N/R 2. 'Bucco-lingual dimensions of the alveolar ridge enabled safe insertion of titanium implant.'
Iasella 2003 RCT Parallel Clin + Histo	1. USA 2. N/R 3. N/R	1. 28-76 (51.5±13.6) 2. 24 (24)	1. Yes 2. N/R	1. Maxillary anteriors, premolars and mandibular premolars 2. N/R	Tetracycline hydrated FDBA + collagen membrane (12/12)	Empty (12/12)	1. Full-thickness without vertical incisions 2. No primary closure 3. Doxycyclin 200mg/day for 1 week + Chlorexidine 0.12% for 2 weeks	1. 4 or 6 months (combined) 2. 0 3. N/R	T: -1.2 ± 0.9* C: -2.6 ± 2.3*	**1. T: +1.3±2.0** **C: -0.9±1.6 ‡** **2. T: -0.1±0.7** **C:-1.0±0.8 ‡** **3. T: -0.1±0.7** **C: -0.8±0.8 ‡** 4. N/R (Acrylic stent)	1. Implants successfully placed at all sites 2. Some sites had slight dehiscence and required further augmentation
Lekovic 1997 CCT Split-mouth Clin	1. Yugoslavia / USA 2. N/R (presumably single centre) 3. University	1. (49.8) 2. 10 (20)	1. N/R 2. N/R	1. Maxillary and mandibular anteriors, premolars 2. N/R	e-PTFE membrane (10/10)	Empty (10/10)	1. Full-thickness with 4 vertical releasing incisions 2. Primary closure 3. Penicillin 1g/day for 7 days + Chlorexidine 0.2%	1. 6 months 2. 3/10 drop-outs due to premature membrane exposure 3. 3/10 exposed, 7/10 no infection	10/10: **T: -1.8±0.51** **C: -4.40±0.61‡** 7/10: **T: -1.71±0.75** **C: -4.43±0.72‡**	1. 10/10: **T: -0.5±0.22** **C:-1.2±0.13*‡** 7/10: **T: -0.28±0.18** **C: -1.0±0.0*‡** 2. N/R 3. N/R 4. 10/10: **T: 4.9±0.86*** **C: -3.0±0.63‡** 7/10: **T: 5.43±0.1*** **C:-2.92±1.61‡** (Titanium tack)	1. Reentry only 2. N/A
Lekovic 1998 RCT Split-mouth Clin	1. Yugoslavia 2. 1 3. University	1. (52.6±11.8) 2. 16 (32)	1. N/R 2. Yes (treated)	1. Maxillary and mandibular anteriors, premolars 2. N/R	PG/PL membrane (16/16)	Empty (16/16)	1. Full-thickness with 4 vertical releasing incisions 2. Primary closure 3. Penicillin 1g/day for 7 days + Chlorexidine 0.12% for 2 weeks	1. 6 months 2. 0 3. Uneventful healing	**T: -1.31±0.24*** **C:-4.56±0.33*‡**	1. **T: -0.38±0.22** **C: -1.50±0.26*‡** 2. N/A 3. N/A 4. **T: -5.81±0.29*** **C: -3.94±0.35*‡** (Titanium tack)	1. Reentry only 2. N/A

