British Journal of Medicine & Medical Research
7(12): 1026-1034, 2015, Article no.BJMMR.2015.418
ISSN: 2231-0614

SCIENCEDOMAIN *international*
www.sciencedomain.org

Synthetic Bone Substitutes in Combination with Growth Factors for Maxillary Sinus Floor Augmentation: A Mini-review

Cleopatra C. Nacopoulos[1*], Ismene Dontas[1], Efstathios Chronopoulos[1], Lubna Khaldi[1], Anna Maria Vesala[1], Ioannis K. Triantafyllopoulos[1] and Nikolaos Papaioannou[1]

[1]Laboratory for Research of the Musculoskeletal System, School of Medicine, University of Athens, Greece.

Authors' contributions

This work was carried out in collaboration between all authors. Author CCN wrote the initial graft and performed the literature search. Author ID had the idea and revised the draft. Authors EC, LK, IT and NP revised the draft. Author AMV contributed to the literature search. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2015/15613
Editor(s):
(1) Ibrahim El-Sayed M. El-Hakim, Ain Shams University, Egypt and Riyadh College of Dentistry and Pharmacy, Riyadh, Saudi Arabia.
(2) Vijay K. Yadav, Systems Biology of Bone Group, Wellcome Trust Sanger Institute, Cambridge, UK.
Reviewers:
(1) Anonymous, Japan.
(2) Angelo Troedhan, Faculty of Dentistry, Health Science University Vientiane, Laos.
(3) Anonymous, USA.
(4) Anonymous, Brazil.
(5) Anonymous, USA.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=952&id=12&aid=8863

Mini-review Article

Received 8th December 2014
Accepted 3rd April 2015
Published 17th April 2015

ABSTRACT

Objective: Growth factors have been applied in maxillary sinus augmentation with clinically successful results. The purpose of this article is to evaluate the effectiveness of growth factors in combination with various synthetic scaffolds.

**Corresponding author: Email: cleopatra.nacopoulos@gmail.com;*

Methods and Materials: A systematic review of studies examining the effects of synthetic materials in combination with growth factors were performed.

Results: Twelve (1 human and 11 animal) studies were eligible for inclusion. Due to the great heterogeneity of the studies regarding design, materials and outcomes, a meta-analysis was not performed. The majority of the studies show a reduction in healing time and enhancement of bone formation within the subantral environment. Bone Morphogenetic Protein-2 and GDF-5 were the two most common osteoinductive factors studied, showing a significant effect on new bone formation. Moreover, initial outcomes of trials with stem cells genetic transformation, that results in increased production of growth factors, are positive and justify further research.

Conclusion: The incorporation of growth factors into the synthetic scaffold may be beneficial regarding the healing process.

Keywords: Sinus augmentation; synthetic materials; PRF; growth factors.

1. INDRODUCTION

Maxillary sinus augmentation technique is a common surgical procedure for creating adequate bone volume before implant placement [1]. During the maxillary sinus floor elevation procedure, the space created between the residual maxillary ridge and the elevated Schneiderian membrane is usually filled with grafting material [2,3]. This membrane is periosteum that acts as a major carrier of bone-regeneration [4-9], whereas the various grafting materials do not provide the cellular elements necessary for osteogenesis and are only osteoconductive [10].

Osteoconductiveness has long been recognized as an important mechanism in bone regeneration. It occurs in the presence of a scaffold that allows for vascular and cellular migration, attachment, and distribution [11]. Factors that accelerate angiogenesis in the periphery of the tissues and stimulate bone healing and remodeling are useful in this respect. It is well known that a close spatial and temporal relationship exists between osteogenesis and angiogenesis and that growth factors can be used to augment both neovascularization and osteogenesis across bone defects [12-14].

The consensus of the sixth European Workshop on Periodontology [15] emphasized the research need to answer comparative questions to establish the clinical benefit of bone augmentation with respect to alternative treatments [7]. This review aims to determine whether there are advantages in using growth and other osteoinductive factors with bone substitutes for sinus floor augmentation.

