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Increased bone formation around coated implants

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Abstract

Aim: We hypothesized that coating threaded, sandblasted acid-etched titanium implants with collagen and chondroitin sulphate (CS) increases bone formation and implant stability, compared with uncoated controls.

Materials and Methods: Three different implant surface conditions were applied: (1) sandblasted acid-etched (control), (2) collagen/chondroitin sulphate (low-dose – CS1), (3) collagen/chondroitin sulphate (high-dose – CS2). Sixty 9.5 mm experimental implants were placed in the mandible of 20 minipigs. Bone–implant contact (BIC) and relative peri-implant bone-volume density (rBVD – relation to bone-volume density of the host bone) were assessed after 1 and 2 months of submerged healing. Implant stability was measured by resonance frequency analysis (RFA).

Results: After 1 month, coated implants had significantly more BIC compared with controls (CS1: 68%, $p < 0.0001$, CS2: 63%, $p = 0.009$, control: 52%). The rBVD was lower for all surface conditions, compared with the hostbone. After 2 months, BIC increased for all surfaces. No significant differences were measured (CS1: 71%, $p = 0.016$, CS2: 68%, $p = 0.67$, control: 63%). The rBVD was increased for coated implants. RFA values were 71–77 at implantation, 67–73 after 1 month and 74–75 after 2 months. Differences in rBVD and RFA were not statistically significant.

Conclusions: Data analysis suggests that collagen/CS has a positive influence on bone formation after 1 month of endosseous healing.

Key words: animal study; chondroitin sulphate; coating; collagen; dental implant; extracellular matrix; osseointegration; resonance frequency analysis

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The coating of implants using biological components represents an approach to influence the process of osseointegration. Such coatings consist of major components of the extracellular matrix (ECM) of bone, either in the anorganic form of hydroxyapatite or using the organic approach based on the protein components of bone ECM. Chief among these is collagen type I, and in vitro studies have shown favourable results for collagen-coated surfaces in terms of cell adhesion and protein expression (Bierbaum et al. 2003b). Animal studies confirmed advantages of collagen I-coated experimental implants in terms of bone formation in comparison to titanium implants after short-term (Bernhardt et al. 2005, Schliephake et al. 2005b) healing intervals. However, collagen-coated implants showed no difference in soft tissue healing compared with uncoated implants after short-term healing (Welander et al. 2007).

Following long-term healing, no detrimental effects on osseous healing could be observed (Stadlinger et al. 2008). The comparison of collagen type I-coated implants to collagen type I-coated implants enriched by chondroitin sulphate (CS) showed a significant higher bone–implant contact (BIC) for CS-coated surfaces after early healing intervals (Stadlinger et al. 2007). Significant effects of collagen-integrated CS were also observed for hydroxyapatite (HA)/collagen/CS cements in rat tibiae compared with HA/collagen cements in terms of direct bone contact after 1 month (Schneiders et al. 2008). Further, enhanced remodelling was described. While these observations suggest an additional effect of CS, no such significant differences between collagen and collagen/CS-coated implants were reported in a dog study (Schliephake et al. 2009). These observations lead to the idea of further modifying the CS contents.

Conflict of interest and source of funding statement

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An effect of coatings consisting of ECM components such as collagen may be due to their provision of an environment beneficial to bone forming cells, facilitating adhesion and cell differentiation (Bierbaum et al. 2003b, Geissler et al. 2000). Also, an unspecific binding of serum proteins is prevented by a prior collagen layer, minimizing unspecific metal–protein interactions which may have adverse effects. Metal–protein interactions are strong hydrophobic interactions that can cause the denaturation of proteins and could be of clinical importance in compromised situations. The characteristic of a protein coating to prevent unwanted interactions with serum proteins is related to the characteristic to induce beneficial interactions. In vivo the matrix not only offers a scaffold for cell adhesion, but is involved directly in influencing cell behaviour. One way in which this may occur is by the binding of factors affecting cells, such as growth factors and cytokines, and by thus modifying their action or accumulating them at the implant site. Glycosaminoglycans (GAG) for instance have been described to interact specifically with certain growth factors, making their inclusion in an implant coating viable. Collagen-coated implants containing the GAG CS have been shown to further promote the positive effect of collagen coatings on implant integration (Stadlinger et al. 2007).

