Effect of Growth Hormone Supplementation on Osseointegration: A Systematic Review and Meta-analyses

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Objectives: *The aim of this study was to assess whether growth hormone (GH) replacement therapy can enhance implant osseointegration.*

Materials and Methods: *A systematic literature search was conducted from 1982 to March 2016. A structured search using the keywords "growth hormone," "implants," and "osseointegration" was performed to identify preclinical and clinical* in vivo *controlled studies and was followed by a 2-phase search strategy. Initially, 31 potentially relevant articles were identified. After removal of duplicates and screening by title and abstract, 10 potential studies were included. Studies were assessed for bias and data were synthesized using a random-effects meta-analysis model.*

Results: *All studies were preclinical animal trials, and the follow-up period ranged from 2 to 16 weeks. Seventy percent of the included studies reported an increase in bone-to-implant contact in animals receiving GH compared with controls. Meta-analysis showed a significant mean difference for bone to implant between GH groups versus controls (no GH supplementation) of 10.60% (95% confidence interval: 3.79%–17.41%) favoring GH administration.*

Conclusion: *GH treatment seems to promote osseointegration around implants in preclinical studies; however, these findings must be assessed in highly controlled human clinical trials as a number of confounding factors may have influenced the outcomes of the included studies. (Implant Dent 2017;26:1–8)*

Key Words: somatotropin, hormone replacement therapy, new bone formation, dental implants

Osseointegration plays a critical role in the long-term success and survival of dental implants.[1–4] Histological studies have used various parameters (such as bone-to-implant contact [BIC], bone volume, and bone area [BA]) to assess osseointegration and periimplant new bone formation (NBF).[5–7] Various methods have been proposed in an attempt to enhance osseointegration and NBF around implants. These included the use of adjunct therapies such as Vitamin-D_3, parathyroid hormone, and various growth factor administration along with conventional implant placement protocol.[8–11] Interestingly, a limited number of studies[12–16] have also assessed the efficacy of growth hormone (GH) administration as an adjunctive therapy on the osseointegration of implants.

GH is an anterior pituitary hormone, which stimulates the liver and cartilaginous tissue to release a variety of bone growth factors.[17] Systemic GH treatment has been used in osteoporotic patients to increase bone turnover and reduce the risk for bone fracture.[18–20] GH is known to increase the mineralization potential of alveolar bone cells and periodontal cells by upregulating the messenger RNA expression of osteogenic markers.[21] Moreover, locally applied GH promotes osteoblast differentiation, increases bone mass and mechanical strength of bone, and stimulates longitudinal bone formation.[22–25] Guicheux et al[26,27] demonstrated that local delivery of GH was beneficial in healing bony defects. Tresguerres et al[28] placed implant in

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sockets containing GH and observed an increased bone formation compared with controls. Likewise, Manzano-Moreno et al[29] also showed a significant improvement in BIC after local delivery of GH when contrasted with BIC in the absence of GH. Interestingly, negative effects of GH on osseous regeneration have also been reported. Blom et al[30] observed that animals receiving GH had lower BA and osseointegration around implants than animals which did receive any GH treatment. In contrast, Stenport et al[31] reported no difference in periimplant bone regeneration between groups that did and did not receive GH therapy.

With this background, there seems to be a debate over the efficacy of GH supplementation in terms of augmenting osseointegration. Therefore, the purpose of this study was to systematically review the available evidence in relation to the efficacy of GH in the osseointegration of implants.

MATERIALS AND METHODS

The systematic search was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[32] Figure 1 illustrates the sequence of this process. Based on PRISMA recommendations, a focused question was created. The question addressed according to the Participants, Interventions, Control, Outcomes (PICO) principle was—What is the effect of GH on the osseointegration around implants?

(P) Participants: Subjects must have undergone implant treatment.
(I) Types of interventions: The intervention of interest was the effect of GH on osseointegration.
(C) Control intervention: Osseointegration in the absence of GH (placebo).
(O) Outcome measures: NBF and/or BIC around implants with or without GH supplementation.

