Non-Union Development Related to Pathologic Callus and Plasma Amino Acid Concentrations

INTRODUCTION

Overall five to 10 percent of all patients with a fracture develop an insufficient healing process resulting in a non-union formation. Malnutrition, drug therapy, inadequate stabilization and fixation of the fracture parts, disturbed mechanical loading, inadequate blood supply and metabolic disorders are several causes for increased risk of fracture non healing. Previous experimental studies showed the importance of sufficient nitric oxide (NO) availability during normal fracture healing.

A strong regulation of NO is essential, since the NO effect appears to have a dual effect on bone metabolism with high NO concentrations being detrimental and low-normal NO concentrations beneficial. There is evidence that arginine (ARG), as the primary precursor for NO synthesis, is essential during NO-regulated fracture healing in experimental settings. ARG is a nonessential amino acid derived from protein breakdown, food intake, and from endogenous conversion of citrulline (CIT) into ARG and degraded into ornithine (ORN) and urea by arginase or into CIT and NO, through NOS-synthases enzymes. During conditions of stress, such as wound healing and inflammation, arginine metabolism changes and ARG availability is probably limited. ARG may therefore become rate-limiting for the production of NO.

We hypothesize that deficient amino acid concentrations, especially ARG, at the fracture site lead to the development of atrophic non-union during fracture healing due to insufficient callus formation.

RESULT SECTION

Thirty patients were included in this study; twelve atrophic non-unions, 6 hypertrophic non-unions and 12 control patients. The control patients were 6 acute fracture patients and 6 patients in whom the osteosynthesis material was removed after normal consolidation. All non-unions healed eventually after surgical interventions.

Callus Arginine concentrations (61.15 µmol/mg vs. 127.50, p<0.05; (Figure 2), CIT (13.0 µmol/mg vs. 29.0, p<0.05) and ORN (24.54 µmol/mg vs. 110.50, p<0.05) were significantly reduced in all atrophic non-union samples compared to control patients. These concentrations were all increased in the hypertrophic non-unions compared to control patients.

ARG plasma concentrations were significantly reduced in hypertrophic non-unions (62.0 µmol/L, p < 0.001, (Figure 3) and acute fracture patients (44.0 µmol/L, p<0.001), but not in the atrophic non-unions (84.17 µmol/L, p>0.001). ORN plasma AA were increased in all three patients groups, respectively 59.83 µmol/L for the acute fractures, 65 µmol/L in the atrophic non-unions and 84.50 µmol/L in the hypertrophic non-unions, compared to control patients (53.89 µmol/L, p < 0.05).

DISCUSSION

In this study, the callus and plasma amino acid concentrations of arginine, citrulline and ornithine were evaluated to detect whether changes in the arginine-NO metabolism are likely to be present in humans during non-union. Interestingly, the amino acids are significantly different, systemically and local, in both non-union patient groups.

According to our hypothesis, atrophic non-unions showed reduced concentrations of arginine, citrulline and ornithine compared with acute fracture patients and normal controls, as hypertrophic non-unions show the opposite phenomenon. Therefore, reduced arginine concentrations during fracture healing may be related to a dysregulation of the normal fracture healing process.