Internal fixation implants are widely used by orthopaedic surgeons to stabilize various types of fractures in injured patients. However, the irregular geometry of the human skeletal system, as well as the significant variation in the size and shape of bones among the population, pose great challenges for developing such devices. As a result, the need for improvement in regard to performance and fit is evident in many current internal fixation implants. For this reason, a comprehensive methodology was developed to design and optimize implants with maximal structural integrity and contour fitting among the population, while minimizing its influence on human biomechanics. The systematic methodology was demonstrated using two case studies involving the design of internal fixation implants used to stabilize various femoral shaft fractures: intramedullary nailing and locking plate systems. Comparison of results obtained from simulating the implant insertion process as well as post-operative loading among the optimized implants and those currently used in the operating room showed much improvement in regard to reliability, fit, and alteration of natural biomechanics. Subsequent experimental testing verified that the results predicted through simulation represented actual physiological scenarios within acceptable percent error and were valid for design purposes.