Nevins 2006 RCT Split-mouth Radiogr + Histo	1. USA / Italy 2. N/R 3. N/R	1. N/R 2. 9 (36)	1. N/R 2. Yes	1. Maxillary anterior 2. Buccal plate was compromised	DBBM (19/9)	Empty (17/9)	1. Partial thickness 2. Primary closure 3. N/R	1. 1 – 3 months (biopsies at 6M) 2. 0 3. N/R	N/A	1. **T: -2.42±2.58** **C: -5.24±3.72 ‡** 2. N/A 3. N/A 4. N/A (At 6 mm ridge width)	1. Implants were placed, but number unknown 2. N/R
Pelegrine 2010 RCT Parallel Clin + histo	1. Brazil 2. 1 3. University	1. 28-70 (47.5±10.3) 2. 13 (30)	1. No 2. N/R	1. Maxillary anteriors 2. Sockets with severe bone loss were excluded	Autologous bone marrow (15/7)	Empty (15/6)	1. Full-thickness with 2 buccal vertical releasing incisions 2. Primary closure 3. N/R	1. 6 months 2. 0 3. Uneventful healing	**T: -1.0*** **C: -2.5*‡**	1. **T: -0.5*** **C: -1.0*‡** 2. N/A 3. N/A 4. T: +10.33* C: +10.32* (Titanium screw)	1. All implants osseointegrated 2. T: without further augmentation C: At 5 sites augmentation/expansion carried out
Serino 2003 CCT Parallel + split-mouth Clin + Histo	1. Italy 2. 1 3. N/R	1. 35-64 2. 45 (39) before drop-out	1. N/R 2. Yes (treated)	1. Any 2. Buccal plate could be partially or completely lost	PG/PL sponge (26/24) after drop-out	Empty (13/12) after drop-out	1. Full-thickness buccally and lingually 2. No primary closure 3. No antibiotics; Chlorexidine 0.2% for 2 weeks	1. 6 months 2. 9 drop-outs for reasons unrelated to the therapy 3. Uneventful healing	N/A	1. T: +1.3 ± 1.9* C: -0.8 ± 1.6 2. T: -0.2 ± 1.0 C: -0.6 ± 1.0 3. T: -0.1 ± 1.1 C: -0.8 ± 1.5 4. N/A (Acrylic stent)	1. Placement of implants in all C and T sites with good primary stability 2. N/R
Serino 2008 CCT Parallel Histo	1. Italy 2. 1 3. N/R	1. 32-64 2. 20 (20) before drop-out	1. N/R 2. Yes (treated)	1. Any non-molars 2. Alveolar bone height ≥8mm	PG/PL sponge (7/7) after drop-out	Empty (9/9) after drop-out	1. Full-thickness buccally and lingually 2. No primary closure 3. No Antibiotics; Chlorexidine 0.2% for 2 weeks	1. 3 months 2. 4 drop-outs for reasons unrelated to the therapy 3. Uneventful healing	N/A	N/A (Acrylic stent)	1. Placement of implants in all C and T sites with good primary stability 2. N/R

**** = statistically significant (p<0.05) intra group, baseline to final; ** = statistically highly significant (p<0.001) intra group, baseline to final; ‡ = statistically significant inter group difference, between test and control (p<0.05); N/A = Not Applicable; N/R = N/R; T = test; C = control; M = month(s); Clin = Clinical Analysis; Histo = Histologic Analysis; Radiogr = Radiographic Analysis; RCT = randomised controlled trial; CCT = controlled clinical trial; PRGF = plasma rich in growth factors; N/A = not applicable; DFDBA = demineralised freeze-dried bone allograft; FDBA = freeze-dried bone allograft; e-PTFE = expanded-polytetrafluorethylen; PG/PL = polyglycolide/polylactide; DBBM = demineralized bovine-bone mineral***

Table 5.

