Bone regeneration in diabetic patients. A systematic review

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Abstract
Background: Oral bone regeneration techniques (OBRT) attempt to provide the appropriate bone volume and density to correctly accomplish dental implant treatments. The objective was to determine whether differences exist in the clinical outcomes of these techniques between diabetic and non-diabetic patients, considering the level of scientific evidence.

Material and Methods: A systematic review following PRISMA statements was conducted in the PubMed, Scopus and Cochrane databases with the search terms: “Diabetes Mellitus”, “guided bone regeneration”, “bone regeneration”, “alveolar ridge augmentation”, “ridge augmentation”, bone graft*, “sinus floor augmentation”, “sinus floor elevation”, “sinus lift”, implant*. Articles were limited to those published less than 10 years ago and in English.

Inclusion criteria were: human studies of all bone regeneration techniques, including at least 10 patients and the use of OBRT in diabetic and non-diabetic patients. Non-human studies were excluded. They were stratified according to their level of scientific evidence related to SORT criteria (Strength of Recommendation Taxonomy).

Results: The initial search provided 131 articles, after reading the abstracts a total of 33 relevant articles were selected to read the full text and analyzed to decide eligibility. Finally, seven of them accomplished the inclusion criteria: two controlled clinical trials, one cohort study and four case series.

Conclusions: A low grade of evidence regarding the use of OBRT in diabetic patients was found. The recommendation for this intervention in diabetic patients is considered type C due to the high heterogeneity of the type of diabetic patients included and the variability of the techniques applied.

Key words: Diabetes Mellitus, guided bone regeneration, bone regeneration.
Introduction

Alveolar crest volume reduction is a common consequence of tooth loss and can be, not only a difficulty for the treatment planning, but also a contraindication for dental implants placement. For this reason, bone augmentation procedures may be required before implant therapy in areas with moderate to severe bone loss. Bone regeneration techniques, include alveolar bone augmentation (ABA), guided bone regeneration (GBR) and sinus lift (SL) procedures.

Systemic diseases including diabetes mellitus (DM) could be formally considered a contraindication (1–3) for these interventions, especially in case of associated implant installation, due to its vascular and immune deficiencies.

One of the most prevalent systemic diseases worldwide is diabetes mellitus (DM), a chronic metabolic disorder composed of two subtypes: Type 1 DM involves 5–10% of diabetic patients and is an autoimmune disorder related to the destruction of pancreatic β-cells and the consequent deficit in insulin production; Type 2 DM, involves 90–95% of diabetic patients and is a multifactorial disease caused by environmental factors (e.g. obesity and sedentary lifestyle, corticosteroids intake) which lead to peripheral or cellular insulin resistance in genetically predisposed cases (4). The final result of decreased pancreatic production (type 1 DM) or peripheral cellular insensitivity to insulin (type 2 DM) is an increase in blood glucose levels (hyperglycemia). Treatment in both types of DM is focused on achieving a proper glycemic control in order to prevent the development of medical complications (3,5). In the long term, hyperglycemia promotes vascular complications which are one of the main causes of morbidity and mortality in this type of patients (6).

Chronic hyperglycemia also affects different tissue structures and produces an inflammatory effect, which results in a negative imbalance in the process of bone remodeling due to a decrease in bone formation rather than an increase in reabsorption as a consequence of the inhibitory effect of hyperglycemia on osteoblastic differentiation, impairment of parathyroid hormone activity which regulates phosphorus and calcium metabolisms (7) and a reduction in adherence, growth and accumulation of the extracellular matrix, as it has been demonstrated in experimental models that mineral homeostasis and osteoid production are significantly decreased in DM patients (6). Conversely, such models also showed that a persistent normoglycemic levels is directly correlated with an increased bone matrix and osteoid generation at a rate similar to controls, increasing bone formation around the dental implants (6–9). DM patients with good glycemic control also demonstrate a markedly reduced rate of periodontal bone loss, and a lower incidence of postoperative complications, compared to those with an inadequate one (3). Several studies have reported that the former group show successful dental implant rates similar to non-DM patients (4,11).

The main objective of this work was to review the current literature, taking into account the level of scientific evidence, to ascertain the rate of success of the oral bone regeneration techniques (OBRT) in DM patients.

Material and Methods

In October 2017 an electronic search was performed using PubMed, Scopus and Cochrane databases, following the PRISMA statements (10), in order to answer the following PICO question: “In patients with DM compared with non-diabetics are there the same results of OBRT in terms of bone regeneration, complications and success of dental implants?”

The search was limited to articles published in English between 2007 and 2017 with the search terms: “diabetes mellitus”, “bone regeneration”, “guided bone regeneration”, “alveolar ridge augmentation”, “bone graft*”, “sinus floor elevation” and “implant*”. A second search was carried out employing Boolean operators such as “OR/AND” and synonyms of the keywords to obtain articles that included two or more of the terms.