This animal study addresses the question of how collagen coatings with two different CS contents compare with uncoated, sandblasted acid-etched titanium implants by evaluating bone formation.

Materials and Methods

Implant coating

Threaded titanium implants (Ø4.5 mm × 9.5 mm) were used. These experimental implants were based on a Xive© (Friadent-Dentsply, Mannheim, Germany) implant. The implant geometry included a circular chamber along the implant axis to create a defined area between the implant surface and the osteotomy. This chamber was designed with a defined width of 1.50 mm and a depth of 0.35 mm. The titanium implants were sandblasted with 250 μm corundum by the manufacturer cleaned with isopropanol, rinsed with distilled water, air dried and acid etched (Fig. 1).

Coating procedure

The coating procedure was performed by the ''Max–Bergmann–Center of Biomaterials'' (Dresden, Germany) (Bierbaum et al. 2003a). Used components for surface coating were acid-soluble bovine skin collagen type I (IBFB Pharma, Leipzig, Germany) and CS from bovine trachea (Sigma-Aldrich Chemie GmbH, Taufkirchen, Germany). All other chemicals were from Sigma-Aldrich Chemie GmbH.

Two different surface coatings were created: CS1 (collagen with low CS content) and CS2 (collagen with high CS content).

Collagen was dissolved at 4 mg/ml in 10 mM acetic acid overnight at 4°C. The collagen solution was then mixed on ice with equal volumes of twofold concentrated fibrillogenesis buffer (60 mM sodium phosphate, pH 7.0). Fibrillogenesis was allowed to take place overnight at 37°C. CS was added to the fibrillogenesis buffer before incubation with 50 μg/1 mg collagen for CS1 and 500 μg/mg for CS2. The resulting gel was homogenized, fibrils were collected by centrifugation at 5000 *g* for 15 min, washed with fibrillogenesis buffer diluted to working concentration and centrifuged again. The pellet was resuspended in the same buffer to a concentration of about 3 mg/ml collagen. The implants were incubated in the suspension at 25°C for 5 min. and air dried. This process was repeated two times; the coated implants were then washed with distilled water and sterilized with ethylene oxide at 42°C for 12 h.

The amount of collagen adsorbed was determined spectrometrically using the collagen binding dye Sirius Red as described by Bierbaum et al. (2006) to 50 ± 5 μg/cm^2 with no differences for the respective coatings. The amount of integrated CS was determined at 25 μg/mg collagen for CS1 and 100 μg/mg collagen for CS2, applying a colorimetric assay (Blyscan, Biocolor Ltd., Carrickfergus, UK). The morphology of the surfaces was characterized after carbon coating by low-voltage electron microscopy (LEO Gemini DSM 982, Carl-Zeiss NTS GmbH, Oberkochen, Germany). The collagen coating appeared as a thin film on titanium (Fig. 2).

Fig. 1. Experimental titanium implant with circular chamber.

Experimental design

Twenty miniature pigs (10 ♂, 10 ♀), approximate age 12 months and weight 60 kg, were used. The study protocol was approved by the commission for animal studies at the district government office Dresden, Germany.

The mandibular premolar teeth were surgically removed under general anaesthesia (midazolam 1 mg/kg i.m.; ketamine 10 mg/kg i.m.; atropine 0.05 mg/kg i.m.) 9 weeks before implant placement. Carprofen (2–4 mg/kg SC) was administered post-surgery.

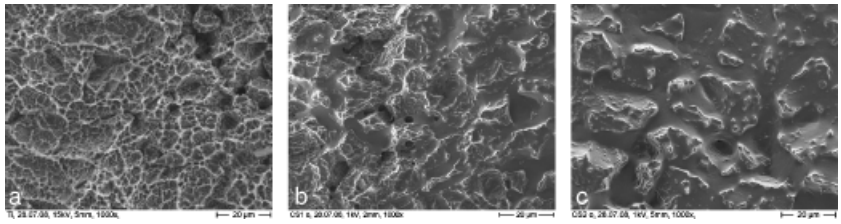

Fig. 2. SEM pictures of the implant surfaces: (a) sandblasted acid-etched titanium, (b) collagen/chondroitin sulphate (CS1), (c) collagen/CS2 Images were acquired with 1 kV for protein-coated samples with no additional surface preparation (LEO Gemini DSM 982).

