Insulin-coated titanium implants – a potential therapy for local bone regeneration

Akademisk avhandling
som för avläggande av odontologie doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i föreläsningssal 3 (F3), Medicinaregatan 12E, Göteborg, torsdagen den 1:e juni, klockan 9.00

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Avhandlingen baseras på följande delarbeten:

I. Malekzadeh B, Tengvall P, Ohrnell LO, Wennerberg A, Westerlund A. Effects of locally administered insulin on bone formation in non-diabetic rats. J Biomed Mater Res A. 2013 Jan;101(1):132-7.

II. Malekzadeh BÖ, Ransjo M, Tengvall P, Mladenovic Z, Westerlund A. Insulin released from titanium discs with insulin coatings – Kinetics and biological activity. J Biomed Mater Res B Appl Biomater. 2016 May 26. doi: 10.1002/jbm.b.33717

III. Shchukarev A, Malekzadeh BÖ, Ransjö M, Tengvall P, Westerlund A. Surface characterization of insulin-coated Ti6Al4V medical implants conditioned in cell culture medium: An XPS study. Journal of Electron Spectroscopy and Related Phenomena. 2017 April;216:33-38. doi:http://dx.doi.org/doi:10.1016/j.elspec.2017.03.001

IV. Malekzadeh BÖ, Erlandsson MC, Tengvall P, Palmqvist A, Ransjo M, Bokarewa MI, Westerlund A. Effects of locally administered insulin on bone formation in osteoporotic rats. Submitted.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR ODONTOLOGI

GÖTEBORGS UNIVERSITET

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Abstract

Background: Insulin is a hormone that regulates glucose metabolism, however, it is also important for bone formation. The anabolic effect of insulin on bone could open up alternative therapies when it comes to local bone regeneration. However, this requires a method for local administration of insulin.

Aim: The overall aim was to determine whether local administration of insulin, coated on a titanium surface has the potential to regenerate bone locally.

Materials and methods: The surface characteristics and release kinetics of the insulin coating were analysed by interferometry, ellipsometry, SEM, XPS, and ECLIA. The biological activity of the released insulin was evaluated *in vitro,* in osteoblast-like cells (MG-63), by a Neutral Red and alizarin red assay. The gene expression and bone formation in healthy and ovariectomised rats were evaluated using quantitative real-time PCR, microcomputer tomography, and histomorphometry.

Results: The insulin-coated titanium surface showed a smooth surface topography on a micrometer level and the coating generated a heterogeneous protein layer. The insulin coating demonstrated a high initial release, with the release continuing over a 6-week period. Titanium surface modifications, increased coating thickness, and incubation in serum-enriched cell culture medium increased the amount of insulin release, while storage decreased the amount of insulin release. When serum-enriched medium was used, the insulin was partially substituted by serum proteins. The remaining insulin layer had direct surface effects by stabilising the structures of protein competitors and supporting the precipitation of CaP on the surface. The released insulin retained its biological activity, as demonstrated by a significant increase in cell number and mineralisation capacity. Insulin-coated implants increased local bone formation in healthy rat tibias, decreased the expression of the early pro-inflammatory cytokine interleukin-1β, and increased periosteal bone formation in osteoporotic rats.

Conclusion: An insulin-coated titanium implant surface represents a potential therapy for local bone regeneration.

Keywords: Insulin, titanium, bone, implant, osteoblast, immobilisation.

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