Wound Healing Around Endosseous Implants in Experimental Diabetes

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Wound healing has been shown to be altered in diabetes mellitus. The aim of this study was to identify the effects of streptozotocin-induced diabetes on osseointegration. Diabetes was induced in 40-day-old rats by intraperitoneal injection of 70 mg per kg streptozotocin. At 14 days postinjection, implants were placed in the femora of 10 diabetic and 10 age-matched normal rats. Animals were sacrificed at 28 and 56 days following implantation. Histometric results indicated that the quantity of bone formation was similar for diabetic and control animals ($P > .05$). However, less bone-implant contact was observed for diabetic compared to control animals at both 28 and 56 days ($P < .0001$). This study demonstrates that the process of osseointegration is affected by streptozotocin-induced diabetes.

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Key words: dental implants, diabetes, osseointegration, wound healing

The clinical applicability and predictability of osseointegrated implants in the healthy patient have been studied extensively. Long-term success has been shown in the use of endosseous implants for prosthetic rehabilitation of both completely and partially edentulous patients.[1–6] Although the replacement of teeth with dental implants has become an effective modality, their predictability relies on successful osseointegration during the healing period.[7] Presently, there is insufficient information available to determine the effects of diabetes on the process of osseointegration. It cannot be assumed that diabetic disturbances in the periodontium apply directly to endosseous implants since there have been no controlled studies relating diabetes to the success or failure of dental implants. It is important to characterize how diabetes affects the process of osseointegration and the maintenance of implants.

Diabetes-specific complications are related to long-term increases in blood glucose concentrations. At the molecular level, there are both reversible and irreversible interactions with glucose metabolites. Reversible interactions occur as glucose metabolites react with proteins to form Schiff bases, which then transform to Amadori-type early glycosylation products.[8,9] The concentration of early glycosylation products is positively correlated to increases in glucose. For example, the early glycosylation product hemoglobin A_{1c} is used to detect recent levels of glycemic control in diabetic patients. Irreversible advanced glycosylation endproducts (AGEs) form as a result of a series of chemical rearrangements of the Amadori product and reactions with other molecules. These AGEs accumulate over a period of years on long-lived macromolecules such as proteins and lipids. This accumulation occurs as a function of glucose concentration and time.[8,10] Small changes in glycemic control may affect the amount of AGEs since they form with second order kinetics in relation to alterations in glucose concentration.[11] Oxidative stress is

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an additive factor that increases the rate of AGE formation. Free radicals are released from the AGE molecules and can react with the complexes that have already been formed.[12,13]

The hypothesis for this study was that osteogenesis around endosseous implants may be altered in diabetes because of changes in extracellular matrix components and bone metabolism caused by AGEs. The purpose of this study was to examine histometrically the rate and extent of bone wound healing associated with endosseous implants in normal and diabetic rats.

Materials and Methods

Animals. The study protocol was approved by the Harvard Medical School Committee on Animal Care. Twenty male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) were used in this study. Rats were 40 days of age at the time of diabetic induction and were age-matched to control animals. All procedures were performed under general anesthesia, specifically intramuscular ketamine, 44 mg per kg (Fort Dodge Laboratories, Fort Dodge, IA) and intramuscular xylazine, 5 mg per kg (Miles, Shawnee Mission, KS).

Diabetic Induction. Rats in the diabetic group were given a single 70 mg per kg intraperitoneal injection of streptozotocin (Zanosar, Upjohn, Kalamazoo, MI). Blood glucose was monitored by the glucose-oxidase method (Glucometer Encore, Miles, Elkhart, IN). Tail-nicked blood samples were obtained prior to diabetic induction, at the time of surgery, and at the day of sacrifice. A blood glucose level greater than 350 mg per dL was considered diabetic. Animals were also monitored for weight loss or gain as an indicator of overall health.

Surgical Procedures. Surgical procedures were performed under sterile conditions using general anesthesia as described above. Custom-fabricated, sterile, commercially pure, solid-cylinder titanium implants with a titanium plasma-sprayed (TPS) surface were designed (Institut Straumann AG, Waldenburg, Switzerland) to the appropriate dimensions for placement into the rat femur (2 mm in length and 1 mm in diameter). A 3-cm long incision was made on the posterolateral aspect of the right leg directly above the femur. A sharp incision through the muscle tissue exposed the midshaft of the femur, which was further isolated circumferentially with blunt dissection. Three osteotomy sites were prepared by rotary instrumentation at 500 rpm with sterile saline irrigation using a 0.9 mm twist drill (Institut Straumann AG), and the implants were then press-fit into position. The surgical field was closed in two layers by means of resorbable sutures. The rats were monitored in the postsurgical period for complications including pain, discomfort, and infection.

Histologic Preparation. Five diabetic and 5 control rats were sacrificed following 4 weeks of healing, and the remaining 10 rats were sacrificed after 8 weeks. Euthanasia was performed with carbon dioxide asphyxiation. Femora containing implants were fixed in 10% formalin, and nondecalcified specimens were prepared using a modified protocol as previously described.[14,15] The tissue blocks were dehydrated in step gradients of alcohol and infiltrated and embedded in methylmethacrylate resin. The embedded femora were sectioned longitudinally using a rotating diamond saw (Isomet, Buehler, Lake Bluff, IL) with a single section containing all three implants from each femur. Sections were ground and polished (Ecomet 3 and Petrographic Slide Holder, Buehler) to a final thickness of approximately 15 to 25 µm. To prepare femora sections, both ends of the implants were ground, resulting in final sections that were in the marrow. Sections were stained with Sanderson's Rapid Bone Stain (Surgipath Medical Industries, Richmond, IL) and then counterstained with Van Gieson's solution.[16,17]

Histometric Analysis. Histometric analysis was performed by means of a computer-digitized image analysis system (Metamorph Image Processing and Analysis System, Universal Imaging, West Chester, PA). Images were obtained using a light microscope with a high-resolution video camera (CDC/RGB-color video camera, Sony, Fujisawa, Japan) and viewed on a video monitor (PVM-1343MD Trinitron, Sony). Histometric analysis included the following measurements:

- Marrow bone density (MBD), the percentage of bone fill in an area circumscribing 250 µm around the implant excluding the cortex. The image analysis system was able to threshold the bone by color and to calculate the area occupied by bone in the designated field.
- Percentage of bone-implant contact (BIC), including the entire perimeter of the implant (both the cortical and marrow bone areas)
- Marrow bone–implant contact (MBIC), the percentage of bone-implant contact excluding the cortical zone

Statistical Analysis. A total of 60 implants were placed into the femora of 20 animals. Of these, 51 implants in 19 rats were available for histologic and histometric analysis. Analysis of variance (ANOVA) was calculated to compare healing among control and diabetic groups at 4 and 8 weeks healing for each histometric parameter. Bonferroni/Dunn multiple com-

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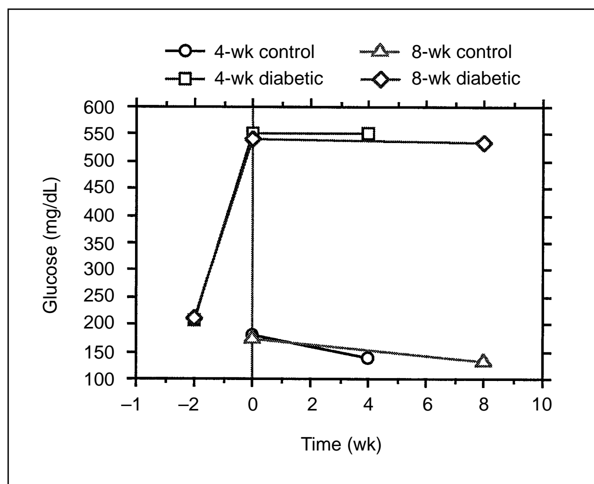

Fig 1 Blood glucose levels were within normal limits prior to diabetic induction. Diabetes was established prior to surgery and maintained throughout the healing period. Control rats maintained blood glucose levels within normal range throughout the experimental period.

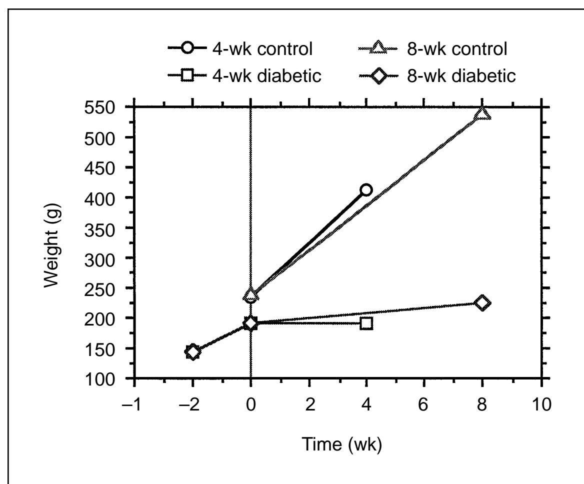

Fig 2 Control rats gained weight throughout the healing period. Diabetic groups gained weight at a reduced rate during the induction phase of the study. The 4-week diabetic group maintained its weight during the healing period, and the 8-week diabetic group continued to gain weight at a reduced rate.

