BIO-IMPLANT INTERFACE

Improving Biomaterials and Tissue Reactions

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Preface

Implanted biomaterials represent rapidly increasing treatment modalities for replacement of anatomical structures like bones and teeth and for restoring lost body functions. Optimal mechanical and biological functioning of implanted materials is of utmost importance for the outcome of such treatments, especially in the fields of implant dentistry and orthopedic and plastic surgery where the biomechanical, biochemical, functional, and esthetic demands on the implanted material are extreme. A good clinical outcome is based on several aspects of the combination (integration) of biological and material sciences and tissue engineering. The rapid progress of modern biomaterial medicine continuously challenges clinicians and scientists alike in the pursuit for new and better designs that will improve biocompatibility and patient responses to implants. The state of the art in biomaterial medicine is continuously changing and improving in combination with technological advances in biology and material science.

The authors of this book, all renowned scientists in their fields, gathered on the *M/S Nordnorge* and sailed the coast of Norway while reviewing and discussing the individual topics now included in this book.

The aim of this work is to present state-of-the-art knowledge of the important interface between materials and living tissue. Its main focus is the interaction of tissues and biomaterials. Controlling and patterning of bio-implant interface reactions are expected to exert tremendous impact on future designs and prospects for implant treatment. Strategies for controlling this intriguing interface are going to arise from a fusion of clinical expertise with several scientific fields including implant design, biomechanics, surface topography, chemistry, matrix biology, cell biology, molecular biology, and synthetic biomaterials design.

It is our hope that this book will update the readers in this important aspect of patient-oriented basic science and initiate and stimulate further work in this important biomedical field. We also hope that such work will eventually benefit the many patients who now remain untreated or suffer poor outcomes.

Jan Eirik Ellingsen
Staale Petter Lyngstadaas

Editors

Jan Eirik Ellingsen earned a D.D.S. in 1982 and a Ph.D. in 1985 and qualified as a clinical specialist in prosthetic dentistry in 1991. He became an associate professor in the department of prosthetic dentistry 1986 and held a position as specialist dentist in that same department from 1991 until 1993. He was appointed professor in dentistry at University of Oslo in 1993 and has served as director of the Oral Research Laboratory since 1996.

His research activity has focused on surface reactions to teeth and biomaterials. In particular, the mechanisms of regeneration and binding of bone tissue to biomaterials following implantation have been given much attention. He has been heading a project on engineering of biomaterial surfaces for improved tissue response. The group is now focusing on chemical, electrochemical, and biological methods for experimental surface modifications of biomaterials for improving the regeneration of the tissue and integration of the biomaterial.

Staale Petter Lyngstadaas earned a B.E. in biochemistry in 1984, a D.D.S. in 1991, and a Ph.D. in 1995 with a thesis on molecular biology and extracellular matrix biomineralization in tooth formation. From 1996 to 1997, he held a fellowship in oral pathology. He became an associate professor in oral pathology in 1997, and later in 2000, in biomaterials research. He was appointed professor of biomaterials in 2001.

His main research interests have focused on the development of the craniofacial complex, including teeth, dental ligaments, alveolar bones, and jawbones. Combining insight in developmental biology and molecular biology with experience from pathology and biomaterials science, he studied mechanisms that operate during development, repair, and regeneration of hard tissues. Much of his work has centered on the formation of extracellular matrix and how the matrix influences growth and guides repair, regeneration, and biomineralization processes in hard tissues. Moreover, he is engaged in designing bioactive biomaterials based on extracellular matrix biology to improve the performance of implants by controlling tissue responses and tissue integration of the implanted materials.

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The editors would also like to thank Astra Tech AB for financial support that made it possible to gather scientists from many nations on a ship on the coast of Norway to focus on the past, present, and future of the bio-implant interface.

The editors also take this opportunity to thank all the contributors to this book. Without their willingness to share their knowledge, it would not have been possible to realize this book.

The publisher, CRC Press, Susan Farmer, Marsha Hecht, and Jamie Sigal are acknowledged for their significant contributions to this effort.