Finally, the Mesh Terms of the keywords were looked for, and a final search was performed: ("Diabetes Mellitus"[Mesh]) AND ("guided bone regeneration" OR “bone regeneration” OR “alveolar ridge augmentation” OR “ridge augmentation” OR bone graft* OR “sinus floor augmentation” OR “sinus floor elevation” OR “sinus lift”) AND implant*.

Inclusion criteria were: human studies, published in English from 2007 to 2017, regarding the use of OBRT in DM and non-DM patients. Exclusion criteria were non-human studies and case series including less than 10 patients or case-control studies. Articles were then stratified according to the level of scientific evidence using SORT criteria (11). On the basis of their scientific quality a grade of recommendation was given respect to the use OBRT in DM patients.

Results

The final electronic search performed on 31st October 2017 provided 58 articles from Pubmed, 72 from Scopus and 7 from Cochrane databases. Another three articles were added after an additional hand search based on the references of the papers already found.

After removing duplicates 131 articles were obtained, and after reading the abstracts, a total of 33 relevant articles were identified and selected to read the full text. Finally seven articles fulfilling inclusion criteria were included (1,5,12-16). The remaining 26 were excluded due to being descriptive studies (14,15), animal studies (16-24), no-DM patients (25), not performing bone
regeneration in the oral region (26) and not specifying whether OBRT was employed in DM patients (27–30). The flow-chart of the review process modified from the PRISMA statement (10) is shown in Figure 1. Two out of the seven selected articles were controlled clinical trials (1,5), one a retrospective cohort study (12) and four were retrospective case series (13-16).

The selected articles were classified according to the level of scientific evidence following SORT criteria (11): 3 of scientific evidence level 2 (1,5,12), and the remaining ones (13–16) of level 3. Table 1 summarizes the level of evidence of each study and the reasons for classifications.

Study design, duration, number of patients, gender, mean age, DM type, and OBRT applied are shown in Table 2.

The main characteristics of each study: number of patients who underwent OBRT (DM patients and non-DM ones), number of implants placed in native and regenerated bone, evaluation technique, failure criteria, and results are synthetized in Tables 3 and 4.

Regarding OBRT in DM patients the strength of recommendation, on the basis of the level of evidence in the available data, is level C. Because the inconsistency of the patients’ characteris-

**Discussion**

Diabetic patients have an increased incidence of periodontal disease and bone reabsorption (5), greater loss of alveolar bone (33,34) and more post-operative com-
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No systematic technique used; Retrospective CR (1). Huynh et al. (12), and Tawil et al. (1). Small sample; variation in treatment procedures; only 3–6 months of follow-up; examiner not blinded. Studies in non-controlled DM patients are even scarcer, implant therapy in such condition having been proven. Nonetheless, due to the increased incidence of risk factors and complications following implant placement surgery than non-DM ones (6). Due to this increased incidence of risk factors and complications, it has been shown that the success rate of dental implants in DM patients should be lower than in non-DM population (1,5,6,19), nevertheless, a good metabolic control can improve the survival rate of dental implants in such patients (1,3,6,20,21). Well-controlled DM is therefore not considered a full contraindication for implant therapy even though current literature suggests a certain decrease in the success rate of concurrent surgical procedures as would be the case of OBRT (5).

In our review process it has been identified some studies evaluating the success of bone regeneration techniques in DM animals (22–30), however, there were few regarding DM in humans despite the safety of performing implant therapy in such condition having been proven. Studies in non-controlled DM patients are even scarcer, probably due to the previously mentioned complications and ethical reasons. Only one publication with respect to OBR in non-controlled DM patients (HbA1c > 9%) was identified and includes only one DM patient underwent surgery (1). The regeneration techniques applied in the seven selected studies for systematic review analysis include GBR, SL, and bone grafts. Out of the 7, only one (5) aimed at comparing OBRT clinical results in DM and non-DM patients. The objective of the remaining six was to identify the predictive failure factors of certain OBRTs (13,14) and for dental implants (1,12,16), as well to compare dental implant survival rate between native and regenerated bone (15).

Some of these studies had a limited number of DM patients and a marked disproportion between both groups (DM and non-DM) (12–14). In addition, relevant DM patient data were only specified in two articles regarding illness duration, treatment applied to control the metabolic state, and pre/post-surgery HbA1c levels (1,5). Only Tawil et al. (1) considered the different glycemic levels as a possible individual risk factor for implant therapy and OBRT, concluding that HbA1c levels were the only multivariable and independent factor affecting the rate of complication.

