

segments with earlier restoration of function and concomitant decreased need for maxillo-mandibular fixation or the wiring of jaws.

The most common location for mandibular fractures was found to be in the third molar or angle region of the mandible. Our overall complication rate was consistent with other large retrospective published studies. Infection accounted for the highest incidence of complications followed by non-union of the fractures. Closed reduction techniques yielded a lower level of complications when compared to open techniques; however, the data were not standardized as to severity of presenting fractures. Most complications encountered in the study population were relatively minor and resulted in eventual favorable outcomes.

Newer techniques of rigid fixation are constantly being developed to optimize treatment outcomes for facial fracture management. We have been involved with laboratory testing of different plating systems including resorbable plates, lag screw systems and most recently mandibular locking screw plates. Recent biomechanical studies involving resorbable plating systems yielded some interesting findings. It is necessary to heat plates in order to adapt the plates to the facial skeleton. Our study involved repetitive heating cycles with adaptation of the plate to the orbital-zygomatic region and stress testing with molecular weight analysis. Molecular weight was found to decrease with repetitive heating and bending by up to 18%. Results of the study indicate that repetitive bending and heating of the resorbable plating systems may affect the mechanical and molecular properties, although not to an extent that is clinically significant. It would be prudent for the surgeon to limit the number of heating cycles when possible.

Another study assessing failure strengths of locking screw plates versus conventional mandibular plates was undertaken utilizing bovine ribs as a model for the human mandible. The premise behind the locking screw plate is to distribute forces between the threaded portion of the plate and screw rather than generating compressive forces between the plate and the lateral cortical plate of the mandible. This is postulated to limit stress shielding and allow for more stable fixation over time, hence preventing failure of rigid internal fixation. From a mechanical perspective, it was determined that there was no statistical difference between both systems. It was concluded that success of the plates may be more related to variables in operator application and bone quality rather than to differences in the hardware. Clinical prospective data are needed to investigate this hypothesis further. It is hoped that studies such as those described above will aid in the development of improved systems and techniques for the surgical treatment and rehabilitation of our facial trauma patients.

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# Impaired bone healing in patients with diabetes mellitus

by Sheldon S. Lin

**F**racture healing is a process of restoring the structural and biological properties of injured bone. It has been well documented that diabetes mellitus (DM), a systemic disease affecting 17 million Americans, causes increased healing time with a concomitant increase in delayed unions and non-unions. Unfortunately, the specific mechanism for the delayed fracture healing in patients with diabetes has yet to be elucidated.

The purpose of our research is to evaluate the role of insulin and glucose control on the fracture healing process using our recently established femur fracture model in diabetic BB Wistar rats. We theorize that insulin plays a critical role in the fracture callus, especially on the early inflammatory phase and the expression of local growth factors, and its relative absence leads to impaired fracture healing in diabetics.

Annually, 6 million fractures are treated in the U.S., with 5-10% exhibiting complications such as delayed union or non-union. Etiologies of impaired fracture healing include smoking, open fractures, presence of underlying infection, certain medications (i.e. steroids) as well as systemic disease such as diabetes mellitus (DM). It is estimated that more than 30 million Americans will be diagnosed with diabetes within the next decade.

The effects of diabetes upon fracture healing have been well documented with increased healing time (2-3 times the normal rate) and concomitant increased complications (delayed union, non-union, etc). In order to study these problems, our lab has established a diabetic femur fracture model for analyzing the effect of tight blood glucose and the role of early critical growth factors upon impaired diabetic fracture healing.

## Diabetic Femur Fracture Model

Previous diabetic models were induced with cytotoxic agents (alloxan, streptozotocin) that preferentially destroy pancreatic beta cells. These cytotoxins result in a clinical condition of insulin-dependent DM, Type I diabetes. The key criticism of this method was its inability to determine whether the deficient diabetic fracture healing process is due to the systemic effect of the cytotoxins, malnutrition and/or the diabetic condition itself.