A systematic search of the literature from 1982 up to and including March 2016 was conducted. The eligibility criteria were as follows: (a) original *in vivo* preclinical and clinical studies; (b) studies which included a control group (NBF around implants without GH administration). Letters to the Editor, reviews, case series, commentaries, conference abstracts, and case reports were excluded. Online databases of PubMed, Scopus, ISI Web of Science, and Google Scholar were searched using a combination of the terms GH, somatotropin, implants, osseointegration, and NBF. An initial evaluation of the title and abstracts of relevant articles was conducted by 2 authors, T.A and S. V.K. Next, screening of full texts of articles was independently performed. Reference lists of potential papers were handsearched to identify any relevant studies. Any discrepancies in the inclusion of an article were resolved by discussion among the authors. A total of 31 articles were identified, of which 10 fulfilled our eligibility criteria and were included in the review. The excluded studies are enlisted in appendix A, with the reason for exclusion in parenthesis. Kappa scores (0.90) were used to determine the level of agreement between the 2 reviewers.[33]

The Critical Appraisal Skills Program (CASP) Cohort Study Checklist[34] was used to conduct a quality assessment of the included studies. The CASP tool uses a systematic approach based on 12 specific criteria, which are as follows: (1) Study issue is clearly focused; (2) Cohort is recruited in an acceptable way; (3) Exposure (GH administration) is accurately measured; (4) Outcome (osseointegration and/or NBF around implants) is accurately measured. (5) Confounding factors are addressed; (6) Follow-up is long and complete; (7) Results are clear; (8) Results are precise; (9) Results are credible; (10) Results can be applied to the local population; (11) Results fit with available evidence; and (12) There are important clinical implications. A response of either Yes, No, or Cannot tell was given to each criterion. A study could have a maximum score of 12. CASP scores were used to grade the methodological quality of each study assessed in the present systematic review.

Pairwise meta-analysis comparing test and controls was conducted for the primary outcome, as previously described.[35,36] Outcome measures were combined with a random-effects model using the DerSimonian-Laird method.[36] Heterogeneity among the included studies for each outcome was assessed using the Q-statistic and I^2-statistic.

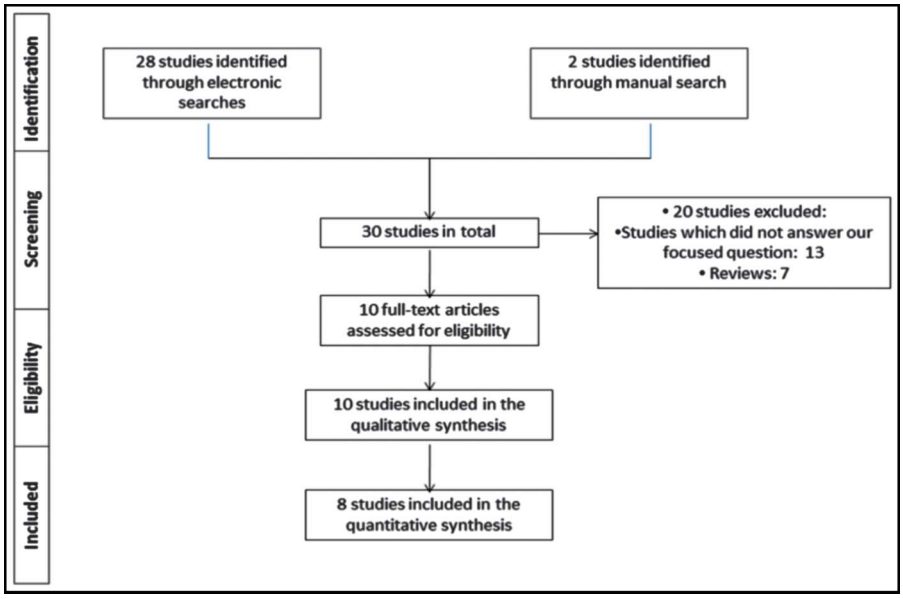

Fig. 1. Article selection flowchart for the systematic review according to the PRISMA guidelines.