Table 1 Blood Glucose Levels of Diabetic and Control Rats (Mean ± SD)

Group	–2 Weeks (mg/dL)	At surgery (mg/dL)	At sacrifice (mg/dL)
4-week diabetic	210 ± 35	553 ± 32	522 ± 59
4-week control		179 ± 70	140 ± 10
8-week diabetic	209 ± 32	541 ± 44	533 ± 79
8-week control		174 ± 32	132 ± 14

Table 2 Weight of Diabetic and Control Rats (Mean ± SD)

Group	–2 Weeks (g)	At surgery (g)	At sacrifice (g)
4-week diabetic	144 ± 11	191 ± 29	192 ± 41
4-week control		234 ± 11	412 ± 19
8-week diabetic	144 ± 6	190 ± 25	225 ± 61
8-week control		237 ± 4	536 ± 5

parisons procedures were performed to test the differences between groups. Analyses were performed with both the animal and the implant as the unit of measurement.

Results

Induction of Experimental Diabetes. The diabetic state (blood glucose ≥ 350 mg/dL) was predictably induced and maintained throughout the healing period. On the day of diabetic induction, the mean blood glucose levels were 210 ± 35 mg/dL and 209 ± 32 mg/dL for the 4- and 8-week groups, respectively. All rats in the diabetic groups had blood glucose levels ≥ 350 mg/dL at the time of surgery. The 4-week diabetic group had mean blood glucose levels of 553 ± 32 mg/dL at surgery and 522 ± 59 mg/dL at the time of sacrifice. The 8-week diabetic group had mean blood glucose levels of 541 ± 44 mg/dL at surgery and 533 ± 79 mg/dL at the time of sacrifice. The blood glucose of the control groups was within normal limits, with levels of 179 ± 70 mg/dL and 174 ± 32 mg/dL for the 4-week and 8-week groups, respectively, at surgery and 140 ± 10 mg/dL and 132 ± 14 mg/dL at the time of sacrifice (Fig 1 and Table 1).

As expected, the control rats' weight increased by approximately 75% and 125% for the 4-week and 8-week control groups, respectively. The diabetic groups continued to gain weight but at a reduced rate during the induction phase of the study. The weight of the 4-week diabetic group remained stable, and the 8-week diabetic group had a weight gain of approximately 20% during the surgical healing period (Fig 2 and Table 2).

Histologic Observations. At 4 weeks, implants in the control rats were osseointegrated with direct bone-implant contact visible at the light microscopic level (Fig 3). No connective tissue was noted between the bone and the implant. The implants were in contact with one of the cortical plates, and a continuous strut of bone encircled the implants. There was minimal new bone formation away from the implant surface, and no signs of an inflammatory or foreign body reaction were observed.

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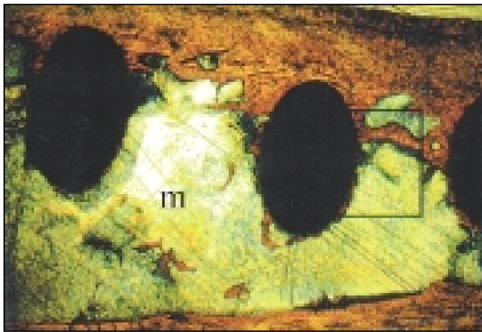
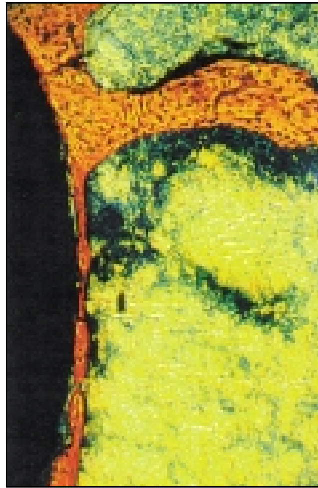
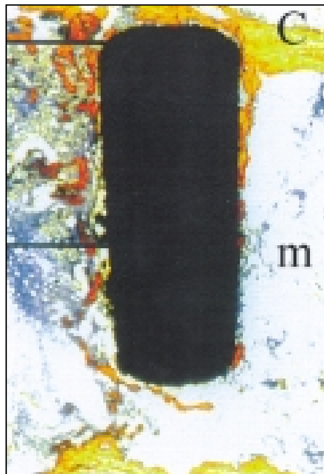




Figs 3a and 3b *(Left)* At 4 weeks, implants in control rats were osseointegrated with visible direct bone-implant contact. The implants were in contact with one of the cortical plates, and a continuous strut of bone encircled the implants. There was little new bone formation away from the implant surface and no signs of an inflammatory or foreign body reaction were observed (M = marrow) (original magnification × 20). *(Right)* Outlined aspect of 3a at higher magnification (× 100). Note absence of connective tissue between the bone and the implant.