First author Year of publication *Follow-up period*	Number of biopsies (test material)	Histomorphology		Histomorphometry (mean/median %)				Statistical difference between test and control
		Test	Control					
Aimetti ***2009*** ***3 M***	T: N/R 22? (MGCSH) C: N/R 18?	No residual graft material. No inflammatory infiltrate. New bone formation in all specimens, 100% living trabecular bone with woven and lamellar structure.	100% living bone (mostly woven) in all biopsies. Lamellar bone remodeling was starting.	***Trabecular bone:*** T: 58.8±3.5 C: 47.2±7.7	***Residual substitute material:*** T: 0.0 C: N/A	***Woven bone:*** *Coronal:* T: 83.6±6.6 C: 88.9±7.6 *Middle:* T: 59.6±13.2 C: 81.1±7.6 *Apical:* T: 56.4±10.9 C: 77.8±8.1	***Lamellar bone:*** *Coronal:* T: 16.4±6.6 C: 11.1±7.6 *Middle:* T: 40.4±13.2 C: 18.9±7.6 *Apical:* T: 43.6±10.9 C: 22.2±8.1	**T vs C ‡**
Anitua ***1999*** ***2.5 – 4 M***	T: N/R (PRGF± autogen bone) C: N/R	Compact mature bone with well-organized trabeculae and morphology in 8/10 patients. Connective tissue with non-organized trabeculae in 2/10 patients. Significant intra-group differences 10 vs. 16 weeks!	Connective tissue fills the main part of the defect. No mature bone.				Ű	N/R
Barone ***2008*** ***7 – 9 M***	T: 20 (Corticocancellous porcine bone+ collagen membrane) C: 20	Residual graft material embedded in newly formed bone in all specimens. Complete bone fill.	Typically trabecular bone pattern. Large marrow spaces filled with adipocytes. Lamellar bone was also present within the bone marrow.	***Total bone volume:*** T: 35.5±10.4 C: 25.7±9.5	***Connective tissue:*** T: 36.6±12.6 C: 59.1±10.4	***Residual graft material:*** T: 29.2±10.1 C: N/A		**Trabecular bone volume: T>C ‡** **Connective tissue: T<C ‡**
Fiorellini ***2005*** ***4 M***	T1: 16 (rhBMP-2 1.5mg/ml) T2: 15 (0,75mg/ml) T3: 11 (Collagen sponge) C: 14	No evidence of inflammation or residual graft. Trabecular bone formation in 2/3 of the samples. Mineralized tissue formation presented with different level of remodeling. Minor osteoclastic activity.						N/R
Froum ***2002*** ***6 – 8 M***	T1: 10 (Bioactive glass) T2: 10 (DFDBA) C: 10	T1: New bone formation. Osteoid surrounded and penetrated the bioactive glass particles. T2: Varying degrees of reossification around DFDBA.	N/R	***Vital bone:*** T1: 59.5 T2: 34.7 C: 32.4	***Connective tissue:*** T1: 35.3 T2: 51.6 C: 97.0	***Residual bone substitute:*** T1: 5.5 T2: 13.5 C: N/A		**Connective tissue: T1<T2/C ‡**

Guarnieri ***2004*** ***3 M***	T: 10 (MGCSH) C: 5	Almost complete absence of MGCSH, connective tissue and inflammatory cells. In all sections trabecular bone formation with no differences between the apical, middle and coronal levels.	Less bone formation compared to test sites.	***Trabecular bone area:*** T: Coronal: 58.6±9.2 Middle: 58.1±6.2 Apical: 58.3±7.8 C: ≤ 46		No statistical significance could be drawn due to small number of control specimens.
Iasella ***2003*** ***4 – 6 M***	T: 4M: 5 6M:7 (Tetracycline hydrated FDBA + Collagen membrane) C: 4M: 5 6M: 5	Residual graft particles surrounded by woven bone or by connective tissue.	N/R (No biopsy from 2 C sites due to minimal bone fill)	***Vital bone:*** **4M** T: 31±9 C: 58±11 **6M** T: 25±17 C: 50±14 **Combined** T: 28±14 C: 54±12	***Non-vital bone:*** **4M** T: 32±19 C: N/A **6M** T: 41±18 C: N/A **Combined** T: 37±18 C: N/A	N/R
Nevins ***2005*** ***6 M***	T: 5 (DBBM) C: 5	DBBM granules present. Apically integrated in cancellous bone but coronally in soft tissue. No signs of inflammation or foreign body reaction.	New bone formation			No comparison made.
Pelegrine ***2010*** ***6 M***	T: 7 (Autologous bone marrow) C: 6			***Mineralized bone:*** T: 45.0 C: 43.75		No significant difference.
Serino ***2003*** ***6 M***	T: 10 (PG/PL sponge) C: 3	No residual graft material. Presence of matured, mineralized bone. Lack of coronal soft tissue ingrowth.	Presence of mineralized bone. Wide marrow spaces.	***Mineralized bone:*** T: 66.7 C: 43.7		Statistical comparison cannot be made due to the small number of control specimens.
Serino ***2008*** ***3 M***	T: 7 (PG/PL sponge) C: 9	No residual graft material. Scarce presence of inflammatory tissue. Coronal: newly formed trabecular bone with large marrow spaces. Apical: more mature and compact bone.	Coronal: trabecular bone with wide marrow spaces with connective tissue. Apical: more mature and compact bone.	***Mineralized bone:*** T: 59.9 ± 22.4 C: 48.8 ± 14.4		No significant difference.