RESULTS

General Characteristics of Included Studies

The general characteristics of the included studies are summarized in

Table 1. General Characteristics of the Included Studies

Authors	Study Subjects	Sex	Mean Age (Range) (mo)	Study Groups (No. of Implants)	Analysis Methods	Specific Parameter	Follow-up (wk)	Outcome
Morberg et al[14]	34 Mice	N.A	N.A (4–6.5)	Control: (22) implants without GH; Test: (12) implants with GH	Histology, HIST	BIC, BA, BT	16	Increased bone formation in test compared with controls
Blom et al[30]	8 Goats	Female	N.A (36–48)	*Control: (20) implants without GH; *Test: (20) implants with GH	Histology	BIC, BA	6	Decreased bone formation in test compared with controls
Stenport et al[31]	16 Rabbits	N.A	16 (N.A)	Control: (16) implants with saline; Test: (16) implants with GH	Histology, HIST, RFA, RTT, DEXA	BIC, BA, BMD	8	No difference in bone formation between test and controls
Tresguerres et al[37]	8 Rabbits	Female	3 (N.A)	Control: (8) implants without GH; Test: (8) implants with GH	Histology, HIST, densitometry	BIC, BA, BMD	2	No difference in bone formation between test and controls
Tresguerres et al[28]	8 Rabbits	N.A	3 (N.A)	Control: (8) implants without GH; Test: (8) implants with GH	HIST	BIC	2	Increased bone formation in test compared with controls
Tresguerres et al[16]	32 Rabbits	Female	3 (N.A)	Control: (32) implants without GH; Test: (32) implants with GH	Histology, HIST densitometry	BIC,† BA, BMD	1, 2, 3, and 6	Increased bone formation in test compared with controls†
Gomez-Moreno et al[29]	12 Dogs	Male	N.A (14–16)	*Control: (24) implants without GH; *Test: (24) implants with GH	HIST	BIC, BA	2	Increased bone formation in test compared with controls
Calvo-Guirado et al[13]	12 Dogs	Male	N.A (14–16)	*Control: (24) implants without GH; *Test: (24) implants with GH	HIST	BIC, BA	5 and 8	Increased bone formation in test compared with controls
Muñoz et al[15]	12 Dogs	N.A	18 (N.A)	*Control: (24) implants without GH; *Test: (24) implants with GH	HIST, SEM	BIC, BA,	2, 5, and 8‡	Increased bone formation in test compared with controls‡
Abreu et al[12]	14 Rabbits	Male	30 (N.A)	Control: (14) implants without GH; Test: (14) implants with GH	Histology, SEM	BIC, pullout test	2 and 6	Increased bone formation in test compared with controls

*Split-mouth design.
†Significant only for BIC.
‡Significant only at 8 weeks.
BMD, bone mineral density; BT, bone thickness; DEXA, dual-energy x-ray absorptiometry scan; HIST, histomorphometry; N.A, not available; RTT, removal torque test; SEM, scanning electron microscope.