Finally, we want to thank our families for their support and patience during the production of this book.

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Success and Failure of Bone–Implant Attachments: An Evidence-Based Approach

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Role of Implant Surface Properties on the Clinical Outcome of Osseointegrated Oral Implant Therapy: An Evidence-Based Approach

Marco Esposito, Helen V. Worthington, Paul Coulthard, Ann Wennerberg, and Peter Thomsen

CONTENTS

1.1 Introduction

Osseointegrated oral implants are available in different materials, body shapes, diameters, lengths, platforms, surface properties, and coatings. In particular, implant surface modifications and coatings have been subjected to aggressive marketing aimed at establishing the superiority of a given surface over the others. In implant research, the word *machined* has been used frequently to describe a turned, milled, or polished surface. However, a machined surface can be any object produced by a machine. Surfaces produced by electrodischarge, polishing, grinding, honing, and sand blasting are all examples of machined surfaces.[1] Thus, an implant surface requires a more precise description.

Numerous surface modifications have been developed and are currently used with the aim of enhancing clinical performance, including turned, blasted, acid-etched, porous-sintered, oxidized, plasma-sprayed, hydroxyapatite-coated surfaces, and combinations of these procedures. It has been estimated that dentists can choose from more than 1300 types of implants that vary in form, material, dimension, surface properties, and interface geometry.[2]

It is therefore important to know whether certain surface modifications or particular materials will improve clinical results and provide the best available treatment. In recent years, the concept of evidence-based practice has become popular.[3–5] The concept implies the integration of the individual experience of a clinician with the best available evidence from systematic research.[6]

Various study designs can be used to investigate specific scientific hypotheses. The ideal study design should be chosen on the basis of parameters to be evaluated. The consensus is that a randomized controlled clinical trial (RCT) is the preferred design to answer questions on the effectiveness of therapeutic intervention.[7,8] Every clinical trial intended to evaluate treatment effectiveness is comparative. Appropriate controls must be included because the only way to assess effectiveness is to compare differences in outcomes between a test group in which the intervention under investigation is administered and a control group in which another intervention or no intervention is delivered. Obviously, the control population should not be different from the test population. Test and control groups should be as similar as possible with the exception of the administered treatment.

The best way to ensure this similarity in groups to be compared is randomization. RCT participants are randomly selected to receive or not receive one or more treatments to be compared. Randomization allows all participants the same chances of assignment to a study group and investigators are prevented from influencing the course of a study by systematically including patients with different prognoses into a certain group. Randomization, if done properly, reduces the risk of serious imbalance in unknown but important factors that can influence the results of a trial.[9] No other study design allows investigators to balance these unknown factors.

Like all studies, RCTs are open to bias if not correctly conducted.[10] In addition, an RCT with an inadequate number of patients (i.e., inadequate statistical power) may be unable to detect a significant difference in interventions even if a difference exists. It has been recently shown that RCTs on oral implants seldom included statistical power calculations[11] and other means must be used to identify the most effective interventions.

One accepted way to overcome this problem is to combine data from different trials if they address similar comparisons and report the same outcome measures. In particular, systematic reviews (SRs) are used to assess the quality of RCTs and, when possible, combine results of different RCTs to reach more reliable conclusions.[8,12] SRs have clearly formulated hypotheses and employ systematic and explicit methods to identify, select, and critically appraise relevant clinical research. Data from original trials are collected, analyzed, and, if possible, summarized in order to produce more precise estimates of the intervention effects than those derived from individual trials.[8,12] SRs, if not properly conducted, may lead to erroneous conclusions.[13–15] It is therefore important that SRs are conducted according to the highest scientific standards.[16]

The QUOROM statement[16] provides guidelines on how to improve the reporting of SRs and meta-analyses of RCTs. Such guidelines will improve not only the reporting, but will also increase the awareness of what is required to conduct a good quality SR.