T = test; C = control; M = month(s); N/R = not reported; N/A = not applicable; vs. = versus; TBV = total bone volume; ‡ = statistically significant difference between test and control (p<0.05) ; MGCSH = medical grade calcium sulphate hemihydrate; DFDBA = demineralised freeze-dried bone allograft; FDBA = mineralised freeze-dried bone allograft; DBBM = demineralised bovine-bone mineral; PG/PL = polyglycolide/polylactide

3. DISCUSSÃO GERAL

Este estudo buscou avaliar, através de um ensaio clínico randomizado, as alterações radiográficas da crista óssea alveolar após a preservação do rebordo alvelar utilizando dois diferentes biomateriais além de, através de uma revisão sistemática da literatura, avaliar as evidências do efeito deste procedimento e se esta técnica possibilita a colocação do implante (com ou sem enxerto adicional). Os achados radiográficos do estudo clínico mostraram que ambos os tipos de materiais de enxerto preservaram as dimensões do rebordo alveolar medidas nas radiografias, além de terem mostrado ganhos similares em níveis de cinza entre os intervalos de tempo. No entanto, nenhum deles mostrou superioridade em termos de alterações radiográficas do osso alveolar no intervalo de tempo analisado (8 meses). Ainda, a investigação clínica mostrou uma redução inferior a 1,0 mm nos níveis ósseos radiográficos interproximais aos 4 e 8 meses após a cirurgia em ambos os grupos. É questionável, todavia, se as alterações radiográficas dos tecidos duros nos sítios interproximais de menos de 1,0 mm representam ou não alguma relevância clínica. Outrossim, a avaliação radiográfica subestimou as medições intra-cirúrgicas (mesial e distal) em 0,3 mm na média. Em linhas gerais, os resultados do estudo clínico estiveram de acordo com as evidências da literatura mostradas na revisão.

Posteriormente, uma revisão sistemática da literatura foi conduzida e os resultados revelaram que, apesar da heterogeneidade de técnicas, materiais e metodologias dos quatorze estudos analisados e da dificuldade de comparação direta entre eles, existem evidências que a reabsorção tridimensional fisiológica do rebordo alveolar pode ser limitada por várias técnicas de preservação do

rebordo. Esta redução é significante na dimensão horizontal/ oro-vestibular assim como na dimensão vertical/ apico-coronal medida no aspecto médio-vestibular. No entanto, nenhuma das técnicas ou materiais relatados possui a capacidade de manter completamente as dimensões do rebordo alveolar.

Os resultados dos grupos controle sustentam os achados amplamente aceitos que, na cicatrização natural do alvéolo após a extração dentária, uma redução estatisticamente significante do rebordo alveolar na dimensão horizontal/ oro-vestibular ocorreria. Estudos clínicos controlados mostraram uma reabsorção óssea vertical média de 0,7 a 1,5 mm, assim como uma reabsorção horizontal média de 4,0 a 4,5 mm (AIMETTI *et al*., 2009). Além disso, Van der Weijden *et al*. (2009), em uma revisão sistemática da literatura, encontraram que, durante o período de cicatrização pós-extração, as médias ponderadas das mudanças mostraram a perda clínica em espessura (3,87 mm) como sendo maior do que a perda em altura, avaliada tanto clinicamente (1,67 – 2,03 mm) como radiograficamente (1,53 mm). No entanto, devido à heterogeneidade dos dados obtidos a partir dos artigos originais, deve-se adotar cautela com a meta-análise realizada na revisão supra citada.

A altura, a espessura e o número de paredes ósseas do defeito ósseo resultante no alvéolo após a extração, assim como a altura do osso alveolar nos aspectos interproximais são também de grande relevância (LEKOVIC *et al*., 1997; DARBY *et al*., 2009). Com base na compilação de dados desta revisão, foi possível corroborar a hipótese que a morfologia do alvéolo exerce um papel primordial no resultado da técnica de preservação, isto é, quanto mais intactas são as paredes ósseas após a extração, mais sucesso da PRA

pode ser antecipado.

Todos os estudos analisados que mostraram diferença significativa entre os grupos teste e experimental, à exceção de um (Aimetti et al. 2009), realizaram o avanço do retalho e fechamento por primeira intenção da ferida cirúrgica. Assim, as evidências mostrando o papel crucial do fechamento por primeira intenção do retalho no desfecho da PRA parecem, por sua vez, ser ainda mais claras.