Our recently published diabetic femur fracture model utilizes BB Wistar rats, which spontaneously develop diabetes through the autoimmune destruction of pancreatic  $\beta$  cells. The spontaneous onset of diabetes in the BB Wistar rat confers advantages over the viral, chemical and immunological induction of DM. Within seven days after glycosuria, the beta cells were completely destroyed and if untreated, marked wasting of the body tissue, including fat, muscles, protein, dehydration and ketosis supervene. Death usually resulted within five to 10 days after onset. These conditions were resolved with insulin treatment. The BB Wistar rat currently represents a close homology of human Type I diabetes in a laboratory animal.

## Diabetic Femur Fracture Model: Effect of Blood Glucose Control

Our published studies were able to demonstrate that femur fracture healing in poorly controlled diabetic rats (blood glucose > 300 mg/dl) is reproducibly delayed compared to non-diabetic control animals. Tight glucose control, through increased insulin treatment resulting in blood glucose val-



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ues of approximately 120 mg/dl, ameliorates impaired diabetic fracture healing. The average blood glucose values for the “loose control” (LC) and “tight control” (TC), and non-diabetic (non-DM) animal were 369.0, 118.9, and 70.5 mg/dl, respectively. The non-diabetic and diabetic (LC, TC) fracture calluses were analyzed for cellular proliferation, histology, growth factor protein/gene expression and biomechanical parameters to identify differences in the fracture healing process.

betic and TC diabetic fracture callus. At four days, there seemed to be a greater number of pre-chondrocytes and immature, proliferating chondrocytes in non-diabetic and the TC diabetic fracture callus compared to the LC diabetic callus. Although the callus area did not differ between the different groups, there appeared to be a greater amount of newly formed osteoid in non-diabetic and TC diabetic fracture callus compared to the LC diabetic fracture callus. At seven days, the periosteal callus appeared similar in all

## WITH TIGHT PHYSIOLOGIC GLUCOSE CONTROL, THE NUMBER OF PROLIFERATING CELLS IN THE TC DIABETIC FRACTURE CALLUS WAS SIGNIFICANTLY INCREASED COMPARED WITH THE LC DIABETIC CALLUS.

### Cellular Proliferation

Cellular proliferation rates were determined at two, four and seven days post-fracture within the fracture callus by immunohistochemical staining for bromodeoxyuridine (BrdU). Its expression can only be detected in the nucleus of proliferating cells and is a specific marker of proliferating cells. We found a statistically significant reduction in proliferating cells in the LC diabetic fracture callus as compared to the non-diabetic callus at days two and four post-fracture. With tight physiologic glucose control, the number of proliferating cells in the TC diabetic fracture callus was significantly increased compared with the LC diabetic callus.

### Qualitative Histology

Histological examination at two days post-fracture showed a fracture callus that was similar in all three groups. However, the LC diabetic fracture callus lacked small areas of intramembranous bone formation found in the non-dia-

three groups but the gap callus in non-diabetic and TC diabetic animals appeared to be more advanced than in LC diabetic animals, with greater areas of cartilage formation characterized by more proliferating and hypertrophic chondrocytes. (See figures 1, 2.)

### Biomechanical Testing

Biomechanical testing was performed using scanning acoustic microscopy (SAM) and a servo-hydraulics mechanical testing apparatus (MTS machine). Acoustic microscopy is a non-destructive ultrasonic technique that has recently been used to study bone remodeling. A positive correlation exists for cortical bone between the acoustic impedance and the mechanical stiffness. The acoustic impedance values in the LC diabetic fracture callus were significantly lower than in the non-diabetic fracture callus at six weeks ( $4.79 \pm 0.34^*$  vs.  $5.62 \pm 0.50$ ;  $p < 0.05$ ) and at eight weeks ( $5.31 \pm 0.34$  vs  $6.11 \pm 0.21$ ;  $p < 0.05$ ). Acoustic impedance values in the TC

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diabetic callus were normalized. Levels at six and eight weeks were  $5.70 \pm 0.23$  and  $6.20 \pm 0.29$ . They were not significantly lower than non-diabetic callus. There was a significant reduction in callus bone content in LC diabetic animals compared to both TC diabetic and non-diabetic animals. The delay in endochondral ossification and subsequent remodeling in the LC

there appeared to be less overall staining in all factors in the LC diabetic callus when compared to the non-diabetic callus. This suggested that the delay in the diabetic fracture healing process may be preceded by a reduction in early growth factors critical for endochondral bone formation.