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Each animal was scheduled to receive three implants (1/surface condition) inserted into one side of the mandible. The positioning of the implants was randomized, using ''permuted block randomization''. The surgeon was masked from placement assignment and surface state. The contralateral jaw quadrant received implants unrelated to this study to be reported separately. Following general anaesthesia a muco-periosteal flap was elevated from the vestibular region and the alveolar crest was exposed under amoxicillin (15 mg/kg i.m.) coverage. Any remaining sharp bone edges were flattened, using a water-cooled surgical drill. The implants were placed following the manufacturer's instructions. Implant stability was analysed immediately post-implantation and pre-euthanasia using an electromagnetic device. The measurements were performed, mounting a transducer onto the implant (Osstell AB®, Gothenburg, Sweden). Each implant was evaluated thrice and a mean value calculated. The transducer was removed and a cover screw was placed onto the implant and the flap was repositioned and sutured using resorbable sutures (PGA Resorba 4×0®, Resorba, Nürnberg, Germany). Surgeries were performed by one experienced maxillofacial surgeon (R. M.). The animals were euthanized in groups of 10 at 1 and 2 months post-implantation using an embutramid/mebezonium iodide/tetracain cocktail (T61®, Intervet Deutschland GmbH, Unterschleissheim, Germany). Block biopsies of the implant sites were fixed in formaldehyde and dehydrated in a graded series of ethanol. Next, the implants with surrounding bone were embedded in methylmethacrylate (Technovit 9100 Neu®, Heraeus Kulzer, Wehrheim, Germany). Undecalcified 100 μm thick sections were cut along the length axis of each implant in bucco-oral direction using a diamond saw microsectioning system (Exakt-Apparatebau, Norderstedt, Germany). These sections were reduced to 30 μm in thickness using Donath & Breuner's (1982) grinding techniques on a roll grinder containing sandpaper (Exakt-Apparatebau). Subsequently a Masson–Goldner staining was performed. The histologic and histomorphometric analyses were performed using light microscopy (Olympus BX 61, Hamburg, Germany). Histology was analysed at up to $\times$ 20 magnification. In order to perform histomorphometry, the sections were imaged by a digital camera (Colour View 2, Olympus Optical GmbH, Hamburg, Germany) at $\times$ 4 magnification, using a motorized measuring stage (Märzhäuser, Wetzlar, Germany) for multiple alignment scanning connected to a computerized system of histomorphometry (Analysis, Soft Imaging Systems, Münster, Germany).

Histology

Two masked, experienced examiners (R. M. and B. S.) performed the histologic evaluation. Descriptive histological evaluation of the implants was primarily focused on the implant chamber and the neighbouring bone. This area was evaluated for bone formation, osteoid reaction, woven and lamellar bone, inflammatory response and bone remodelling.

Histomorphometry

Following the histological analysis, the percentage of BIC along the entire implant surface and separately within the implant chamber was measured by one masked examiner (S. G.) for every histological section. Mean values were calculated for each implant and for each group of implant surface coatings.

Next, the amount of bone within the chambers was assessed by calculating the percentage of the surface area inside the chambers occupied by bone. This surface area was measured by placing a borderline at the implant core surface, thereby defining the area within the chamber. Owing to the fact that three to four histological slices per implant are evaluated, this area is referred to as bone-volume density. The percentage of bone within this enclosed area was compared with the percentage of bone within a neighbouring region of reference (RoRef), defining the relative bone-volume density (rBVD). The RoRef was equal in size and had an identical vertical position. The horizontal position was located within the host bone. This position was determined by placing a tangent line at the tips of the implant threads. The RoRef was placed within the host bone, bordering but avoiding any lateral contact to the osteotomy (Fig. 3).

Statistical analysis

Means and their 95% confidence intervals are presented. Spearman's rank correlation coefficient was used to examine the correlation between resonance frequency analysis (RFA) at the time of euthanasia, BIC along the entire implant surface, BIC within the chamber and bone volume within the chamber. The experiment was planned as a full balanced one factorial design. To take the blocking effect of the experimental units into account, a mixed model was applied. The model approach enables the simultaneous modelling of fixed factors, random factors and covariates. The level of significance was set at 0.05 in all statistical tests. A mixed linear model was applied to determine the intra-examiner reproducibility for histomorphometric measurements. Statistical analysis was performed by SPSS for Windows® 15.0.1 (SPSS, Inc., Chicago, IL, USA) and by SAS for Windows® 9.2 (SAS Institute Inc., Cary, NC, USA).