Dentre os estudos incluídos na revisão, houve uma distribuição uniforme com relação à localização dos sítios experimentais. Assim, os dados disponíveis não permitem que conclusões sejam tiradas a respeito de um possível favorecimento da técnica em virtude da localização do sítio. Além do mais, as evidências levantadas na presente revisão mostraram que o sucesso da técnica de PRA independe do tempo de cicatrização, os quais variaram de maneira muito parecida em ambos os estudos que mostraram diferença significativa e os que não mostraram diferença significativa. Ainda, baseada em dados limitados, a presente revisão falhou em detectar evidências do benefício com o emprego de antibióticos. Isto pode ser explicado pelo fato que o uso de antibimicrobianos não foi a intervenção principal e o foco da pesquisa, embora na grande maioria dos experimentos um regime antibiótico tenha sido instituído como procedimento de rotina.

Com relação a fatores confundentes, nenhuma conclusão pôde ser tirada nesta revisão de que o fumo exerce algum papel sobre a eficácia da técnica de PRA, uma vez que não existiram evidências substanciais dentre os artigos incluídos. Isto contraria, de certa forma, alguns indícios existentes na literatura

de que o fumo pode conduzir a uma redução aumentada do rebordo alveolar residual e retardar a cicatrização do alvéolo pós-extração (SALDANHA *et al*., 2006). Por outro lado, nenhum estudo relatou ter incluído pacientes com doença periodontal enquanto que apenas três estudos relataram ter incluído pacientes tratados periodontalmente, não mostrando diferenças nos resultados em relação aos pacientes periodontalmente saudáveis. Isto indica que o ambiente periodontal tratado pode não impedir o sucesso da PRA.

Devido à ampla variedade das técnicas utilizadas, a morfologia do alvéolo, o tempo de cicatrização assim como o tamanho das amostras relativamente pequenos, a diferença entre os métodos e materiais aplicados não pode ser avaliada. Assim ainda não foi encontrada evidência sólida para afirmar que um material ou método serve de maneira superior a outro. Também não foram encontrados dados investigando as taxas de sobrevivência ou sucesso dos implantes colocados tanto nos sítios de preservação do rebordo quanto nos controles. Por último, não foram encontrados dados sobre qualidade de vida, preferência do paciente ou custos do tratamento comparando a preservação do rebordo no momento da extração versus o aumento do rebordo antes ou no momento da colocação do implante.

No melhor de nosso conhecimento, nenhuma revisão avaliou até o momento o aspecto histológico da técnica de preservação do rebordo alveolar. Os achados da presente revisão mostraram que o preenchimento do alvéolo pode ser significativamente melhorado pelas técnicas de preservação e a maturação e mineralização do osso neoformado no alvéolo de extração podem ser aceleradas ou melhoradas com a preservação do alvéolo. Porém, a

diversidade nos métodos de obtenção das amostras para as análises histológicas, além de outros aspectos já mencionados, impedem uma comparação mais conclusiva dos resultados histológicos dos artigos originais. Este aspecto pode ser decisivo clinicamente por ocasião da confecção do alvéolo ósseo do implante. Um tecido com aspecto imaturo pode ser encontrado mesmo meses após a extração do dente e preenchimento do alvéolo com material de enxerto. Isto pode levar a uma estabilidade inicial do implante, medida através do torque de inserção, abaixo dos parâmetros ideais.

Não há registros de revisões sistemáticas anteriores neste mesmo assunto que analisaram a qualidade da metologia de pesquisa empregada nos experimentos originais, atribuindo, mesmo que de forma arbitrária, valores estimados de risco de viés aos artigos. Existem, de fato, muitos artigos apresentando conclusões semelhantes, porém com duvidosos métodos experimentais e de obtenção e interpretação dos resultados. Para estimar o potencial risco de viés dos experimentos incluídos na nossa revisão, um valor alto foi estabelecido na meticulosa avaliação das metodologias de pesquisa. Assim, foi possível estabelecer uma estratificação da qualidade dos artigos, o que por sua vez possibilitou sua interpretação de forma mais prudente.