The aim of this chapter is to assess possible differences in performance among various root-formed osseointegrated implant types with respect to surface characteristics, materials, and shapes of implants. This was done by conducting a Cochrane systematic review (http://www.update-software.com/ccweb/cochrane/cc-broch.htm)[12,17] with the Cochrane Oral Health Group (http://www.cochrane-oral.man.ac.uk/).

1.2 Materials and Methods

All RCTs of root-form osseointegrated oral implants comparing different implant types (surface properties, materials, and shapes) having minimal follow-up periods of 1 year in function were considered for this review. Studies reporting on bone grafting, guided bone regeneration procedures, and placement of implants in freshly extracted tooth sockets were not considered. Endpoints were 1, 3, and 5 years. Longer follow-up periods may be considered in the future.

The following true or primary outcome measures[8] were considered in this review:

1. **Biological implant failure**, defined as implant mobility and removal of stable implants dictated by progressive marginal bone loss.[18,19] Biological failures were grouped as early (failure to estab-

lish osseointegration) and late (failure to maintain established osseointegration). Failures occurring before bridge placement or, in the case of immediate or early loaded implants, soon after (weeks or a few months) prosthesis insertion, were considered early failures.

2. **Mechanical implant failure**, defined as implant fracture and all other mechanical complications not allowing use of the implants.

The surrogate or secondary outcome measure[8] was the appearance of marginal bone level changes on intraoral radiographs taken with the paralleling technique.

1.2.1 Search Strategy for Identification of RCTs

To identify trials on oral implants included or considered for this review, detailed search strategies were developed for each database searched. These were based on the search strategy developed for MEDLINE (Table 1.1) and revised appropriately for each database. The searched databases were:

1. Cochrane Oral Health Group Specialised Register
2. Cochrane Controlled Trials Register, Cochrane Library Issue 1, 2002
3. MEDLINE (1966 through May 2002)
4. EMBASE (1974 through May 2002)

The following journals were hand-searched by the Cochrane Collaboration or by one of the authors as being important for this review: *British Journal of Oral and Maxillofacial Surgery*, *Clinical Implant Dentistry and Related Research*, *Clinical Oral Implants Research*, *Implant Dentistry*, *International Journal of Oral and Maxillofacial Implants*, *International Journal of Oral and Maxillofacial Surgery*, *International Journal of Periodontics and Restorative Dentistry*, *International Journal of Prosthodontics*, *Journal of the American Dental Association*, *Journal of Biomedical Materials Research*, *Journal of Clinical Periodontology*, *Journal of Dental Research*, *Journal of Oral Implantology*, *Journal of Oral and Maxillofacial Surgery*, *Journal of Periodontology*, and the *Journal of Prosthetic Dentistry*.

The bibliographies of identified RCTs and review articles were checked for studies beyond the listed journals. PubMed was independently searched using the "related articles" feature. Personal references were also searched. Correspondence was conducted with professional contacts, authors of identified RCTs, and 55 oral implant manufacturers in attempts to identify unpublished or ongoing studies. No language restrictions were applied.

1.2.2 Study Selection, Quality Assessment, and Data Extraction

The titles and abstracts (when available) of all reports identified were scanned independently by two reviewers (ME and PC). For studies appear-