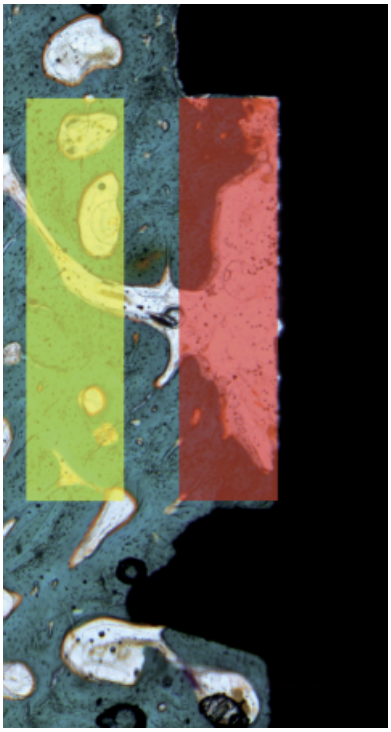

Fig. 3. Histomorphometric analysis of relative bone-volume density, showing the region of interest (red) and the bordering region of reference (RoRef – yellow).

Results

Animal experiment

All pigs survived the procedures and were available for evaluation. Two implants were clinically found mobile

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at the time of euthanasia and considered as implant loss (1 × CS2 – 1 month group, 1 × control – 2 months group). These two implants showed localized dehiscences. All other implants were covered by alveolar mucosa. Four implants were in touch with the alveolar canal and not included in the analysis (2 × CS1 – 2 months group, 1 × CS2 – 2 months group, 1 × control – 1 month group).

Histology

After 1 month of healing formations of woven bone around titanium control implants could be observed. This was combined with a pronounced osteoid reaction (Figs 4a and 5).

For CS1 implants woven bone could be found within implant threads, while the neighbouring chamber was predominately filled by lamellar bone. Observing the rectangular chambers, especially the side walls (which were perpendicular to the length axis) were entirely covered by bone. Single bone-surface contacts could be observed at the depth of the chamber (Fig. 4c).

Bone formation around CS2 implants was characterized by woven bone formation that extended from the borders of the osteotomy into the host bone. An osteoid reaction was clearly detectable. Bone texture within the chamber was primarily characterized by stroma. A tight BIC could be detected along the chamber surface (Fig. 4e).

After 2 months of healing, the chamber of control implants was entirely filled by regularly formed lamellar bone. However, an osteoid reaction could still be observed, indicating a process of secondary remodelling. Overall, BIC could be found along the entire chamber surface (Fig. 4b).

CS1 implants also showed formation of lamellar bone that filled the entire chamber. The activity of the osteoid reaction within the chamber was comparable to that found in the host bone. Stromal compartments were rarefied and the bone structure appeared to resemble cortical bone. This resulted in a high bone density (Figs 4d and 6).

CS2 implants, on the other hand, still showed some transformation of lamellar bone in the hard tissue. The osteoid reaction was pronounced Fig. 7. Stromal compartments were still wide and showed a lack of BIC along the entire chamber (Fig. 4f).

