2010; Yamaguchi and Weitzmann, 2011). Strontium induces osteoblastic proliferation, differentiation, and endurance by way of activation of calcium sensing receptor (Coulombe et al., 2004; Brown, 2003) (CaSR). CaSR activation elevates the OPG (osteoprotegerin) levels, which is a protein that suppresses RANKL by behaving as a duplicate receptor (Kostenuik and Shalhoub, 2001), thus inhibiting osteoclastic function by way of inducing apoptosis (Saidak and Marie, 2012). Manganese superoxide dismutase neutralizes ROS, which improves bone resorption and reduces bone apposition. Manganese seems to have an important role in parathyroid hormone signaling pathway, a crucial calcium regulator.

Metal ions causing angiogenesis

Mg^{2+}, Cu^{+}, CO^{2+}

Magnesium acts the same way as VEGF by promoting the formation of nitric oxide by the endothelial cells to augment blood vessel formation (Maier et al., 2004; Cooke and Losordo, 2002). Copper promotes blood vessel formation by enhanced VEGF production. Copper can cause toxicity in elevated concentrations through increased ROS (reactive oxygen species) production damaging the DNA strands and breakdown of bases (Gaetke and Chow, 2003; Jomova et al., 2012). Cobalt causes the generation of genes such as VEGF, EPO (erythropoietin) to compensate the hypoxia caused by itself. Cobalt at higher concentrations generates ROS causing cell damage and also increases osteoclastic activity.

Metal ions causing osteogenesis and angiogenesis

B^{3+}, Si^{4+}

Boron activates the proteins TGF-β and VEGF (Dzondo-Gadet et al., 2002). Silicon improves angiogenesis by increased expression of VEGF through NOS (nitric oxide synthase) and nitric oxide production from endothelial cells. It plays a crucial role in the mineralization process (Pietak et al., 2007) by synthesis and stabilizing of collagen.

Since single dopants have given desirable results, multiple element incorporated biomaterials have also been tried. When magnesium and strontium were used together it enhanced the healing of defects, early bone formation, and remodeling in comparison with undoped (Bose et al., 2011) β-TCP. Improved bone formation was noticed in β-TCP doped with zinc and strontium (Roy et al., 2012). Some of the elements can cause toxicity in particular doses, but generally are safe even in high concentrations (Habibovic and Barralet, 2011). Care should be taken to ensure that optimum amount of ions are released within the therapeutic level (Bohner, 2009; Mouriño et al., 2011). Toxicity of the whole chemical entity should be considered though the single dopant maybe harmless (Lakhkar et al., 2013).

The proceedings of angiogenesis are controlled by proangiogenic factors, which form and repair blood vessels, and antiangiogenic chemical signs which inhibit the process. The complete balance between these is important (Mohammad et al., 2015). In cases of tumor, new blood vessel formation is