**Appendix**

**Table A1:** Summary of current evidence regardingtreatment of stress fractures and bone defects with direct injectable bony treatment modalities. (BMA = Bone marrow aspirate, DBM = Demineralized bone matrix, PRP = Platelet-rich plasma, VAS = Visual analog scale, IKDC = International knee documentation committee, FAOS = Foot and ankle outcome score, KOOS = Knee injury and osteoarthritis outcome score)

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| **Treatment Option** | **Authors** | **Level of Evidence** | **Outcomes/ Conclusions** |
| **Concentrated bone marrow aspirate** |  |  |  |
|  | Jäger M et al.8 | Level IV case series. (*n = 10 human patients)* | Mesenchymal stem cells isolated from BMA produced osteogenic differentiation in vitro without osteogenic stimuli. |
|  | Gianakos A et al.10 | Systematic Review of 35 articles | 100% of articles demonstrated significantly increased bone formation on radiographs when BMAC was applied. |
|  | Lee DH et al.11  | Level I RCT of 44 tibias | Tibial osteotomy sites treated with BMA and PRP showed faster healing at all cortices than controls. |
|  | Imam MA et al.12 | Systematic Review of 31 articles (minimum Level IV) | Current uses of BMA for bone include non-union and fracture healing, bone defects, spine fusion, and distraction osteogenesis. |
|  | Murawski CD et al.13 | Level IV case series. (*n=26 human patients*) | 23 of 26 athletes with proximal 5th metatarsal Jones fractures returned to previous level of sport at mean 5 weeks post internal fixation with BMA applied.  |
|  | Lovy AJ et al.14 | Level III retrospective case control (*n=33 humans*) | 11 atypical femur fractures treated with IM rod fixation and BMA united significantly faster than 22 controls that did not receive BMA. |
| **Autologous Platelet-Rich Technologies** |  |  |  |
|  | Guzel Y et al.18 | Level II prospective randomized controlled trial. (*n=60 rats*) | Femur fractures in PRP-treated group demonstrated earlier weight-bearing, accelerated fracture healing and greater maximum loading force than controls.  |
|  | Gianakos A et al.19 | Systematic review of 29 articles.  | 89% of articles reported significant improvement in earlier bone healing on histologic evaluation when PRP was applied. 100% of articles reported increased radiographic bone formation when PRP was applied.  |
|  | Simman R et al.20 | Level III case-control series. (*n = 48 male rodents*) | Rat femur fractures showed increased cortical width and callus at 4 weeks post fracture compared with saline controls.  |
|  | Griffin XL et al.21 | Systematic Review of 1 article.  | 21 patients undergoing corrective osteotomy showed a statistically significant increase in union rate at one year when PRP was applied.  |
|  | Gandhi A et al.23 | Level I prospective randomized trial. (n=92 rodents) | 24 diabetic rats with femur fracture treated with PRP showed normalization of early fracture callus compared to non-PRP treated rats.  |
|  | Malhotra A et al.24 | Review article | PRP appears to benefit bone healing only when used in combination with osteoconductive scaffolds. |
| **Injectable bone graft substitutes** |  |  |  |
|  | Tiedeman JJ et al.25 | Level III prospective case series. (*n=24 canines*) | Combined bone marrow and DBM produced a synergistic response at bony defects which was equal to autogenous bone grafting.  |
|  | Elena N et al.25 | Case report and technique description. | Mixed PRP and DBM were injected after core decompression of a proximal tibial subchondral lesion. |
| **Calcium phosphate bone substitute** |  |  |  |
|  | Cohen SB et al.26 | Level IV Consecutive Case Series (*n = 66 human patients*) | Improved mean VAS, IKDC, and subjective knee evaluation scores at 2 years postop in patients who underwent subchondral injection of calcium phosphate bone substitute.  |
|  | Pelucacci LM et al.27 | Review and technique description.  | Intraosseous injection of calcium phosphate has been successfully performed in the bones of the hindfoot and midfoot including the talus and metatarsals. |
|  | Chan JJ et al.28 | Level IV prospective case series. (*n=11 human patients*) | Significant improvements in mean VAS and FAOS scores at one year post subchondroplasty of the talus. 10 of 11 patients reported that they would undergo the procedure again.  |
|  | Bernhard K et al.29 | Case Report and technique description.  | Calcaneal bone marrow lesion in a runner was treated with injection of calcium phosphate bone substitute. The athlete remained pain free 10 months post-procedure.  |
|  | Bonadio MB et al.30 | Level IV Prospective case series. (*n = 5 human patients*) | Bone marrow lesions of the distal femur and proximal tibia showed significant improvement in mean VAS and KOOS scores at 1,3,6,12, and 24 weeks post-procedure.  |
|  | Astur DC et al.31 | Systematic review of 8 articles.  | 164 patients with bone marrow lesions of the distal femur or proximal tibia. All studies showed improvement in pain and knee functional scores. |
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**Table A2:** Summary of current evidence regarding treatment of stress fractures and bone defects with indirect systemic treatment options. (PTH = Parathyroid hormone, PEMF = Pulsed electromagnetic field, LIPUS = Low intensity pulsed ultrasound, 25(OH)D = 25-Hydroxyvitamin D)