2. METHODS AND MATERIALS

A systematic search strategy was used. In the initial phase of the review, a computerized literature search was performed in Medline and Embase databases. Keywords were “sinus augmentation” OR “sinus floor augmentation” OR “sinus floor elevation” OR “sinus grafting” OR “sinus lift” AND “growth factors” OR “osteoinductive factors”. There was no language restriction. Additional publications were identified from the reference lists of the retrieved articles. A search with the utilization of MeSH terms ("Sinus Floor Augmentation" AND "Vascular Endothelial Growth Factors", "Hematopoietic Cell Growth Factors", “Endothelial Growth Factors", "Transforming Growth Factors", Fibroblast Growth Factors", "Growth Differentiation Factors") did not provide additional publications.

2.1 Inclusion Criteria

Studies examining the effects of synthetic materials in combination with growth factors.

2.1.1 Exclusion criteria

- Reports with a sample size of less than 5 patients or 5 animals, in case of experimental studies.
- Redundant publications.
- Letters, reviews and comments.
- PRP studies (since there are a number of systematic reviews and meta-analyses indicating that PRP treatment does not seem to improve the clinical outcome of sinus lift procedures [16,17] or may lead to inferior outcomes with regard to the osseointegration of dental implants and the

height of new bone as compared with the use of pure growth factors [18].

Titles, abstracts or articles derived from this broad search were independently screened by two authors (CCN and AMV) based on the inclusion criteria. |Newcastle-Ottawa Quality Assessment Scale Case Control Studies" was utilized for the evaluation of human studies [19].

3. RESULTS

By the electronic literature search, a total of 114 titles were identified. One more study was added after the manual screen of the references lists. Twelve original articles fulfilled the inclusion criteria (1 human and 11 animal studies) as shown in supplementary Fig. 1 (Link: www.sciencedomain.org/download.php?f=Supplimentary7122014BJMMR15613.pdf&aid=8863&type=a) and Table 1.

A variety of animal models were utilized for experiments with rabbits being the most common.

Synthetic materials tested were hydroxyapatite (HA), b-Tricalcium phosphate (β-TCP), calcium phosphate cement (CPC), poly-d, l-lactic-co-glycolic acid gelatine (PLPG) sponge, silk gel and others.

Osteoinductive factors that were most studied were Bone Morphogenetic Protein (BMP) and Growth and Differentiation Factor-5 (GDF-5).

Osseointegration of dental implants, implant success rate, bone-to-implant contact, histologic or radiological evaluation of new bone formation were the most common outcomes.

Only one human study was identified of relatively good quality based on NEWCASTLE-OTTAWA QUALITY ASSESSMENT SCALE for case control studie (Table 1). Due to the great heterogeneity of the studies regarding design, materials and outcomes, a meta-analysis was not performed.

As it can be seen in Table 1, synthetic materials combined with growth factors lead to superior results than alloplasts alone in the majority of studies. In more details, animal studies examined this combination have shown superior results in regard to osseointegration of dental implants, implant success rate, bone-to-implant contact, histologic and radiological evaluation of new bone formation. Moreover, both human and animal studies have induced comparable histologic, histometric and radiological evidence of bone formation with autologous bone.

As shown in animal studies, bone tissue engineering is a promising method, especially with the use of bone marrow mesenchymal stem cells (bmMSC) that have been genetically modified to express growth factors (Table 1).

4. DISCUSSION

Although, hydroxyapatite, β-TCP, bioactive glass and xenografts have demonstrated almost equal efficacy for use in sinus lift procedures the question on how to achieve the most favorable bone-healing capacity, from a biological prospective, remains [32,33]. Most research studies on the bone biomaterials for sinus-lift tried therefore to improve the quality of the regenerated bone volume and to accelerate its healing for early implant placement [13,17]. Noteworthy research activity (both experimental and clinical) was identified in the area of growth factors-induced bone augmentation [15] with promising results.

4.1 Special Considerations

Although, sinus lift is one of the best *in vivo* human model for the testing of bone biomaterials in the maxillofacial area [13] and the combination of bone grafts and osteoinductive factors is currently being discussed as a suitable method for enhancing de novo bone formation, there are several considerations regarding favorable outcomes of this method.

