Osteonecrosis in genetic disorders

Laura Masi
Alberto Falchetti
Maria Luisa Brandi

Department of Internal Medicine
University of Florence, Florence, Italy

Address for correspondence:
Laura Masi
Department of Internal Medicine
Viale Pieraccini 6, 50134 Florence, Italy
Ph. +39 055 4271502
Fax +39 055 4271506
E-mail: l.masi@dmi.unifi.it

Summary

The avascular necrosis of bone is characterized by an abnormality of tissue that can occur whenever a disease process causes major cell stress. Some evidence supports a role for genetic factors in some avascular necrosis suggesting that gene mutations could play a role in the pathogenesis of osteonecrosis. These genetic studies provide hope that tools for identifying high risk patients will be available in the future.

KEY WORDS: genetic of osteonecrosis, sickley cell anemia, hypercoagulability, corticosteroid therapy; collagen type II.

The term “avascular necrosis (AVN) of bone” is often used improperly to designate any bone lesion that contains some histological evidence of necrosis or that is misinterpreted as exhibiting imaging features of AVN. Bone tissue necrosis is a non specific abnormality that can occur whenever a disease process causes major cell stress (1).
So far, there is not accepted definition of osteonecrosis of jaw (ONJ). However, clinically it typically appears as an area of exposed alveolar bone that can occur in the mandibule or the maxilla (2). It may or may not be painful and may or may not be associated with infection or local trauma. Some evidence supports a role for genetic factors in some of avascular necrosis.

Sickle cell anemia results from homozygosity for the Glu6Val mutation in the hemoglobin beta chain gene (*HBB*) (3). Osteonecrosis is a common sequela of sickle cell disease and several studies indicate that by the age of 35 years, one half of all patients with this disease have osteonecrosis (4). Baldwin et al. hypothesized that the presence or absence of osteonecrosis could be influenced by genetic variability in genes other than *HBB* that are expressed in either bone or vasculature (3). They examined the potential association of osteonecrosis with single nucleotide polymorphisms (SNPs) in candidate genes of different functional classes, including those involved in vascular function, inflammation, oxidant stress, and endothelial cell biology. SNPs in three genes were found associated with the development of osteonecrosis. These genes are important in bone metabolism. In particular, *KL* gene encodes a glycosyl hydrolase that participates in a negative regulatory network of the vitamin D endocrine system and may be important for a wide variety of other cellular processes, including regulation of antioxidative defense, angiotensin converting enzyme activity, arteriosclerosis, and aging (5). Bone morphogenic proteins (BMPs) genes, including *BMP6* gene, encoding for pleiotropic secreted proteins structurally related to transforming growth factor β (TGFβ) and activins. BMP6 is involved in inflammatory processes (6) and is important for bone formation and, in association with parathyroid hormone (PTH) and vitamin D, appears to be involved in inducing bone development by human bone marrow-derived mesenchymal stem cells (7). *ANXA2* gene encoding for a member of the calcium-dependent phospholipid-binding protein family and regulates cell growth and is involved in signal transduction pathways (8).
Although several genes have been identified that may play a significant role in the pathogenesis of sickle cell osteonecrosis by altering protein function of gene expression, the role of these polymorphisms in the pathogenesis of the sickle cell osteonecrosis is not known. However these data may suggests that the vascular complications due to the presence of “genetic risk factors“ may improve the possibility to develop an osteonecrosis in patient affected by sickle cell disease.

Hypercoagulability has been identified recently as a possible contributor to AVN. Procoagulant abnormalities have been found in patients with AVN or Legg Perthes disease (9). Glueck et al. (10) assessed whether heterozygosity for the thrombophilic Leiden mutation of the factor V gene (*MFV*) was pathogenic for alveolar osteonecrosis of the jaw and whether a synergism between exogenous estrogens and MFV for development of osteonecrosis was present. They found that subjects with MFV have a higher risk both for venous thrombosis and osteonecrosis and in these subjects the use of oral contraceptives may be contraindicated (10).
Primary thrombophilia and hyperfibrinolysis appear to be common, heritable, pathophysiologic risk factors for idiopathic osateoncerosis of the jaws (11). In addition, factor V Leiden, a genetic risk factor for venous thrombosis, has been associated with non traumatic osteonecrosis of the femoral head, supporting the hypothesis that intravascular coagulation is a major pathogenetic mechanism of the disease (12). Recently coagulation abnormalities in the form of *factor V Leiden* and the *prothrombin 20210A* gene mutations have been associated also with a higher incidence of osteonecrosis of the knee (13).