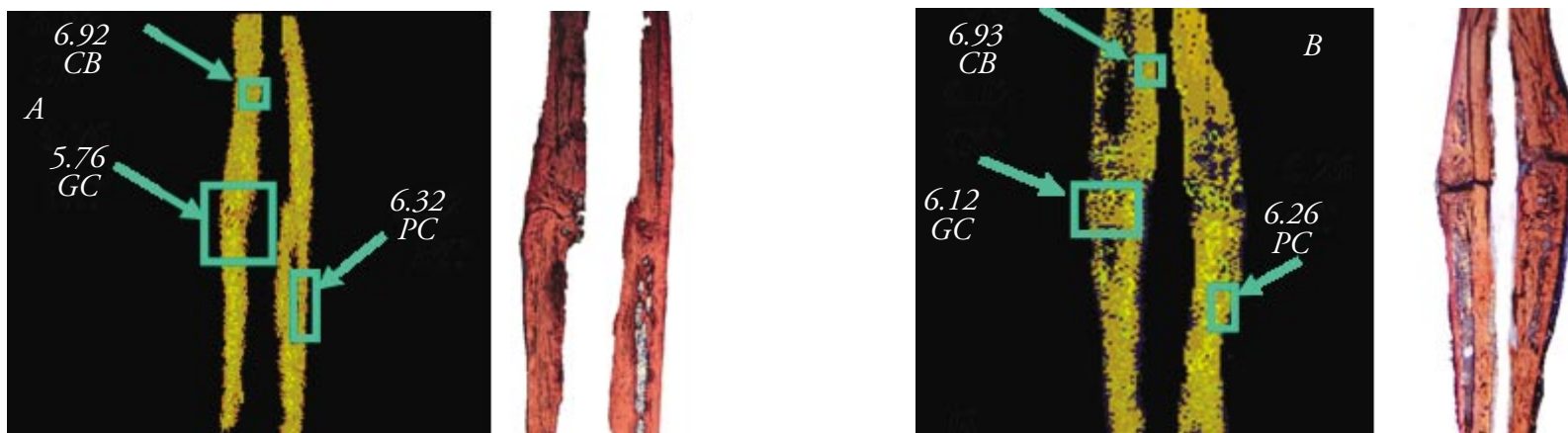


Figure 1: SAM images and corresponding histology at 8 weeks: pseudo-color maps of acoustic impedance values determined by the SAM, with corresponding histology in A) non-diabetic and B) tightly controlled diabetic animals. CB= cortical bone, GC=gap callus, PC=periosteal callus.

diabetic callus was normalized in TC diabetic animals at six and eight weeks.

Mechanical testing supported the earlier parameters of the positive effect of tight blood glucose control. At six weeks post fracture, torque to failure and stiffness in the TC diabetic fractured femur were normalized to values not statistically different from non-diabetic values. Values of polar moment of inertia and area were also statistically lower in the LC diabetic fracture callus when compared to the non-diabetic callus. These geometric parameters were normalized in the TC diabetic callus. When data was normalized to contralateral, intact limbs, both percent of torque to failure and percent of stiffness were significantly reduced in LC diabetic animals compared to non-diabetic and TC diabetic animals.

In an attempt to understand possible mechanisms of impaired DM fracture healing process and its resolution with systemic insulin (tight control), we theorized impaired DM fracture healing occurs secondary to the decreased and/or uncoordinated release of local growth factors at the fracture site, an impairment of the early inflammatory phase leading to insufficient growth factor production. With the established model, the presence and expression of the early critical growth factor were analyzed using immunohistochemistry and quantitative competitive RT-PCR.