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| **Treatment Option** | **Authors** | **Level of Evidence** | **Outcomes/ Conclusions** |
| **Pulsed Parathyroid Hormone (PTH)** |  |  |  |
|  | Wang Y et al.33 | Review article.  | Recombinant PTH induces an anabolic response in bone that improves rates of callus formation, callus mineralization, and bone remodeling. |
|  | O'Loughlin PF et al.32 | Level I Randomized controlled trial. (*n = 44 rabbits*) | 22 rabbits treated with subcutaneous PTH showed significant increases in fusion callus mass and osteoblast percentage on histology of posterolateral spine fusions compared to controls.  |
|  | Manabe T et al.34 | Randomized controlled trial. (*n = 17 monkeys*) | High dose subcutaneous PTH accelerated callus maturation mineralization in femur fractures of monkeys. |
|  | Andreassen TT et al.35 | Prospective controlled trial. (*n = 107 rodents*) | Administration of subcutaneous PTH to rats with tibia fractures increased ultimate load to failure and the external callus volume at 20 and 40 days of healing.  |
|  | Aspenberg P et al.36 | Level I Multicenter randomized trial. (*n = 102 human patients*) | Nonoperative distal radius fractures treated with 20 micrograms of PTH had shorter time to cortical continuity compared to placebo. |
|  | Zhang D et al.37 | Systematic review of 19 articles.  | Anecdotal evidence indicates increased rate of fracture healing with PTH though definitive results and treatment protocols in humans are yet to be determined.  |
| **Electrical Osseous Stimulation**  |  |  |  |
|  | Longhino V et al.38 | Review article. | PEMF stimulates gene transcription of BMPs, TGF-β, and calmodulin contributing to bone cell proliferation and fracture healing. |
|  | Daish C et al.42 | Review article.  | PEMF activates osteogenic markers increasing proliferation and differentiation. The parameter window for its application is undetermined.  |
|  | Benazzo F et al.40 | Level IV case series. (*n = 21 human patients*) | 22 of 25 lower extremity stress fractures in athletes healed at a mean 52 days after application of capacitive electric fields.  |
|  | Streit A et al.40 | Level I Prospective randomized trial. (*n = 8 human patients*) | Mean time to healing in PEMF treated 5th metatarsal nonunions and delayed unions was 8.9 weeks compared 14.7 weeks in placebo controls.  |
|  | Tomohiko T et al.41 | Level IV Case series. (*n = 5 human patients*) | 5 high school and collegiate soccer players with 5th metatarsal fractures treated with LIPUS were able to continue athletic activity without fracture progression and achieve union.  |
| **Vitamin D Supplementation** |  |  |  |
|  | Shimasaki Y et al.46 | Level III Case-control (*n = 37 human patients*) | Serum 25(OH)D < 30 ng/mL was an independent risk factor for 5th metatarsal stress fracture. Serum 25-OHD < 20 ng/mL increased odds of 5th metatarsal fracture by 2.9 times.  |
|  | Davey T et al.47 | Level IV Prospective case series. (*n = 1,082 human patients*) | Baseline serum 25(OH)D concentration below 50 nmol was associated with an increased risk of stress fracture in 78 marine recruits undergoing a 32-week training program. |
|  | Dao D et al.49 | Systematic review and Meta-analysis of 8 articles.  | Mean serum 25(OH)D level was lower in 761stress fracture cases than in 1,873 controls at the time of entry into basic military training and at the time of stress fracture diagnosis. |
|  | Lappe J et al.50 | Level I Prospective trial. (*n = 3,700 human patients*)  | Female military recruits treated with calcium and vitamin D supplementation (800 IU/day) had a 21% decreased incidence of stress fractures compared with controls treated with placebo.  |
|  | Miller JR et al.51 | Level IV Retrospective case series. (*n = 53 human patients*) | 44 of 53 patients with stress fractures had serum 25(OH)D levels of < 40 ng/mL.  |