Table 2. GH Form, Route of Administration, and Frequency of the Studies Included

Authors	Type	Form	Route of Administration	Concentration	Duration (wk)	Frequency	Mode of Delivery
Morberg et al[14]	Bovine	Transgenic mice	Endogenously produced	1124 ng/mL	N.A	Preimplant and postimplant	Systemic
Blom et al[30]	Human	Powder	Implant coating	3 IU	6	Postimplant	Local
Stenport et al[31]	Human	N.A	Subcutaneous pump	0.3 $U \cdot kg^{-1} \cdot d^{-1}$	8	Postimplant	Systemic
Tresguerres et al[37]	Human	Powder	Placed in implant socket	4 IU	2	Postimplant	Local
Tresguerres et al[28]	Human	Powder	Placed in implant socket	4 IU	2	Postimplant	Local
Tresguerres et al[16]	Human	Powder	Placed in implant socket	4 IU	1,2,3, and 6	Postimplant	Local
Gomez-Moreno et al[29]	Human	Powder	Placed in implant socket	4 IU	2	Postimplant	Local
Calvo-Guirado et al[13]	Human	Powder	Placed in implant socket	4 IU	5 and 8	Postimplant	Local
Muñoz et al[15]	Human*	Powder	Placed in implant socket	4 IU	2, 5, and 8	Postimplant	Local
Abreu et al[12]	Human	Powder	Placed in implant socket	1 IU	2 and 6	Postimplant	Local

*1.2 mg of melatonin added to GH.
IU, international unit.

Table 1. All studies[12–16,28–31,37] were experimental and performed in a university setting. Rabbits, dogs, goats, and mice were used in 5, 3, 1, and 1 study, respectively.[12–16,28–31,37] Five studies[13,16,29,30,37] reported the sex of the animals: 2 studies used female rabbits,[16,37] 2 studies used male dogs,[13,29] and in 1 study female goats[30] were used. The mean age for the rabbits and dogs was 3 to 16 months and 18 months, respectively.[15,16,28,31,37] In all studies, the study group received GH and implants, and the control group where implants were placed without GH.[12–16,28–31,37] A split mouth design was used in 4 studies.[12,13,15,30] In the study by Tresguerres et al,[37] rabbits were ovariectomized to create osteoporosis-like conditions. The follow-up duration after implant placement ranged from 2 weeks to 16 weeks.[12–16,28–31,37]

GH-Related Characteristics

Details on GH administration are enlisted in Table 2. Human GH was used in 8 studies,[12,13,16,28–31,37] and in the study by Morberg et al[14] transgenic rats expressing bovine GH were used. Munoz et al[15] used GH along with 1.2 mg of melatonin. In 8 studies,[12,13,15,16,28–30,37] GH was provided in the powder form. Stenport et al[31] used a subcutaneous pump to administer GH. In 8 studies,[12,13,15,16,28–30,37] GH was locally administered, of which in 7 studies[12,13,15,16,28,29,37] GH was placed in sockets before implant placement and in 1 study[30] it was used as a coating on the implants. GH was administered systemically in 2 studies.[14,31] The concentration of GH ranged from 1 to 4 IU.[12,13,15,16,28,29,37] The duration for administration

Table 3. Implant Type, Shape, Location, and Surface-related Characteristics in the Included Studies

Authors	Number and Type	Implant Dimensions (D × L × W in mm)	Location of Implant	Implant Shape	Surface Characteristics
Morberg et al[14]	(N.A) Ti	1.4 × 2	Nasal cavity	Screw	N.A
Blom et al[30]	40 Ti alloy	5.1 × 5	Femur	Grooved cylindrical	Rough
Stenport et al[31]	32 Ti	3.7 × 6	Tibia	Screw	N.A
Tresguerres et al[37]	(N.A) Ti	5 × 10 × 0.5	Tibia	Sheet	Rough
Tresguerres et al[28]	(N.A)	3.3 × 8	Tibia	Screw	Rough
Tresguerres et al[16]	(N.A) Ti	5 × 10 × 0.5	Tibia	Sheet	Rough
Gomez-Moreno et al[29]	96 (N.A)	3.25 × 10	Mandible	Threaded cylindrical	Rough
Calvo-Guirado et al[13]	48 (N.A)	3.25 × 10	Mandible	Threaded cylindrical	Rough
Muñoz et al[15]	96 (N.A)	3.25 × 10	Mandible	Threaded cylindrical	Rough
Abreu et al[12]	14 Ti	2.2 × 6	Tibia	Cylindrical	Rough

N.A indicates not available; Ti, Titanium implant.