Os achados da presente revisão estão, em sua maioria, de acordo com os achados de outras revisões abordando o mesmo assunto (FIORELLINI & NEVINS, 2003; FUGAZZOTTO, 2005; JOHN *et al*., 2007; DARBY *et al*., 2008; DARBY *et al*., 2009). Todavia, faz-se necessário salientar que estes estudos não estabeleceram critérios transparentes e convincentes de inclusão ou exclusão dos artigos. A ausência de uma pergunta focada levou à uma busca

ampla, com resultados bastante heterogêneos e algumas vezes controversos. Além disso, estudos pré-clínicos com animais de laboratório, estudos retrospectivos, cujos procedimentos e tempos de acompanhamento muitas vezes não eram idênticos entre os grupos, além de relatos de caso e séries de casos sem a comparação da intervenção com a cicatrização natural do alvéolo, foram incluídos. A razão pela qual estudos pré-clínicos não participaram da nossa revisão foi porque evidências em animais não devem ser mescladas com evidências em humanos e transportadas para a realidade clínica de maneira direta. Além do mais, a não adoção de um rigoroso protocolo de busca, com mais de um revisor e incluindo relevantes bases de dados, além de restrições de idioma e ano de publicação, podem ter conduzido a um viés de publicação. Em outras palavras, informações relevantes podem ter ficado de fora da compilação dos dados devido à ausência de uma simples tradução ou sua inclusão em outras bases de dados que não o *Medline*. Desta forma, os resultados dos trabalhos acima citados devem ser interpretados com cuidado.

Em suma, a revisão sistemática mostrou que a preservação do rebordo alveolar, apesar das diferentes técnicas, materiais e metodologias analisadas, limita, porém não evita completamente a reabsorção do rebordo alveolar após a extração dentária. Os achados do estudo clínico confirmaram esta conclusão, quando tanto um substituto ósseo sintético ou um xenoenxerto bovino, ambos em combinação com uma barreira de colágeno, preservaram igualmente os níveis ósseos radiográficos até 8 meses após o enxerto dos alvéolos.

Dentro das limitações do estudo clínico e da revisão sistemática da literatura, as seguintes conclusões podem ser tiradas a partir dos resultados:

i. Nenhuma das técnicas ou materiais descritos possui a capacidade de manter inteiramente as dimensões do rebordo alveolar após a extração dentária.
ii. Porém, a reabsorção tridimensional fisiológica do rebordo alveolar pode ser limitada pela técnica de preservação do rebordo. A redução é significante na dimensão horizontal/ vestíbulo-palatina, assim como na dimensão vertical/ ápico-coronal medida no sentido médio-vestibular.
iii. A redução vertical/ ápico-coronal tende a ser significante principalmente nas áreas interna e médio-vestibular, mas falha em mostrar significância nas áreas mésio-vestibular, disto-vestibular e lingual/palatina.
iv. Não foram encontradas evidências claras para afirmar a superioridade de um material ou método sobre outro.
v. Existe ainda uma falta de dados avaliando o papel da espessura da tábua vestibular remanescente no sucesso da preservação do rebordo.

Além disso, no que diz respeito aos achados exclusivos da revisão sistemática, pode-se concluir que:

i. Os resultados dos grupos controle (alvéolo vazio) sustentam os achados amplamente aceitos que, após a extração dentária, uma redução estatisticamente significante do rebordo alveolar na dimensão horizontal/ vestíbulo-palatina ocorre no caso de o alvéolo não sofrer nenhum tipo de tratamento.

ii. O preenchimento ósseo do alvéolo pode ser melhorado significativamente pelas técnicas de preservação.

iii. A maturação e mineralização do osso neoformado no alvéolo de extração pode ser acelerado ou melhorado com a preservação do rebordo.

iv. Devido à grande variedade de técnicas utilizadas, morfologia do defeito ósseo, período de cicatrização, assim como os tamanhos de amostras relativamente pequenos, as diferenças entre os métodos e materiais aplicados não pôde ser avaliada.

v. Não foram encontrados dados investigando a taxa de sucesso e sobrevivência de implantes colocados tanto em sítios de preservação de rebordo quanto em sítios controle.

vi. Não foram encontrados dados sobre qualidade de vida, preferência do paciente ou custos do tratamento comparando a preservação/ aumento no momento da extração vs. o aumento no momento da instalação do implante.

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