Figs 4a and 4b *(Left)* At 4 weeks, implants in diabetic specimens were osseointegrated (× 20). There was direct bone-implant contact, and no evidence of an inflammatory reaction or foreign body response was found (C = cortical bone; M = marrow). *(Right)* Same aspect of 4a at a higher magnification (× 100). Note bone formation away from implant surface.

At 4 weeks, implants in diabetic animals were also osseointegrated (Fig 4). There was direct bone-implant contact; however, the majority of new bone formation was localized away from the implant surface within the marrow space. Again, no evidence of an inflammatory reaction or foreign body response was observed.

At 8 weeks, both groups revealed similar trends as shown at week 4. Implants in the 8-week control specimens were osseointegrated and had more mature and extensive bone formation, as evidenced by the frequent presence of reversal lines (Fig 5). The 8-week diabetic specimens were quite similar to those of the 4-week diabetic group. While the implants were osseointegrated, the bony architecture was located a distance away from the implant surface and appeared to be more immature and woven in nature (Fig 6).

Histometric Observations. Measurements for MBD and MBIC were taken on a total of 51 implants, while 45 implants had cortical contact and could be analyzed for BIC. In the marrow evaluations, a total of 9 implants were dislodged during histologic processing, including 4 implants from the normal group and 5 implants from the diabetic group. In the evaluation of the BIC alone, 15 implants were excluded, 7 from the normal group and 8 from the diabetic group.

Since diabetes is a systemic disease, the following results are reported with the individual rat as the unit of measure. The quantity of new bone formation around the implants was similar for diabetic and control groups. The rate and extent of new bone formation did not significantly increase from 4 to 8 weeks. At 4 weeks, the quantity of bone around the implants as measured by MBD was 0.10 ± 0.04 and 0.12 ±

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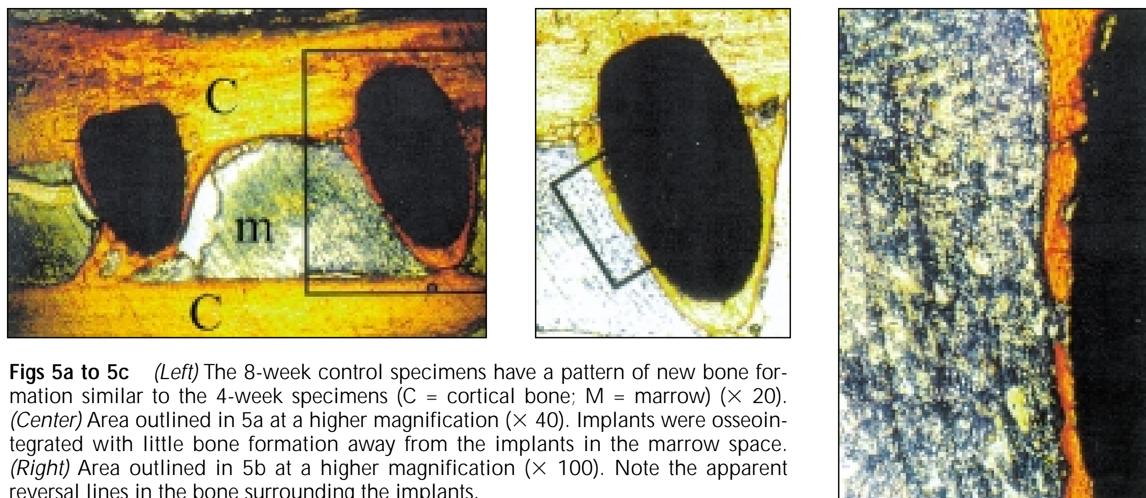
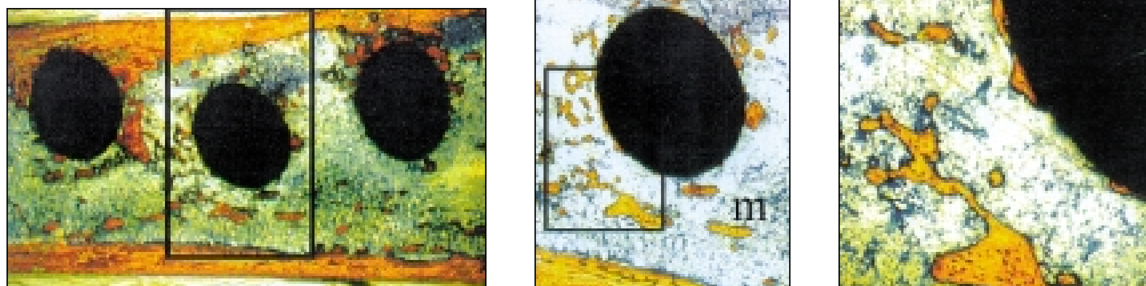