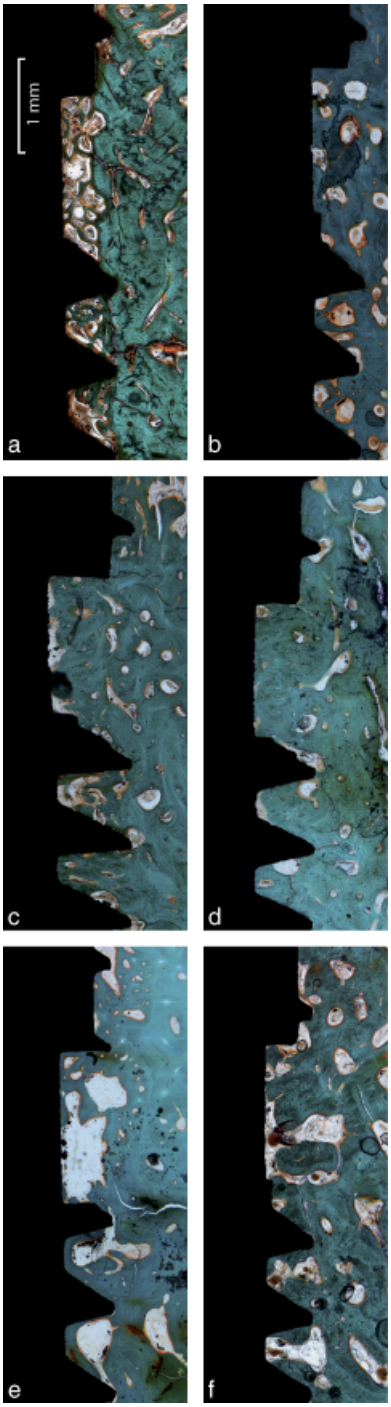

Fig. 4. Histologic analysis: chamber and thread area left – 1 month, right – 2 months. (a) control 1 month, (b) control 2 months (c) chondroitin sulphate (CS) 1 1 month, (d) CS1 2 months. (e) CS2 1 month, (f) CS2 2 months (Masson–Goldner, magnification × 4, multiple alignment technique).

Histomorphometry

Calibration of intra-examiner errors in the histomorphometric measurements demonstrated >99% intra-examiner (S. G.) reliability for BIC (entire surface) and BVD measurements and >97% for BIC (chamber) measurements.

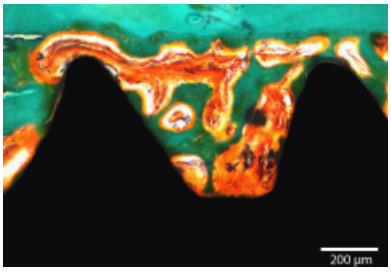

Fig. 5. Histologic section with newly formed bone at the border of the osteotomy and a pronounced osteoid reaction (control implant, 1 month healing, magnification × 10, Masson–Goldner).

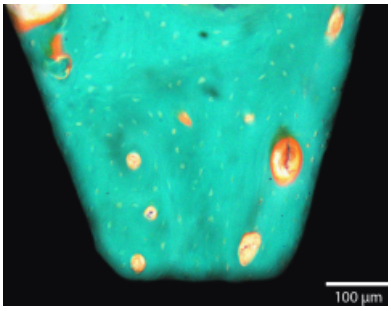

Fig. 6. Histologic section with tight lamellar bone structures [chondroitin sulphate (CS) 1-coated implant, 2 months healing, magnification × 20, Masson–Goldner].

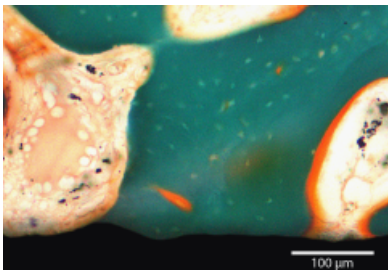

Fig. 7. Histologic section with pronounced osteoid reaction [chondroitin sulphate (CS) 2-coated implant, 2 months healing, magnification × 20, Masson–Goldner].

One month healing

After 1 month of healing, CS1 implants exhibited a BIC along the entire surface of 68.4%. This was significantly higher than for titanium controls (51.6%, $p < 0.0001$). Implants coated with CS2 had an average BIC of 63.1%, which also differed significantly from controls ($p = 0.0087$). No significant difference could be found between CS1 and CS2.

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Observing the BIC within the chamber, CS1 reached a BIC of 76.8%, CS2 of 76.5%, again with significant differences to the 51.5% BIC of controls ($p = 0.0027$ and $p = 0.0088$, respectively).

Comparing bone-volume density within the chamber to that of the neighbouring RoRef, rBVD for both CS1 and uncoated control implants was found to be 70.3% (29.7% lower compared with the RoRef), while CS2 implants reached a rBVD of 90.6% (9.4% lower compared with the RoRef). These differences were statistically not significant.

Two months healing

After 2 months, mean BIC increased for all surfaces, though without statistical significance. CS1 implants had a BIC of 71.0%, followed by CS2 with 67.9% and titanium controls with 62.7%. No significant differences between the three surface conditions could be found.

Observing BIC within the chamber, CS1 reached a value of 78.2%, followed by CS2 (78.1%) and controls (66.2%). No significant differences between the three surface conditions and no significant increases in bone formation from months 1 to 2 could be found.