Table 4. Methodological Quality Assessment Using CASP for the Studies Included

Authors	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Total Quality Score Outof 12
Morberg et al[14]	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Cannot tell	Yes	7
Blom et al[30]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Cannot tell	Yes	8
Stenport et al[31]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Cannot tell	Yes	8
Tresguerres et al[37]	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Cannot tell	Yes	8
Tresguerres et al[28]	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Cannot tell	Yes	7
Tresguerres et al[16]	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Cannot tell	Yes	7
Gomez-Moreno et al[29]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Cannot tell	Yes	8
Calvo-Guirado et al[13]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Cannot tell	Yes	8
Muñoz et al[15]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Cannot tell	Yes	8
Abreu et al[12]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Cannot tell	Yes	8

varied from 1 to 8 weeks.[12,13,15,16,28–31,37] GH was provided in the preimplant and postimplant placement period in the study by Morberg et al,[14] and in the remaining 9 studies GH was available only after implant placement.[12,13,15,16,28–31,37]

Implant-Related Characteristics of the Studies

Table 3 summarizes the implant-related characteristics of the studies that fulfilled our eligibility criteria. In these studies, the numbers of implants placed ranged between 14 and 96.[12,13,15,29–31] In 5 studies,[12,13,15,29–31] cylindrical implants were used. Screw-shaped and sheet implants were used in 3 and 2 studies,[14,16,28,31,37] respectively. The lengths and diameters of implants used ranged between 2 to 10 mm and 1.4 to 5 mm, respectively. In the studies by Morberg et al[14] and Blom et al,[30] implants were placed in the nasal cavities and femurs, respectively. In the remaining studies, the mandible[13,15,29] or tibia[12,16,28,31,37] was the site of implant placement. Seven studies specified that rough-surfaced implants were placed in the animals.[12,13,15,16,29,30,37]

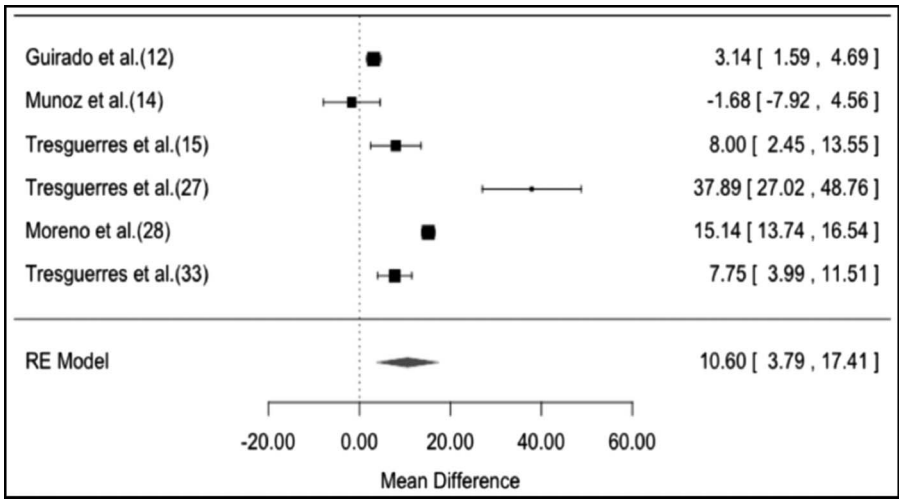

Fig. 2. Forest plots presenting mean difference for bone-to-implant between GH groups versus controls (no GH supplementation) for the included studies.

Main Outcome of Studies

Outcomes of all studies were based on histomorphometric analyses and/or histological, scanning electron microscope, or mechanical testing.[12–16,28–31,37] The specific parameters that were recorded were BIC, BA, bone thickness, and bone mineral density.[12–16,28–31,37] Seven studies[12–16,28,29] reported an increase in bone formation around implants in the presence of GH compared with controls, 2 studies[31,37] reported no effect of GH on bone formation around implants, and Blom et al[30] reported a decrease in periimplant bone formation in animals receiving GH compared with control animals.