TABLE 1.1

Search Strategy Used in Medline Database to Identify Trials on Oral Implants

#1 randomized controlled trial.pt.
#2 controlled clinical trial.pt.
#3 randomized controlled trials.sh.
#4 random allocation.sh.
#5 double blind method.sh.
#6 single blind method.sh.
#7 latin square.ti,ab.
#8 crossover.ti,ab.
#9 (split adj (mouth or plot)).ti,ab.
#10 or/1–9
#11 (ANIMAL not HUMAN).sh.
#12 10 not 11
#13 clinical trial.pt.
#14 exp clinical trials/
#15 (clin$ adj25 trial$).ti,ab.
#16 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
#17 placebos.sh.
#18 placebo$.ti,ab.
#19 random$.ti,ab.
#20 research design.sh.
#21 or/13–20
#22 21 not 11
#23 22 not 12
#24 12 or 22
#25 exp Dental Implants/
#26 exp Dental Implantation/or dental implantation.mp.
#27 exp Dental Prosthesis, Implant-Supported/
#28 ((osseointegrated adj implant$) and (dental or oral)).mp. [mp = title, abstract, registry number word, mesh subject heading]
#29 dental implant$.mp. [mp = title, abstract, registry number word, mesh subject heading]
#30 (implant$ adj5 dent$).mp. [mp = title, abstract, registry number word, mesh subject heading]
#31 dental-implant$.mp. [mp = title, abstract, registry number word, mesh subject heading]
#32 (((overdenture$ or crown$ or bridge$ or prosthesis or prostheses or restoration$) adj10 (Dental or oral)) and implant$).mp. [mp = title, abstract, registry number word, mesh subject heading]
#33 "implant supported dental prosthesis".mp. [mp = title, abstract, registry number word, mesh subject heading]
#34 ("blade implant$" and (dental or oral)).mp. [mp = title, abstract, registry number word, mesh subject heading]
#35 ((endosseous adj5 implant$) and (dental or oral)).mp. [mp = title, abstract, registry number word, mesh subject heading]
#36 ((dental or oral) adj5 implant$).mp. [mp = title, abstract, registry number word, mesh subject heading]
#37 25 or 26 or 27 or 28 or 29 or 30 or 32 or 33 or 34 or 35 or 36
#38 24 and 37

ing to meet the inclusion criteria and those whose titles or abstracts were insufficient to enable the reviewers to make a clear decision, full reports were obtained. The full reports obtained from all electronic and other methods of searching were assessed independently by ME and PC to determine whether the studies met the inclusion criteria. Disagreements were resolved by dis-

cussion. All studies meeting the inclusion criteria then underwent validity assessment and data extraction.

Quality assessment of the included trials was undertaken independently and in duplicate by ME and PC. Three main quality criteria were examined: allocation concealment, blindness of patients and outcome assessors, and the completeness of reporting on follow-up. Further quality assessments were carried out to assess the definition of exclusion and inclusion criteria, adequate definition of success criteria, and comparability of control and treatment groups at entry. The quality assessment criteria were pilot-tested using several articles.

Data were extracted by ME and HW independently using specially designed data extraction forms. The forms were tested on several papers and modified as required before use. All disagreements were discussed and a third reviewer (PC) consulted where necessary. All authors were contacted to obtain clarification or missing information. Data were excluded until further clarification was available if agreement could not be reached.

For each trial, the following data were recorded: year of publication, country of origin, source of study funding, details about participants including demographic characteristics, details of types of interventions, and details of outcomes reported including methods of assessment and time intervals.

1.2.3 Data Synthesis

For dichotomous outcomes, the estimates of effects of interventions were expressed as relative risks together with 95% confidence intervals. For continuous outcomes, mean differences and 95% confidence intervals were used to summarize the data. Meta-analyses were to be attempted only when studies comparing similar interventions reported the same outcome measures.

1.2.4 Descriptions of Studies

Of the 30 eligible articles[20–49] reporting data of 14 different trials, we excluded 23 articles,[20,21,23–25,27,28,31–40,42,43,46–49] representing 9 trials due to problems with the data presented (Table 1.2). Of the five trials included (seven articles)[22,26,29,30,41,44,45] (Table 1.3), two were conducted in Sweden,[29,30,41] one in Finland,[22] one in New Zealand,[44,45] and one in The Netherlands.[26] All five trials had parallel group study designs. Four trials[22,26,29,30,44,45] received support from industry. Four were conducted at university dental clinics and one in a hospital.[29,30] All studies included adults.

Biological and mechanical failures and bone level measurements were recorded in all studies. However, in one trial,[41] peri-implant bone level measurements were partly performed on panoramic radiographs and were not included in the present analyses. In another trial,[26] insufficient data on bone level assessment were presented and the authors were not able to supply the required data. All trials reported on implants functionally