Osteonecrosis of the femoral head also occurs in association with *corticosteroid treatment.* The pathology of femoral head osteonecrosis has not been fully clarified, but it is though those drastic ischemic changes occur in femoral head and then bone necrosis develops (14). Several studies have reported a relationship between plasma lipoprotein(a) [Lp(a)] concentration and vascular lesions such as coronary heart

disease, stroke and carotid atherosclerosis (15). Lp(a) is a low-density lipoprotein (LDL)-like lipoprotein that has a component of two disulfile-linked high molecular weight proteins, apolipoprotein(a) and apolipoprotein B100. Apo(a) is considered a lipoprotein that induces both artheriosclerosis and thrombogenesis (16).
Testsurom et al. (14) examined the relationship between corticosteroid-induced femoral head osteonecrosis after renal transplantation in Japanese patients and apo(a) gene polymorphism. They found that subjects with gene haplotype CC had significantly higher plasma Lp(a) levels than those with gene haplotype DD. In addition, they found that the risk of osteonecrosis was high in patients with low molecular weight apo(a) isoforms (14). In a study of 136 renal transplant recipients, the risk of AVN was closely dependent on the multidrug resistance (MDR) gene, of which the ABCB1 C3435 TT haplotype was strongly protective (odds ratio, 0.10) (17). This haplotype was associated with decreased intracellular concentrations of glucocorticoids (1, 17).

Some genes involved in the pathogenesis of *AVN* are represented by the *ADH2*, *ADH3*, *ALDH2* and *P450E1*. These genes are involved in the alcohol metabolism and polymorphisms of these genes have been associated with the risk of AVN. In particular, analysis revealed that *ADH2*1* allele may diminish the risk of AVN related to *alcohol abuse* (18).

In Taiwan, Chen et al. (19) identified two families with *ANV* of the femoral head (*ANFH*) showing autosomal dominant inheritance. By linkage analysis in a 4-generation family, they excluded linkage with antithrombotic protein C (PROC), protein S (PROS1), and PAI, which had been implicated in thrombophilia or hypofibrinolysis. Furthermore, by a genome-wide scan, a significant 2-point lod score of 3.45 (theta = 0.0) was obtained between ANFH and marker D12S85 on chromosome 12. High-resolution mapping was conducted in a second family with ANFH, with replication of the linkage to D12S368. When an age-dependent penetrance model was applied, the combined multipoint lod score was 6.43 between D12S1663 and D12S85, a 15-cM region on 12q13 (19). Liu et al. identified three families in which there was autosomal dominant inheritance of ANFH, with mapping of the phenotype to 12q13. They carried out haplotype analysis in the families, selected candidate genes in the critical interval for *ANFH* on 12q13, and sequenced the promoter and exonic regions of the *type II collagen gene* (*COL2A1*) from patients with inherited and sporadic forms of *ANFH*. The same gly1170-to-ser mutation was found in two separate families, with the mutant allele occurring on different haplotype backgrounds. In the third family, a gly717-to-ser mutation was detected. No mutation was found in the COL2A1 coding region in sporadic cases of *ANFH*. The authors pointed out that in families with *ANFH*, haplotype and sequence analysis of the *COL2A1* gene can be used to identify carriers of the mutant allele before the onset of clinical symptoms, allowing the initiation of measures that may delay progression of the disease (20).
Finally, as endothelial nitric oxide synthase (*eNOS*) has beneficial effects on skeletal, vascular and thrombotic systems, the association between non traumatic femoral head osteonecrosis and eNOS polymorphisms has been investigated (21). Microsatellite polymorphism in intron 4 of *eNOS* gene was significantly associated with idiopathic femoral head osteonecrosis in Korean patients indicating a possible protective role of nitric oxide in the pathogenesis of the disease (20).

In conclusion, some results suggest that defective cartilage function or abnormal bone homeostasis, for example due to *COL2A1* gene mutations, could play a role in the pathogenesis of osteonecrosis. These genetic studies provide hope that tools for identifying high risk patients will be available in the future.

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