On the other hand, as the principal aim of OBRT is to permit posterior implant therapy to be correctly performed, it is difficult to clearly separate the implant success/failure or complication rates from each other (15,16), neither to compare OBRT because there is no unified methodology to evaluate the results. One study only specified the OBR procedures without detailing the implants placed later, as Kaing et al. (13), or only described the implants placed in regenerated bone, ignoring the patients who underwent OBRT or the number of OBR procedures performed, as Tran et al.(15), Hasegawa et al. (16), and Tawil et al. (1). Huynh et al. (12) report the number of patients who underwent OBRT, but do not specify whether they were DM or non-DM ones. Tran et al. (15) and Hasegawa et al. (16) counted the number of implants placed in native and regenerated bone and compared survival rates, without specifying complications following implant placement surgery than non-DM ones (6).
| Author and year of publication | Study design | Follow-up period | Number (n), mean age (years) and gender of patients | DM type | Technique and material of OBR |
|--------------------------------|--------------|------------------|---------------------------------------------------|---------|-------------------------------|
| Tawil et al. 2008 (1)          | Prospective CCT | 1-12 years       | 90  
64.7 (43-84)  
57 M and 36 F | DM II WC, MC and NC  
SL and GBR  | |
| Edogan et al. 2015 (5)         | Prospective CCT | 1 year           | 24  
DP: 52.6±7.3 yNDP: 49.5±9.3  
11 M and 11 F | DM II WC  
GBR: CM + 50% AB + 50% mixture of AB and synthetic bone substitute. | |
| Huynh et al. 2008 (12)         | Retrospective CS | 7 years          | 136  
54.21 ±13.21 (16-82)  
78 M and 58 F | DM WC  
SL: G1: one-step antrostomy (28 impl)  
G2: two-steps antrostomy (58 Impl)  
G3: osteotome sinus floor–elevation technique. (30 Impl)  
IO bovine (100 Impl) and MRC in lateral window (37 Impl) | |
| Kaing et al. 2011 (13)         | Retrospective CS | 6 years          | 75  
37 (18-77)  
36 M and 49 F | DM WC non-insulin dependent.  
BG (86):  
- 41 particulate BG and 45 block grafts.  
- 64 AB.  
- 4 bone substitute.  
18 a combination of both. | |
| Moreno Vazquez et al. 2014 (14) | Retrospective CS | 8 years          | 127  
49 (19-77)  
50 M and 77 F | DM WC  
SL: (202): modified Cadwell-Luck procedure.  
- 55 block BG (115 Impl): 49 Onlay (93 Impl) y 6 Inlay (22 Impl)  
-147 particulate BG (249 Impl): 6 from cancellous tibia or iliac crest and 141 bone recovered by filter. | |
| Tran et al. 2016 (15)          | Retrospective CS | 27 years         | 1.222  
52.2 ±14.6 (18-87)  
518 M and 704 F | DM WC  
BRP (953):  
That includes all the GBR, SL, and socket/ridge preservation techniques with BG including auto, allo, xenografts and alloplasts. | |
| Hasegawa et al. 2016 (16)      | Retrospective CS | 84.8 months     | 366  
56.5±11  
144 M and 222 F | DM WC  
OBR:  
GBR: (739 Impl) CM  
SL: (196 Impl)  
Xenogeneic bone substitute mineral, bone replacement material, AB or mixture of these materials. | |

**Notes:**  
AB: autogenous bone, BG: bone grafts, BRP: bone regeneration procedures, CCT: controlled clinical trials, CM: collagen membrane, CS: cohort study, DISR: dental implant survival rates, DM: diabetes mellitus, DM II: type 2 DM, DM WC: DM well-controlled metabolically, DM MC: DM moderately controlled, DM NC: DM non-controlled, DP: diabetic patients, F: females, G (1-3): groups 1-3, GBR: guided bone regeneration, m: months, M: males, NB: native bone, Impl: implants, NDP: non-diabetic patients, NS: not specified, OBR: oral bone regeneration, SL: sinus lift, y: years.
Table 3. Number of patients who underwent OBRT (DM patients and non-DM ones), number of implants placed in native and regenerated bone, evaluation technique, failure criteria, and results.