Quality Assessment of Included Studies

Quality assessment of the individual articles is summarized in Table 4. Quality assessment showed that all studies[12–16,28–31,37] were conducted in experimental animals, and the total quality score ranged from 7 to 8. As all the studies were performed in animals, the application of these results to human population is limited. The most common shortcoming among

Table 5. Mean Values and SDs for Bone-to-Implant of Studies Included in Meta-analysis

	Test		Control			
Authors	Mean	SD	Mean	SD	Study Groups (n)	Outcome Measure
Blom et al[30]	0.11	0.38	0.41	1.28	Control:(5); Test: (5)	% BIC
Stenport et al[31]	29	8	31	11	Control: (16); Test: (16)	% BIC
Tresguerres et al[37]	45.25	1.22	37.5	1.48 (SE)	Control: (8); Test: (8)	% BIC
Tresguerres et al[28]	66.67	4.9	28.78	2.6 (SE)	Control: (8); Test: (8)	% BIC
Tresguerres et al[16]	34	2	26	2 (SE)	Control: (32); Test: (32)	% BIC
Gomez-Moreno et al[29]	40.19	2.51	25.05	2.43	Control: (24); Test: (24)	% BIC
Calvo-Guirado et al[13]	39.61	2.34	36.47	3.09	Control: (24); Test: (24)	% BIC
Muñoz et al[15]	31.47	10.69	33.15	11.35	Control: (24); Test*: (24)	% BIC, Test group: GH and melatonin

% BIC indicates bone/implant contact percentage (ratio of the part of implant in contact to bone tissue and the implant perimeter).

all studies was the short term and incomplete follow-up of the experimental groups. Furthermore, confounding factors were not discussed in any of the studies.[12–16,28–31,37] Thus, on average, the quality of studies assessing the influence of GH on NBF and osseointegration around implants was good. The studies were clearly focused, with well-reported results, and most studies[3,12,13,15,30,31] reported receiving ethical approval to conduct the experiments.

Quantitative Results of Studies

After data extraction and, when necessary, communication with authors, 8 studies[13,15,16,28–30,37] were included in the meta-analysis of the weighted mean differences of BIC (Fig. 1). The remaining 2 studies[12,14] were excluded from the meta-analysis because of lack of BIC data. Figure 2 presents the forest plots and summary estimates for weighted mean differences of BIC between test animals receiving GH and control animals, respectively. A significant difference was found between control and test groups with a mean of 10.60% (SE:3.48) favoring the test group ($P = 0.002$) (Q [df = 5] = 166.8, P-val < 0.001, $I^2 = 97\%$). The mean differences between BIC among test and control groups were estimated as the effect-size measure (Table 5).

DISCUSSION

In this study, we evaluated the role of adjunct GH therapy on osseointegration of implants through a systematic review of pertinent studies. In total, 10 studies[12–16,28–31,37] were included of which 70% of the studies[12–16,28,29] showed that GH increased NBF around implants. The strength of this observation is supported by the meta-analyses results. From these results, it is tempting to speculate that GH administration plays a role in the osseointegration around implants. However, it is likely that the results of these studies[12–16,28,29] may have been influenced by a variety of factors. First, all studies were performed in animal models with a maximum follow-up duration of 16 weeks. From these results, it seems difficult to hypothesize the long-term effects of GH on osseointegration. Clinically, long-term GH administration has shown to increase bone resorption up to the initial 6 months of therapy.[38,39] Hence, it is emphasized that the results of these studies be prudently interpreted if GH is to be used to improve primary implant stability and aid early loading protocols in humans. Other parameters that may have influenced the results reported in the present systematic review include the dosages, route, type of GH administered, and different animals in the studies[12–16,28,29] reporting a positive role of GH in implant osseointegration. For example, Morberg et al[14] reported an increase in NBF around implants placed in the nasal cavity of transgenic mice producing bovine GH at almost 10 times the concentration of GH in normal mice. Abreu et al[12] compared the effects of 1 IU of powdered human GH in the tibiae of male rabbits with control rabbits not receiving GH. Calvo-Guirado et al[13] reported enhanced bone regeneration in mandibular implants of beagle dogs receiving 4 IU of locally delivered GH compared with controls. Although these studies[12–16,28,29] all reported an increased NBF in animals receiving GH, because of the variation in the dose of GH provided, it is difficult to estimate the precise concentration at which this effect can be expected in humans. In addition, it raises the question of which form of GH (human/bovine) might be more effective in promoting implant osseointegration. Also, it is difficult to determine the contribution of the route of GH delivery (local/systemic) on improving BIC. Therefore, these results must be interpreted with caution before they can be applied in clinical settings.