Comparing bone-volume density within the chamber to that of the neighbouring RoRef, CS1 implants reached 125.9% rBVD (25.9% higher compared with the RoRef), while CS2 implants reached 106.5% (6.5% higher, compared with the RoRef). Titanium controls showed 98.2% rBVD (a minor decrease of 1.8%, compared with the RoRef). No statistical differences between the coatings and no significant differences in comparison to the 1 month healing period could be found Tables 1 and 2.

Resonance frequency analysis

At the time of implant placement, mean ISQ values of the different implant surfaces were found to be between 71 and 77. After 1 month of healing, the mean ISQ values were slightly decreased, ranging between 67 and 73. After 2 months of healing, mean ISQ values were slightly increased but still lower than at the time of implant placement with values between 74 and 75. The changes and differences between the surface states were statistically not significant. Table 3.

Table 1. Percentage of BIC for the entire implant surface and the chamber at 1 and 2 months of healing

Healing time	Surface	BIC (%)	95% confidence interval		BIC (chamber) (%)	95% confidence interval	
			lower bound	upper bound		lower bound	upper bound
1 month	Control	51.6	45.2	58.1	51.5	36.9	66.2
	CS1	68.4	62.0	74.7	76.8	62.3	91.4
	CS2	63.1	56.4	69.9	76.5	61.1	93.4
2 months	Control	62.7	56.0	69.3	66.2	51.1	81.4
	CS1	71.0	64.3	77.7	78.2	63.1	93.4
	CS2	67.9	61.3	74.6	78.1	63.0	93.1

BIC, bone–implant contact; CS, chondroitin sulphate.

Table 2. Ratio of the percentage of bone within the chamber in relation to the percentage of bone within the region of reference at 1 and 2 months of healing

Healing time	Surface	rBVD (%)	95% confidence interval	
			lower bound	upper bound
1 month	Control	70.3	33.9	106.8
	CS1	70.1	34.1	106.5
	CS2	90.6	50.1	131.2
2 months	Control	98.2	60.0	136.4
	CS1	125.9	87.5	164.3
	CS2	106.5	68.3	144.7

rBVD, relative bone-volume density.

Correlation analysis

A statistical correlation analysis (rank correlation coefficient by Spearman) showed a significant but weak correlation between the RFA at the time of euthanasia, compared with BIC along the entire implant surface ($r_S = 0.349$), BIC within the chamber ($r_S = 0.466$) and BVD within the chamber ($r_S = 0.536$). BVD within the chamber showed a more pronounced correlation to the BIC along the entire implant surface ($r_S = 0.659$) and to the BIC within the chamber ($r_S = 0.770$).

Table 3. Mean values and SD (standard deviation) for RFA (resonance frequency analysis) measurements

Surface	Time of measurement	Healing time (month)	Mean (ISQ)	SD
Control	Implantation		77.3	8.4
	Euthanasia	1	70.4	5.1
	Implantation		75.6	7.2
	Euthanasia	2	74.9	5.3
CS1	Implantation		75.1	5.4
	Euthanasia	1	67.3	9.3
	Implantation		70.7	19.8
	Euthanasia	2	74.7	6.8
CS2	Implantation		74.4	5.4
	Euthanasia	1	73.1	3.5
	Implantation		71.5	19.2
	Euthanasia	2	73.9	6.7

CS, chondroitin sulphate.

Discussion

The aim of this study was to evaluate whether a coating of collagen with two different amounts of integrated CS would promote bone formation for dental implants compared with sandblasted acid-etched titanium. Further, the influence on implant stability was assessed. The implants healed submerged for 1 and 2 months in mandibular bone of 20 minipigs.

Collagen/CS coatings had a positive influence not only on the quality, but also on the quantity of the newly formed bone. While control implants showed a comparatively slower bone formation both within the chamber and the threads, mature stages of bone formation were reached around collagen/CS-coated surfaces at the earlier time interval. This was independent of the applied amounts of CS.

A quantitative effect of both collagen/CS-coated surface conditions on implant integration could be observed in a significantly higher BIC after 1 month. As this effect levelled out after 2 months, the assumption was made that the coating enhances initial healing processes. Such early bone formation and

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apposition are essential for the early establishment of secondary stability.

In the present study, an increase in the CS amount as in the CS2 coating did not further increase BIC, indicating that there may be a threshold level. It is important to note, though, that the higher amount of CS also had no detrimental effects on BIC, as for the rBVD this higher dosage showed slightly positive results.