First of all, implant survival may be confounded by factors other than the graft material used for sinus floor augmentation, like patients' age or smoking habits [8]. Moreover, osseointegration of implants placed in the augmented area is a poor parameter for comparing different biomaterials, because integration is always present, regardless of the materials used [9]. Finally, one should also keep in mind that implant success as presented in animal research cannot be extrapolated as such to the clinical situation [9].

Table 1. Human and animal studies combining growth factors or PRF with various types of bone substitutes NOS: NEWCASTLE-OTTAWA QUALITY ASSESSMENT SCALE

Studies	Humans/Animals	Test group (TG)	Control group (CG)	Results	Conclusion-commends
Stavropoulos A, et al. [20], 2011	humans	two groups: rhGDF-5/β-TCP with at 3-month or 4-month healing period	autologous bone/ β-TCP	91,5 success rate in EG, 28-31,4% new bone formation in TG vs 31,8% in CG	combination of alloplast with a growth factor resulted in comparable amounts of new bone and of similar quality as those obtained with an autologous bone/ β-TCP composite graft, NOS********
Allegrini S Jr, et al. [21], 2003	rabbits	bovine bone powder/HA/collagen/ BMP	bovine bone powder/HA/collagen	BMP stimulated bone formation during the early period of healing and resulted in more newly formed bone	
Gruber RM, et al. [22], 2008	pigs	two groups: 400μgr rhGDF-5/TCP, 800μgr rhGDF-5/TCP	TCP	more volume density and bone-to-implant contact rates in the experimental groups	
Gruber RM, et al. [23], 2009	pigs	rhGDF-5/β-TCP	autogenous/β-TCP	more volume density and bone-to-implant contact rates in the experimental group	GDF-5 significantly enhanced bone formation
Jiang XQ, et al. [24], 2009	rabbits	three groups: bmMSC/TCP, AdEGFP-bmMSC/TCP, AdBMP-2-bmMSC/TCP	TCP	more bone formation in the AdBMP-2-bmMSC/TCP group	Commend: this study as well Sun's and Xia's utilize gene modified growth factor producing MSC rather than pure growth factors
Sun XJ, et al. [25], 2010	rabbits	two groups: AdBMP-2-bmMSC/ ceramic material	AdEGFP-bmMSC/ ceramic material	more bone formation in AdBMP-2-bmMSC/ ceramic material group	growth factors-gene enhanced bone tissue engineering is a promising method

Ho SK, et al. [26], 2010	rabbits	three groups: DBM, DBM/BMP, poloxamer gel/BMP	autogenous bone	DBM/BMP resulted in more bone formation in 2 week and in equal amount of new bone with control group in 8 weeks	BMP-containing bioimplants demonstrated promise as alternatives to autogenous bone grafts for sinus-augmentation procedures. These bioimplants had more rapid initial bone production than all other materials
Gutwald R, et al. [27], 2010	sheeps	rhBMP-2/PLPG sponge	autograft	bone-to-implant contact (BIC) and bone density (BD) were significantly higher in the test group if the implants were placed at the time of the sinus lift	growth factors may be proved useful in early implant placement
Kim BJ, et al. [28], 2011	rabbits	two groups: rhBMP-2/TCP, PRF/TCP	TCP	more bone formation in TGs and especially in PRF/TCP group	
Xia L , et al. [29], 2011	rabbits	four groups: BMP-2/CPC, bmMSC/CPC, bmMSC/BMP-2/CPC	CPC	more bone formation in experimental groups especially those with bmMSC	rhBMP-2/CPC possessed excellent osteoinductive ability, while combining with bMSCs could further promote new bone formation and maturation in maxillary sinus elevation
Zhang W, et al. [30], 2011	rabbits	three groups: silk gel/BMP-2, silk gel/VEGF, silk gel/VEGF/BMP-2	silk gel	more bone formation in silk gel/VEGF/BMP-2 group	
Xia L, et al. [31], 2011	rabbits	four groups: BMP-2 and Nell-1 modified bmMSC and TCP, BMP-2 modified bmMSC and TCP, Nell-1 modified bmMSC and TCP, EGFP modified bmMSC and TCP		Nell-1 and BMP-2 gene-transduced autologeous bMSCs/β-TCP complex had the largest bone area and most mature bone structure among the groups	nell+1 and BMP-2 have a synergistic effect

Probably, one of the most noticeable facts in this review's Table is the great heterogenicity in methods and outcomes of the studies. Various defects, surgical procedures, synthetic materials, growth factors and their concentration, as well as animal species were used. One or two stage techniques and lateral or crestal approaches have different indications [34]. The various ceramics or other synthetic materials have distinct absorption rates and histomorphometric results.