Figs 5a to 5c *(Left)* The 8-week control specimens have a pattern of new bone formation similar to the 4-week specimens (C = cortical bone; M = marrow) (× 20). *(Center)* Area outlined in 5a at a higher magnification (× 40). Implants were osseointegrated with little bone formation away from the implants in the marrow space. *(Right)* Area outlined in 5b at a higher magnification (× 100). Note the apparent reversal lines in the bone surrounding the implants.

Figs 6a to 6c *(Left)* The 8-week diabetic specimens were similar to those of the 4-week diabetic group (× 20). *(Center)* Area outlined in 6a at a higher magnification (× 40). The implants were osseointegrated with bone formation away from the implant surface in the marrow space (C = cortical bone; M = marrow). *(Right)* Area outlined in 6b at a higher magnification (× 100). Note the direct bone-implant contact in this diabetic specimen.



0.06 for control and diabetic groups, respectively. At 8 weeks, MBD was 0.16 ± 0.11 and 0.14 ± 0.04 for control and diabetic groups. ANOVA found no significant differences ($P > .05$) for MBD around the implants between the control and diabetic groups at 4 weeks (Fig 7) or 8 weeks (Fig 8). There also was no increase in MBD when the 4- and 8-week results were compared ($P > .05$; Fig 9).

At 4 weeks, the quantity of BIC was 50 ± 11% and 29 ± 4% for control and diabetic groups, respectively. At 8 weeks, BIC was 16 ± 11% and 14 ± 4% for control and diabetic groups. ANOVA found significant differences in the percentage of BIC between groups ($P < .005$). At 4 weeks, the difference in BIC between control and diabetic groups (Fig 10) was statistically significant ($P < .005$). While there were differences between the 8-week control and 8-week diabetic groups (Fig 11), these differences were not significant by Bonferroni/Dunn comparison at $P = .0122$ (significance at $P < .0083$). BIC did not increase for control or diabetic groups with the longer healing period (Table 3).

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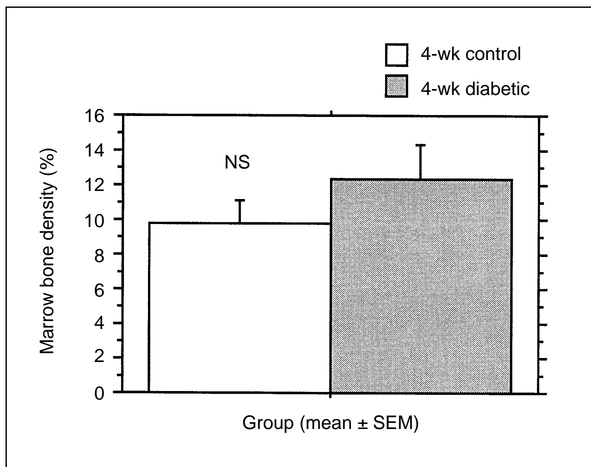

Fig 7 Marrow bone density at 4 weeks showing no significant difference between control and diabetic groups ($P > .05$).

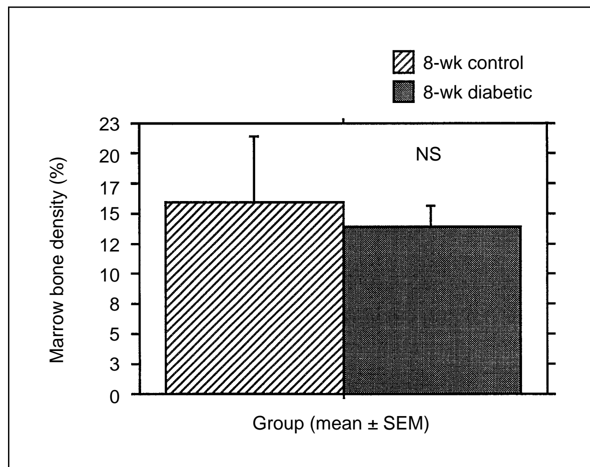

Fig 8 Marrow bone density at 8 weeks showing no significant difference between control and diabetic groups ($P > .05$).

