Predicting Fracture Healing with Biomarkers: The Potential for Precision Medicine to Assess Patient Risk of Fracture Nonunion

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Objective:

To provide a comprehensive survey of the literature related to the current efficacy of biomarkers for predicting fracture healing.

Methods:

EMBASE and PubMed, were searched using the following terms: fractures, biomarkers, ununited, and nonunion with the assistance of a medical librarian. The initial search yielded 199 records. Additional search of Google Scholar and review of the references yielded zero additional records. The 165 unique records were screened, of which 105 were excluded due to experimental treatments, non-fracture related bone healing, animal studies, and study group design failure to compare union versus nonunion fracture outcomes. This left 21 articles for full review.

Results:

19 serum biomarkers were reviewed for nonunion predicative capability. From this cohort 9 biomarkers had promising results including; bone formation markers OC and PINP, bone resorption markers TRAP and OPN, growth factors VEGF and PGF-1, T_{EMRA} and T_{Reg} cells, and miR-193a-3p. 15 SNPs on 11 genes were examined. The polymorphisms with the greatest potential for increased risk of nonunion based on odds ratio include; SMAD6 rs2053423 T/T genotype OR = 10.27. IL-1b rs2853550 T allele OR = 5.9. NOG rs1372857 G/G genotype OR = 4.56. NOS rs2297514 OR = 3.98. and PDGF CCG haplotype OR = 3.57

Conclusion:

There remains an unmet clinical need to develop predictive parameter(s) for bone healing that are objective, reproducible, preferably continuous, unique to the individual, and optimally based on a readily accessible biologic measurement. Ultimately yielding a biomarker predictive of future nonunion that is additive, or superior, to that of known clinical risk factors for nonunion.

Clinical Implications:

Accurate biomarkers could identify patients at early times post-injury who may benefit from intervention to promote healing, thus circumventing unnecessary delays in nonunion intervention. Additionally, biomarkers could eliminate preemptive surgery in patients with early slow progression who are otherwise on a healing trajectory.