Moreover, different growth factors elicit diverse molecular signaling pathways in cells that participate in bone regeneration and animal models are not necessarily identical regarding bone trauma responses. In addition, bone formation, volume density, implant survival, and bone-to-implant contact are the most common outcomes reported in the various studies and these are not necessarily inter-related significantly. Despite this great diversity of the studies regarding their methods and outcomes, valuable conclusions can still be elicited.

4.2 Osteinductive Factors

BMP-2 and GDF-5 were the two most common osteoinductive factors studied, showing a significant effect on new bone formation [23,29]. Both belong to the TGF-β superfamily of proteins acting as potent regulators during embryogenesis and bone and cartilage formation and repair in adults. Growth differentiation factor 5 is a member of the bone morphogenic protein (BMP) family. BMPs have attracted a lot of publicity lately, especially in the developing field of regenerative medicine since BMP-functionalised coatings have proven to be a simple and effective strategy for osteoinductive functionalisation of orthopaedic implants [35]. These glycoproteins act as a disulfide-linked homo- or heterodimers, being potent regulators of bone and cartilage formation and repair, cell proliferation during and bone homeostasis [36].

4.3 Future Directions

Sinus augmentation is considered to be a very secure procedure, and the consensus is that most bone materials can give good results in terms of bone healing and implant survival [13]. Furthermore, surgical intervention itself can liberate growth factors and autogenous bone morphogenic proteins responsible for wound healing and bone regeneration [37-39]. However, there are clinical and experimental indications that the incorporation of additional growth factors into the sinus graft may reduce the healing time and enhance bone formation within the subantral environment.

Finally, tissue engineering with the incorporation of mesenchymal stem cells may be the most promising technology [40]. In this new cell-based tissue engineering approach, stem cells are combined with an osteoconductive scaffold and growth factors and applied immediately to the patient [41,42]. As it can be seen in Table 1, even more advanced techniques have been developed lately concerning stem cells' genetic transformation in order to produce increased concentrations of growth factors and experimental data have yielded positive results.

5. CONCLUSION

The overarching aim of this review was to determine whether there are advantages in using growth and other osteoinductive factors with bone substitutes for sinus floor augmentation. Despite the great heterogeneity of the related studies in design, materials and outcomes, incorporation of growth factors into the synthetic scaffold appears to have positive results regarding healing time, bone formation and avoidance of autologous grafts.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Del Fabbro M, Corbella S, Weinstein T, et al. Implant survival rates after osteotome-mediated maxillary sinus augmentation: A systematic review. Clin Implant Dent Relat Res. 2012;4:S1.
2. Del Fabbro M, Testori T, Francetti L, et al. Systematic review of survival rates for implants placed in the grafted maxillary

sinus. Int J Periodontics Restorative Dent. 2004;24:565–577.