MBIC, bone-implant contact excluding the cortical zone, showed significant differences between the groups ($P < .0001$). Values for MBIC were greater for control groups than for diabetic groups at 4 weeks ($P < .0001$, Fig 12) and 8 weeks ($P < .0001$, Fig 13). MBIC did not increase for the control or diabetic groups for the extended healing period (Table 4).

Statistical analyses using the implant as the unit of measurement produced results similar to those using the animal as the unit of measure (data not shown).

Discussion

This study reports on the effects of experimental diabetes on osseous healing around endosseous implants. Diabetes was predictably induced and maintained by a single intraperitoneal injection of streptozotocin in this rat model. Osseointegration was established for both diabetic and control groups, and analysis at the light microscopic level revealed differences in the pattern of bone formation between the groups. Implants placed in control rats were consistently embedded in bone, with minimal to no bone formation located in the marrow space away from the implant surface (Figs 3 and 5). In the diabetic animals, osseointegration was observed, although with an altered pattern of bone quality (Figs 4 and 6). The morphology of the newly formed bone appeared immature and disorganized as compared to normal controls. Most apparent was bone formation away from the implant surface in the region of the marrow space. Histometric evaluation demonstrated that the quantity of new bone in the peri-implant region 250 µm from the surface was similar for diabetic and control groups (Figs 7 and 8).

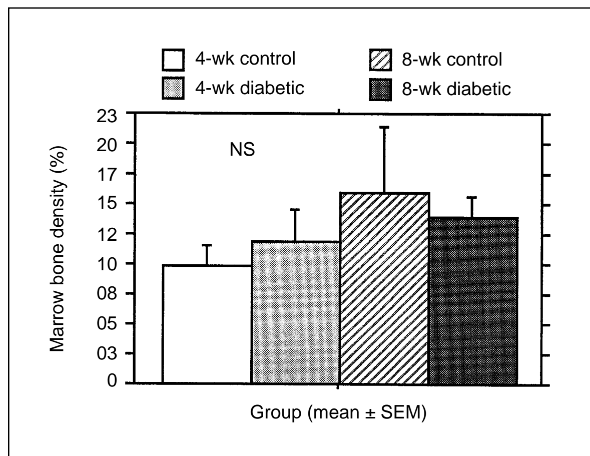

Fig 9 Comparison by ANOVA did not find differences among the groups for marrow bone density ($P > .05$).

The rate of osteogenesis did not significantly increase from 4 to 8 weeks (Fig 9). However, there was significantly more bone-implant contact in the control compared to the diabetic rats. There was also a corresponding reduction in the percentage of osseointegration in diabetic compared to control animals, as measured by direct bone-implant contact (Figs 10 to 13). These results were consistent for analysis around the entire perimeter of the implant (BIC) and when the analysis was limited to the part of the implant within the marrow space (MBIC).

Specific alterations in bone formation and remodeling have been associated with diabetes. Insulin is an important hormone not only for glucose control,

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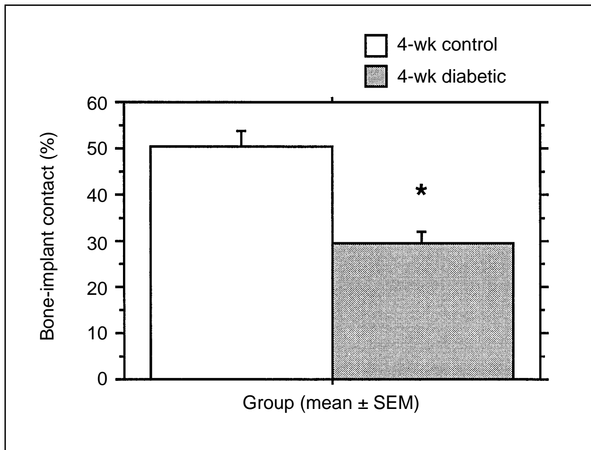

Fig 10 Bone-implant contact at 4 weeks (*P = .0027).

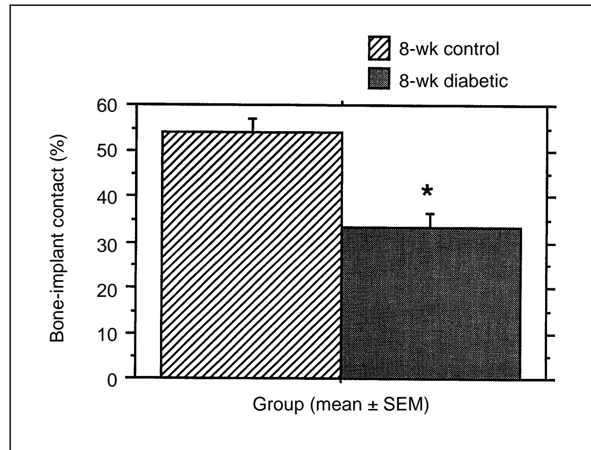

Fig 11 Bone-implant contact at 8 weeks (*P = .0122).