A shortcoming of the present study might be the lack of a pure collagen coating. In this respect it must be mentioned that main interest was to test different collagen/CS contents against a recognized reference implant surface.

The comparison of an experimental implant surface-to-surface-treated titanium is clinically essential. Present results show a significant increase in BIC after 1 month. Literature mainly reports on significant increases in comparison to machined surfaces (Schliephake et al. 2005a, b), however, no significant difference compared with dual acid-etched (Schliephake et al. 2009) or sandblasted acid-etched surfaces (Langhoff et al. 2008). The assessment of peri-implant bone volume and removal torque testing in sheep iliac bone showed no significant differences between collagen/CS and sandblasted acid-etched surfaces after short-term healing (Ferguson et al. 2008). Nevertheless, Schliephake et al. (2009) conclude, that the present stage of organic coatings merely represent the first steps in an iterative approach to design a coating assembly that closely resembles its natural environment.

It could be argued that organic coatings survive installation of the implants in the healing chamber but however, might be lost from the thread area during insertion of the implants. To assess this question, an in vitro test series was performed before this study. Collagen-coated dental implants were placed in artificial bone specimen using proper implantation procedures. Friction between the artificial bone specimen and the implant surface was comparable to living bone tissue. After implant retrieval, the amount of collagen remaining on the implant surface was measured and found to be in the same order of magnitude as before the implantation, the deviation being $<5\%$ (data not shown).

Peri-implant bone structure is suggested to influence implant stability. For rBVD, differences for the CS content could be observed. After 1 month, a creeping bone formation along the side walls of the chambers could be observed for both CS contents. However, bone volume within the chamber was still lower for all surface conditions compared with the surrounding host bone. Collagen/CS2-coated implants showed the comparably highest rBVD after the 1 month.

After 2 months, bone volume within the chamber for both collagen/CS-coated surfaces was higher compared with bone volume of the surrounding host bone; for uncoated controls there was no comparable increase. This correlated with the histological detection of mature lamellar bone within the chamber. Although these differences were not significant due to the large variation in the individual rBVD values measured, this can indicate a positive effect of collagen/CS coatings on bone formation.

Reasons for this difference could be a different mechanism of action. Another explanation would be the partial release of CS from the coating to diffuse outward. For higher CS amounts this would result in an effective CS concentration at a greater distance from the coating which may explain the enhancement of bone density. Immediately adjacent to the coating, the CS concentration would be high enough in both cases. This, however, remains to be proven.

The RFA analysis showed no significant differences between the surfaces for the two time points studied, so that all implants were considered stable. This non-destructive method has been developed to give a correlate for implant stability (Meredith et al. 1996, Sennerby & Meredith 1998). The measured decrease in stability after 1 month for all surfaces is contradictory compared with another study, measuring a slight increase for equally unloaded implants after 1 month (Schliephake et al. 2006). This could indicate some unintentional loading of the implants due to the animal's soft diet. RFA values after 2 months were comparable to the initial levels after implantation. At this time, secondary stability following new bone formation should already be present. Owing to the large amount of cortical bone present in the mandible, possible changes in spongious bone texture that tend to influence RFA might be of little consequence. The weak positive correlation of RFA to BIC and bone volume with the chamber is in accordance to various studies, showing only minor correlations under clinically relevant conditions (Schliephake et al. 2006, Ito et al. 2008).

In conclusion, implants of this study were placed in the mandible where tight bone architecture with its pronounced cortical bone offers an ideal environment for implant placement. In clinical practice, however, soft bone, bone atrophy or defects due to trauma offer more challenging situations, where the potential of coatings to influence bone formation might be more pronounced. The enhanced amount of BIC after 1 month could be shown to be significant. Such differences could be beneficial for earlier loading protocols or implant placement in compromised sites. Increased bone formation compared with sandblasted acid-etched titanium in this unloaded state could be advantageous under load-bearing conditions.

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Clinical Relevance

Scientific rationale for the study: A mean to stimulate osseointegration is the application of biological implant surface coatings. Such coatings resemble their natural surrounding. The ECM represents the natural environment of an implant in bone. The utilization of components of the ECM on implant surfaces could therefore foster bone formation.

Principle findings: The histomorphometric evaluation showed an increased BIC for coated implants after 1 month of healing compared with sandblasted acid-etched titanium implants.

Practical implications: A higher BIC at earlier times of healing can offer new approaches for healing and loading protocols.

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