3. Wallace SS, Froum SJ, Cho SC, et al. Sinus augmentation utilizing an organic bovine bone (Bio-Oss) with absorbable and nonabsorbable membranes placed over the lateral window: histomorphometric and clinical analyses. Int J Periodontics Restorative Dent. 2005;25:551–559.
4. Celik D, Turan T, Kabukcuoglu F. Bone induction capacity of the periosteum and neonatal dura in the setting of the zygomatic arch fracture model. Archives of Facial Plastic Surgery. 2003;5:301–308.
5. Lundgren S, Andersson S, Gualini F, Sennerby L. Bone reformation with sinus membrane elevation: a new surgical technique for maxillary sinus floor augmentation, Clinical Implant Dentistry and Related Research. 2004;6:165–173.
6. Ortak T, Ozdemir R, Uysal A, et al. Osteogenic capacities of periost grafts, periost flaps and prefabricated periosteal flaps: experimental study, Journal of Craniofacial Surgery. 2005;16:594–600
7. Srouji S, Kizhner T, Ben David D, et al. The schneiderian membrane contains osteoprogenitor cells: in vivo and in vitro study, Calcified Tissue International. 2009;84:138–145.
8. S. Srouji, D. Ben-David, R. Lotan, M. et al. The innate osteogenic potential of the maxillary sinus (Schneiderian) membrane: an ectopic tissue transplant model simulating sinus lifting. International Journal of Oral and Maxillofacial Surgery. 2010;39:793–801.
9. Troedhan A, Kurrek A, Wainwright M, et al. Membrane Detachment Using transcrestal Hydrodynamic Ultrasonic Cavitational Sinuslift: A Human Cadaver Head Study and Histology Analysis. Journal of Oral and Maxillofacial Surgery. 2014.02.021,e1-e10, 2014.
10. Thorwarth M, Srour S, Felszeghy E, et al. Stability of autogenous bone grafts after sinus lift procedures: a comparative study between anterior and posterior aspects of the iliac crest and an intraoral donor site. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;100:278–84.
11. Helm GA, Dayoub H, Jane JA Jr Bone graft substitutes for the promotion of spinal arthrodesis. Neurosurg Focus. 2001;10:E4
12. Dirckx N, Van Hul M, Maes C. Osteoblast recruitment to sites of bone formation in skeletal development, homeostasis, and regeneration. Birth Defects Res C Embryo Today. 2013;99(3):170-91.
13. Simonpieri A, Del Corso M, Vervelle A, et al. Current knowledge and perspectives for the use of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in oral and maxillofacial surgery part 2: Bone graft, implant and reconstructive surgery. Curr Pharm Biotechnol. 2012;13:1231-1256.
14. Oryan A, Alidadi S, Moshiri A, et al. Bone regenerative medicine: classic options, novel strategies, and future directions. J Orthop Surg Res. 2014;179(1):18.
15. Tonetti MS, Hammerle CH. Advances in bone augmentation to enable dental implant placement: Consensus Report of the Sixth European Workshop on Periodontology. J Clin Periodontol. 2008;35:168–172.
16. Del Fabbro M, Bortolin M, Taschieri S, Weinstein RL Effect of Autologous Growth Factors in Maxillary Sinus Augmentation: A Systematic Review. Clin Implant Dent Relat Res. 2011;15:205-216.
17. Esposito M, Grusovin MG, Rees J, et al. Effectiveness of sinus lift procedures for dental implant rehabilitation: a Cochrane systematic review. Eur J Oral Implantol. 2010;3:7-26.
18. Roldán JC, Jepsen S, Schmidt C, et al. Sinus floor augmentation with simultaneous placement of dental implants in the presence of platelet-rich plasma or recombinant human bone morphogenetic protein-7. Clin Oral Implants Res. 2004;15:716-723.
19. Available:http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf
(Last accessed April 2015)
20. Stavropoulos A, Becker J, Capsius B, et al. Histological evaluation of maxillary sinus floor augmentation with recombinant human growth and differentiation factor-5-coated β-tricalcium phosphate: results of a multicenter randomized clinical trial. J Clin Periodontol. 2011;38:966-974.
21. Allegrini S Jr, Yoshimoto M, Salles MB, et al. The effects of bovine BMP associated to HA in maxillary sinus lifting in rabbits. Ann Anat. 2003;185:343-349.
22. Gruber RM, Ludwig A, Merten HA, et al. Sinus floor augmentation with recombinant

human growth and differentiation factor-5 (rhGDF-5): a histological and histomorphometric study in the Goettingen miniature pig. Clin Oral Implants Res. 2008;19:522-529.