Implant surface roughness plays an important role in osseointegration.[40,41] It is known that implant surface roughness is osteopromotive and increases periimplant cellular adhesion which promotes primary stability at the time of placement.[42–44] In addition, Butz et al[45] recommended using acid-roughened implants over machined implants for superior osseointegration and improved biomechanical properties of bone. Approximately 85% of studies that showed a positive effect of GH on BIC used rough-surfaced implants in both the experimental and control groups. Therefore, it is likely that the positive influence of GH on NBF may be attributed to the surface characteristics of the implants used in these

studies. It is hypothesized that further studies with smooth and rough-surfaced implants are warranted to clarify the influence of GH supplementation on osseointegration.

In 90% of the studies,[12–16,28–31,37] implants were placed in dense cortical bone (tibia, femur, and mandible). Jaffin and Berman[46] have shown that implants placed in bones, dense cortical bone, have a significantly higher success rates compared with implants placed in cancellous bone. Thus, the application of the outcomes of the included studies to implants placed in the maxilla, where the bone is more trabecular, may be questionable. Similarly, whether GH will have a beneficial effect on periimplant NBF in persons with compromised bone quality because of osteoporosis, resorbed ridges or long-term bisphosphonate therapy, remains to be determined. It would be interesting to know if locally applied GH can be used to assist bone formation in guided bone regeneration before implant placement in such cases. Furthermore, it is tempting to speculate whether GH can promote NBF among patients with periimplant diseases. Surgical management of periimplantitis involves resective and regenerative techniques using a variety of materials to aid NBF such as hydroxyapatite, porous titanium granules, and xenografts.[47] Whether GH can be used in a similar manner to stimulate bony healing around diseased implants remains to be determined. Future studies in this regard are warranted.

It is likely that apart from the dissimilarities in GH parameters, there are other factors that may have influenced the outcomes of the reviewed studies. From a clinical perspective, local and systemic factors such as poor oral hygiene, smoking, poorly controlled diabetes mellitus, and advancing age have been shown to jeopardize BIC.[48,49] Therefore, it remains to be determined whether the GH will facilitate osseointegration in persons with poor plaque control, elderly individuals (>65 year old), and poorly controlled metabolic diseases. Further randomized controlled trial with standardized parameters may be helpful in this regard.

Conclusions

Within the limits of this review, GH treatment seems to promote osseointegration around implants. However, these findings must be applied to clinical setting with caution as a number of confounding factors may have influenced the outcomes of the included studies.

Disclosure

The authors claim to have no financial interest, either directly or indirectly, in the products or information listed in the article.

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Roles/Contributions By Authors

T. Abduljabbar, F. Vohra, and G. E. Romanos: Performed the literature search and wrote the background. S. V. Kellesarian: Formatted the tables. Z. Akram: Performed the meta-analysis. G. A. Kotsakis and M. Yunker: Wrote the results and revised the manuscript for English vocabulary and expression. F. Javed: Designed and supervised the study and wrote the discussion.

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