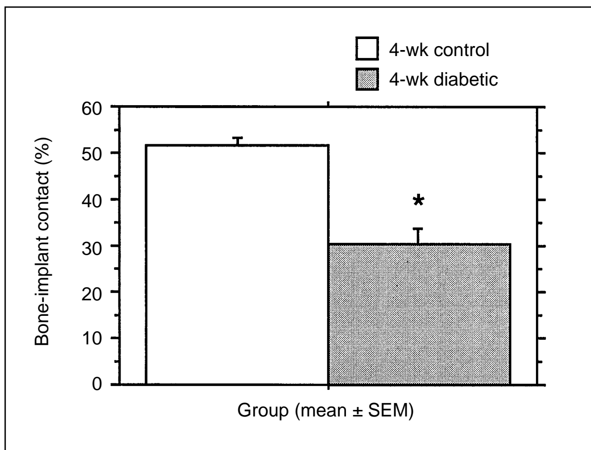

Fig 12 Marrow bone–implant contact at 4 weeks (*$P < .0001$).

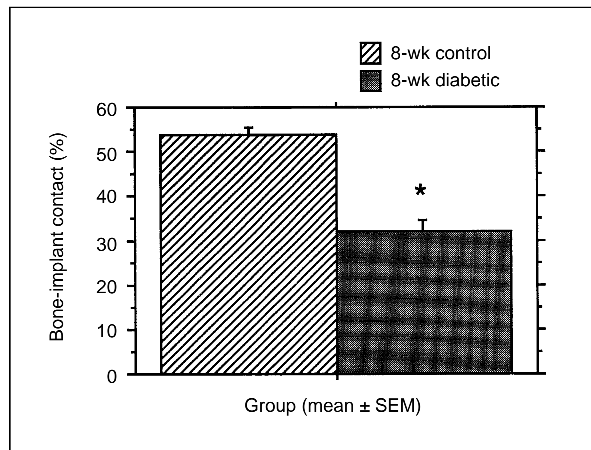

Fig 13 Marrow bone–implant contact at 8 weeks ($P < .0001$).

Table 3 Bonferroni/Dunn Comparisons* for Bone-Implant Contact

Group A	vs	Group B	*P* value
4-week control		4-week diabetic	.0027
8-week control		8-week diabetic	.0122
4-week control		8-week control	.7165
4-week diabetic		8-week diabetic	.3356

*Comparisons are not significant unless the corresponding *P* value is less than .0083.

Table 4 Bonferroni/Dunn Comparisons* for Marrow Bone–Implant Contact

Group A	vs	Group B	*P* value
4-week control		4-week diabetic	< .0001
8-week control		8-week diabetic	< .0001
4-week control		8-week control	.5872
4-week diabetic		8-week diabetic	.3932

*Comparisons are not significant unless the corresponding *P* value is less than .0083.

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but in modulating normal skeletal growth.[18] It does not regulate bone resorption, but stimulates bone matrix synthesis, and it has both direct and indirect effects on bone metabolism. Insulin stimulates osteoblast matrix synthesis directly and stimulates insulin-like growth factor-I (IGF-I) production by the liver indirectly.[19] IGF-I increases bone formation directly and indirectly by expanding osteoblastic populations (as a mitogen) and inducing the bone cell phenotype (as an osteoinductive molecule).[20]

Additional bone-related characteristics, including mineral homeostasis, osteoid production, and bone formation, are also reduced in experimental diabetic models.[21–23] Goodman and Hori[21] reported that the volume of mineralized bone and bone matrix was reduced in diabetic animals. In addition, the lag time for osteoid mineralization was increased for uncontrolled diabetic animals. In the same study, diabetic animals treated with insulin showed bone growth and osteoid formation at rates similar to those of controls. Bone turnover, as measured by percentages of osteoclasts, osteoblasts, and osteoid surface, failure to incorporate bone fluorochromes, and decreases in osteocalcin synthesis, has been shown to be reduced.[24–27]

