Decreased Levels of Growth Factors at the Fusion Site of Diabetic Patients Who Experience Non-Union After Hindfoot Fusion

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ABSTRACT INTRODUCTION:
The association between diabetes mellitus (DM) and impaired osseous healing has been examined in both clinical and laboratory settings (1-3). Studies have shown that DM patients have an increased incidence of delayed union, non-union, and pseudarthrosis (4-7).

One hypothesis explaining impaired fracture healing in DM patients can be attributed to deficiency in growth factor levels. At any trauma site involving bone, a clot forms with platelet alpha granules acting as a reservoir of exogenous growth factors. The degradation of the alpha granules results in the release of platelet derived growth factor-AB (PDGF-AB), vascular endothelial growth factor (VEGF), insulin growth factor-1 (IGF-I), and transforming growth factor β1 (TGF-β1) among a host of other growth factors providing an environment localized to the site of injury.

Growth factors are locally produced within the fusion bed, and play a critical role in cellular chemotaxis, cellular proliferation, extra-cellular matrix production, and angiogenesis. Although specific studies regarding growth factor localization during the inflammatory phase following a fracture in a DM animal model are few, growth factors during the inflammatory phase of wound healing have been extensively studied. The defect during DM wound healing appears to be partly due to deficient local growth factor concentrations.

METHODS:
This prospective study included 12 adult diabetic subjects requiring hindfoot fusion from one U.S. center. Institutional board ethics committee approval was obtained. These were adult patients with an average age of 59 years old (range 49-71), and all had been diabetic for at least ten years. During each procedure, a bony bed sample was taken from the fusion site immediately frozen at -80 °C, then analyzed for growth factors (PDGF-AB, VEGF, IGF-I, TGF-β1) using ELISA kits (R&D Systems), and for total protein level using BCA analysis (Pierce). Union was defined by two independent board certified orthopaedic surgeons using x-rays and physical examination.

RESULTS SECTION:
Table 1 indicates the average level of each growth factor, after normalization to total protein level, in relation to the outcome of that patient. Four of twelve patients went onto non-union after the procedure. Hindfoot fusion site from the four non-unions, had a 65% decrease in PDGF-AB (Figure 1) and a 48% decrease in VEGF (Figure 2) compared to patients who do achieve union and pink shows level for those with non-union (* represents statistical significance).

Quantifying the levels of growth factors of interest, after normalizing to BCA total protein levels, found that the four non-union samples had a 65% decrease in PDGF, a 48% decrease in VEGF, no change in IGF-I, and a non-significant increase in TGF-β1. These results confirm our hypothesis that certain growth factor levels within the fusion site of DM patients have an impact upon the success of the hindfoot fusion.

Limited research studies demonstrate that high risk patients have significant growth factor deficiencies. DM fracture models using BB Wistar rats have shown significantly lower growth factor levels, correlating to impaired fracture healing (8,9). This data was corroborated by our study as we saw significant decreases in PDGF-AB and VEGF levels in patients who had non-unions. However, our study showed no difference in local IGF-1 levels and showed a non-significant increase in local TGF-β1 levels in patients with non-unions.

Elusive arthrodesis in patients with DM has been analyzed in several series, with higher complication rates compared to their non-DM cohort (5,6). These complications and non-unions can be due to decreased levels of growth factors in DM patients shown by our study.

In conclusion, the results of our study illustrate that DM patients who have non-unions have decreased levels of growth factors, specifically PDGF-AB and VEGF, when compared to patients who do achieve union. Our results imply that local growth factors, such as PDGF-AB and VEGF, play an integral role in the early bone healing.

REFERENCES: