Although numerous synthetic biomaterials have been developed to overcome the problems associated with autologous or allogeneic therapeutic bone grafts, there remains a great challenge to design an ideal bone substitute that emulates natural bone architecture and function. Given that natural bone is a nano-scale array of two phases, inorganic (mineral) and organic (protein), much recognition has been given to nano-hydroxyapatite (nHA)/collagen(Col) composites due to their structural and compositional similarity to bone as well as their mechanical and physical superiority as a nanocomposite.

To provide an overview of the possible synthetic approaches of developing bone grafts, this article extensively reviewed various crosslinking methods for improving the overall strength of collagen scaffolds. Moreover, calcium, strontium and carbonate containing HA materials have also been respectively discussed from their synthesis to biological influence on bone regeneration. Various promising techniques for the scaffold fabrication were concluded. The key intention of this chapter is to describe an innovative strategy to fabricate an ideal bone substitute with sufficient mechanical and physiological properties.

**KEYWORDS:** NanoHydroxyapatite, collagen scaffold, crosslink, bone tissue engineering.