The differences in bone quality for diabetic animals resulted in subsequent reductions in osseointegration of the implants at 4 and 8 weeks. The inhibition of osseointegration in our diabetic model may be the result of interactions between AGEs and the TPS surface of the implants. It is important that future studies attempt to identify the localization of AGEs in the peri-implant zone. Surface inhibition may decrease the amount of direct bone-implant contacts. Future studies may use in vitro approaches to examine the effect of AGEs on osteoblastic cells cultured on TPS or pure titanium.[28] It may be postulated that the presence of AGEs in the osseous tissues produces a less than favorable environment for osseointegration. It is important to recognize that osseous healing has previously been noted to be impaired in diabetes.[19,21–23,29] It may be that the extent of osseointegration achieved in this study is consistent with a decreased rate of bone healing and bone homeostasis and is not affected by a direct interaction between AGEs and the implant surface.

AGEs have been highly implicated in the pathogenesis of diabetes, since they cause qualitative and quantitative alterations in extracellular matrix components such as collagen, laminin, and vitronectin. The quality and quantity of proteoglycans have also been shown to be affected in experimental diabetes, including a decrease in the total number of proteoglycans as well as in the size of the aggregate molecules.[29] AGEs disturb cell adhesion, growth, and matrix accumulation, and may directly alter DNA and nuclear proteins.[10] Collagenase production in healing wounds is increased and has been shown to correlate with nonenzymatic glycosylation of collagen (AGE formation).[30] AGE molecules specifically inhibit the lateral association of collagens into the normal network-like structure.[31,32] Efforts have been made to pharmacologically inhibit this increased collagenase activity with tetracycline or chemically modified tetracyclines (CMTs). These treatments have decreased collagenase in animal models, and they have been effective in preventing bone loss in experimental periodontitis lesions.[33–35] These CMTs may have potential in lowering collagenase levels, which may affect the process of bone formation and remodeling, and therefore osseointegration.

Drug-induced and genetic diabetic rat models have been used extensively to study the effects of diabetes on wound healing. The genetic model exhibits many similarities to human diabetes and uses animals that develop an inherited form of diabetes.[36,37] The chemically induced model has been economical and predictable in obtaining uncontrolled diabetes, and can be maintained for several months.[38] Streptozotocin has been shown to be toxic to the beta cells in the pancreas, resulting in high blood glucose, diuresis, and failure to gain weight.[39,40] Nanci et al[41] have placed titanium miniscrews in the rat tibia and studied osseointegration in normal rats at the ultrastructural and immunocytochemical level. In an effort to understand how healing mechanisms of osseointegration are affected by diabetes, our group proposed using a new model system as presented in this investigation.

All histometric analyses were performed as a proportion calculation versus an absolute value measurement. This eliminated the possibility of bias caused by the angle of histologic sectioning. The implants were sectioned longitudinally, with one section per femur for the three implants. Some specimens include the whole implant longitudinally, while others project the implant more in cross section. A large sample size was used to minimize the effects of these factors. The differences in wound healing around the implants in diabetic and control specimens can be attributed to the hyperglycemia induced by the streptozotocin.

Considerations were made as to the effects of nutrition on the changes observed in bone healing around the implants in this study. The control animals gained weight as expected and the diabetic animals exhibited minimal weight gain (Fig 2) as shown previously with this animal model.[42] If the rats had lost body weight, there may have been a protein-wasting state. The effects of limited weight gain, weight loss, and specific nutritional deficiencies in

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relation to diabetes have been investigated.[43] Weight loss or nutritional deficiencies failed to reveal independent effects on wound healing. In studies on bone morphology, Verhaeghe et al[24] found that semi-starved rats with the same body weight as diabetic animals had similar delays in rate of bone growth, but did not reveal the same cellular and molecular defects as the diabetic animals. Diabetic rats had decreased numbers and/or function of osteoblasts, decreased osteoid surface, decreased mineral apposition rate, and decreased plasma osteocalcin levels. The study concluded that these changes in bone metabolism could not be attributed to weight loss alone, in concurrence with similar investigations.[15]

Conclusion

The streptozotocin-induced diabetic model produced altered blood glucose levels to allow the study of the effects of diabetes on osseointegration of titanium implants. Diabetes was predictably induced and maintained, and osseointegration was consistently found in diabetic and control specimens. The rate of new bone formation in a zone circumscribing 250 µm around the implants was similar for diabetic and control animals. However, bone-implant contact was significantly reduced for diabetic compared to control animals. It is important to recognize that the model used in this study was of an uncontrolled diabetic status. The results imply that patients with elevated glucose levels should not be treated with dental implants. Future investigations should aim to better understand the role of insulin control, the molecular mechanisms involved in diabetic bone wound healing, and endosseous implant osseointegration.

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