23. Gruber RM, Ludwig A, Merten HA, et al. Sinus floor augmentation with recombinant human growth and differentiation factor-5 (rhGDF-5): a pilot study in the Goettingen miniature pig comparing autogenous bone and rhGDF-5. Clin Oral Implants Res. 2009;20:175-182.
24. Jiang XQ, Sun XJ, Lai HC, et al. Maxillary sinus floor elevation using a tissue-engineered bone complex with beta-TCP and BMP-2 gene-modified bMSCs in rabbits. Clin Oral Implants Res. 2009;20:1333-40.
25. Sun XJ, Xia LG, Chou L, et al. Maxillary sinus floor elevation using a tissue engineered bone complex with BMP-2 gene modified bMSCs and a novel porous ceramic scaffold in rabbits. Arch Oral Biol. 2010;55:195-202.
26. Ho SK, Peel SA, Hu ZM, et al. Augmentation of the maxillary sinus: comparison of bioimplants containing bone morphogenetic protein and autogenous bone in a rabbit model. J Can Dent Assoc. 2010;76:a108.
27. Gutwald R, Haberstroh J, Stricker A, et al. Influence of rhBMP-2 on bone formation and osseointegration in different implant systems after sinus-floor elevation. An in vivo study on sheep. J Craniomaxillofac Surg. 2010;38:571-579.
28. Kim BJ, Kwon TK, Baek HS, et al. A comparative study of the effectiveness of sinus bone grafting with recombinant human bone morphogenetic protein 2-coated tricalcium phosphate and platelet-rich fibrin-mixed tricalcium phosphate in rabbits. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113:583-592.
29. Xia L, Xu Y, Wei J, et al. Maxillary sinus floor elevation using a tissue-engineered bone with rhBMP-2-loaded porous calcium phosphate cement scaffold and bone marrow stromal cells in rabbits. Cells Tissues Organs. 2011;194:481-493.
30. Zhang W, Wang X, Wang S, et al. The use of injectable sonication-induced silk hydro gel for VEGF (165) and BMP-2 delivery for elevation of the maxillary sinus floor. Biomaterials. 2011;32:9415-9424.
31. Xia L, Xu Y, Chang Q, et al. Maxillary sinus floor elevation using BMP-2 and Nell-1 gene-modified bone marrow stromal cells and TCP in rabbits. Calcif Tissue Int. 2011;89:53-64.
32. Binderman I, Yaffe A, Samuni Y, et al. Tissue Engineering of Bone: Critical Evaluation of Scaffold Selection, Bone Regeneration, Prof. Haim Tal (Ed.), ISBN: 978-953-51-0487-2, 2012.
33. Troedhan A, Schlichting I, Kurrek A, Wainwright M. Primary implant stability in augmented sinuslift-sites after completed bone regeneration: a randomized controlled clinical study comparing four subantrally inserted biomaterials, Scientific Reports. 2014;4:5877.
34. Tan WC, Lang NP, Zwahlen M, Pjetursson BE. A systematic review of the success of sinus floor elevation and survival of implants inserted in combination with sinus floor elevation. Part II: Transalveolar technique. J Clin Periodontol. 2008;35(Suppl. 8):241–254.
35. Wang J, Guo J, Liu J, et al. BMP-functionalised coatings to promote osteogenesis for orthopaedic implants. Int J Mol Sci. 2014;15(6):10150-68
36. Carreira AC, Alves GG, Zambuzzi WF, et al. Bone Morphogenetic Proteins: structure, biological function and therapeutic applications. Arch Biochem Biophys. 2014:1;561:64-73.
37. Schlegel KA, Zimmermann R, Thorwarth M, et al. Sinus floor elevation using autogenous bone or bone substitute combined with platelet-rich plasma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;104:e15-e25.
38. Marx RE, Carlson E, Eichstaedt RM, et al. Platelet rich plasma: growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol. 1998;85:638-46.
39. Frost H. The regional acceleratory phenomenon, a review Henry Ford Hosp Med J 1983;31:3-9.
40. Badylak SF, Weiss DJ, Caplan A, Macchiarini P. Engineered whole organs and complex tissues. Lancet. 2012;10:943-952.
41. Farré-Guasch E, Prins HJ, Overman JR, et al. Human maxillary sinus floor elevation as a model for bone regeneration enabling the application of one-step surgical

procedures. Tissue Eng Part B Rev. 2013;19:69-82.

42. Wang Z, Weng Y, Lu S, et al. Osteoblastic mesenchymal stem cell sheet combined with Choukroun platelet-rich fibrin induces bone formation at an ectopic site. Journal of Biomedical Materials Research Part B: Applied Biomaterials; 2014.
DOI:10.1002/jbm.b.33288 [Epub ahead of print].

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=952&id=12&aid=8863