### Immunohistochemistry

Significant reduction in the local growth factor expression and production in the LC diabetic fracture callus was observed compared to the non-diabetic callus. Although most of the patterns identified for the localization of each of the growth factors investigated at 4 days were comparable between the non-diabetic and LC diabetic callus,

### mRNA Quantitation

The amounts of PDGF-B, TGF- $\beta$ 1 and IGF-I mRNA were significantly reduced in DM animals when compared to controls. By seven days, PDGF-B and IGF-I mRNA levels were normalized in DM animals while TGF- $\beta$ 1

expression remained significantly lower in DM callus. VEGF mRNA levels were significantly reduced in the DM when compared to the non-DM fracture callus at day seven.

Our data supports the theory that the deficiency in DM fracture healing occurs early, with a delay in the expression of these growth factors concurrent with a histologic delay in the progression of chondrogenesis. These findings provide the impetus for our lab's current focus into the application of fracture healing adjuncts including local insulin delivery, low intensity pulsed ultrasound, pulsed electromagnetic field, and local growth factor delivery, as possible fracture healing treatments in diabetic patients.

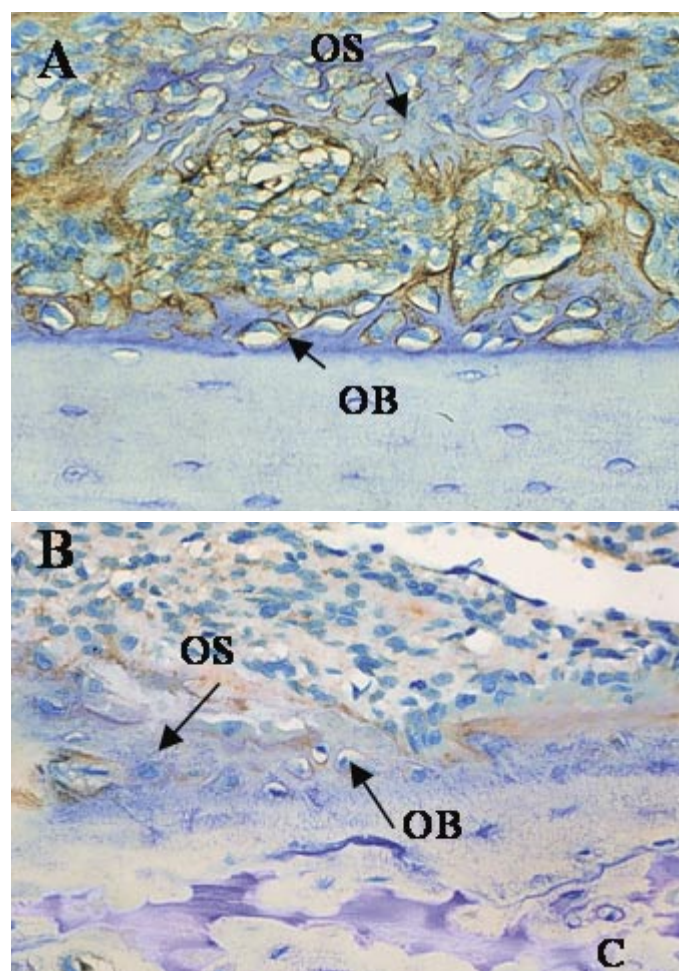


Figure 2: TGF-b1 Immunolocalization in Periosteal Callus: TGF-b1 localization by immunohistochemistry at 4 days post fracture in A) non-DM and B) LC-DM callus. C= cortical bone, OB= osteoblast, OC= osteocyte, OS= osteoid.

Sheldon S. Lin, MD, attended Pennsylvania State University as part of a six year BS-MD program and earned his MD from Jefferson Medical College. He continued his studies as research fellow under Rocky Tuan, PhD, his orthopedic residency under Richard Rothman, MD, PhD, at Thomas Jefferson University Hospital and his foot and ankle fellowship at the Medical College of Wisconsin. He has held an appointment since 1996 in the Department of Orthopaedics of UMDNJ-New Jersey

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