| Author and year of publication | Patients distribution | Patients who had OBRT | Implants | Evaluation | Failure criteria | Results |
|-------------------------------|----------------------|-----------------------|----------|------------|-----------------|---------|
|                              |                      |                       |          |            |                 |         |
| Tawil et al. 2008 (1)         | TOTAL 90 NS          |                       | 285 214  | CE, periodontal parameters and R (periapical radiographs). | Implant loss. | *95% confidence interval and significance level 0.05. |
|                              | DP 45 NS             |                       | 143 112  |            |                 |         |
|                              | NDP 45 NS            |                       | 142 102  |            |                 |         |
| Erdogan et al. 2015 (5)       | TOTAL 24 30 0 43     |                       |          | MBL, histomorphometric analysis, RFA and wound-healing parameters. | Absence of bone formation at the recipient site. | *0.5 of standard deviation in both groups and significance level 0.05. |
|                              | DP 12 15 0 22        |                       |          |            |                 |         |
|                              | NDP 12 15 0 21       |                       |          |            |                 |         |
| Huynh et al. 2008 (12)        | TOTAL 136 57 157 116 |                       |          | CE and R DISR. | Implant failure: radiographic radiolucency, clinical mobility, pain and/or infection. | *Significance level 0.05. |
|                              | DP 7 NS 10 9         |                       |          |            |                 |         |
|                              | NDP 129 NS 147 107   |                       |          |            |                 |         |

BGSR: bone graft survival rates, CBCT: cone beam computed tomography, CE: clinical evaluation, DICR: dental implant complication rates, DIFR: dental implant failure rates, OPG: orthopantomogram, PC: postoperative complications, MBL: marginal bone loss, R: radiographs, SC: surgical complications.

the number of implants or techniques in both groups of patients. Huynh et al. (12) also calculated implant survival and success rates, specifying how many of each type were placed in DP and non-DP patients, and the total number who underwent OBRT. In the studies by Erdogan et al. (5) and Moreno Vazquez et al. (14) all the patients underwent OBRT and subsequent implant installation. Erdogan et al. (5) provide exact information regarding the number of placed implants (all with OBRT) in DM and non-DM patients, while Moreno Vazquez et al. (14) do not specify the number of implants placed in each group. In the case of Kaing et al. (13), all the patients had an OBRT and the study is focused on their results, without specifying the number of implants later inserted. Finally, in the study by Tawil et al. (1), patients were divided into DM and non-DM, and in both groups implants were placed with and without OBRT. In this way, they could estimate the differences related to the results between implants installed in regenerated bone and conventional ones in the two types of patients.

Finally, other factors contributing to the inconsistency of the results were: not mentioning or not classifying the bone defect, diagnostic methodology, and the criteria and methodology employed to evaluate the OBRT success or failure. Nonetheless, one study (13) did report differences in OBRT results in DM patients compared to non-DM ones.
Table 4. Continuation of table 3.

| Author and year of publication | Patients distribution | Patients who had OBRT | Implants | Evaluatio | Failure criteria | Results |
|--------------------------------|-----------------------|-----------------------|----------|-----------|----------------|---------|
| Kaing et al. 2011 (13)         | TOTAL 75              | 75                    | NB NS    | CE and R (OPG and CBCT) | BG failures; Complete or partial grafts failures, or any graft that had to be removed or regrafted for any reason. | * Significance level 0.05. |
|                               | DP 1                  | 1                     | NS NS    |           | BGSR.         | DM is a failure factor of the BG ($P=0.006^*$) |
|                               | NDP 74                | 74                    | NS NS    |           |                |         |
| Moreno Vazquez et al. 2014 (14) | TOTAL 127            | 127                   | 0 364    | CE and R.  | PC.            | * Significance level 0.05. |
|                               | DP 2                  | 2                     | 0 NS     |           |                | No differences between groups. |
|                               | NDP 125               | 125                   | 0 NS     |           |                |         |
| Tran et al. 2016 (15)          | TOTAL 1.222           | NE 1819               | 910      | CE of the implants; the absence or not of the implant at any point. | All dental Implants that were removed due to implant fracture, mobility, or non-reattachable peri-implant infections. | *95% confidence interval and significance level 0.05. |
|                               | DP 114                | NE NE                 | NE       |           |                | DM is not a failure factor of the Implant (with or without OBRT) ($P=0.07$) |
|                               | NDP 1.108             | NE NE                 | NE       |           |                | DISR (5 years) = 90% (OBR) y 92% (NB). DISR (10 years) = 79% (OBR) y 87% (NB). |
| Hasegawa et al. 2016 (16)      | TOTAL 366             | NE 967                | 935      | Clinical and radiographic MBL (OPG). | Significative MBL. Factors with a level of significance < 0.05. | *95% confidence interval and significance level 0.05. |
|                               | DP 22                 | NE NE                 | NE       |           |                | DM does not affect MBL (in NB or OBR) ($P=0.0244$) |
|                               | NDP 344               | NE NE                 | NE       |           |                |         |

RFA: resonance frequency analysis.

Conclusions
As OBRT is a fairly new surgical intervention, and the available literature is not only scarce but extremely heterogeneous, it is not possible to categorically assert the reliability of this procedure in well-controlled DM patients. As consequence, and following the principles of evidence-based odontology, the present analysis reports a grade C of recommendation regarding its use.

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Conflicts of Interest
The authors declare that there are no conflicts of interest in this study.