

# Infections Resulting from Bone Grafting Biomaterials

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## ABSTRACT

Use of bone grafting is a boon in saving ailing and failing bony structure. Today in dentistry all types of grafts are used, autogenous, xenografts, allografts, all giving favorable results. Yet, all have demerits. Xenografts and allografts have high chances of transmission of infection. This article highlights grafts and transmission of such infections.

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## INTRODUCTION

Bone grafts are extensively used in dentistry for reconstruction of atrophied alveolar ridges, around endosseous implants for regeneration of missing bony wall to provide support and stability to implants, for sinus floor elevation procedures, for healing of intrabony peri-implantitis defects, in periradicular surgery and large periapical lesions, in periodontal bony defects and for reconstruction of maxillofacial defects. There are various bone grafts used in dentistry. The best being autografts, however, the chance of second surgical site, limited amount and their rapid resorption has encouraged clinicians to use xenografts or allografts.<sup>1</sup>

Xenografts are grafts shared between different species. There are many available sources of xenografts used as bone replacement grafts: Bovine bone, porcine bone, horse bone and natural coral.<sup>2</sup> The advantage of these grafts is that they are osteoconductive and undergo through extensive processing techniques, providing products which are

biocompatible and structurally similar to human bone. Other advantages include readily availability and risk free of disease transmission; however 'risk free of disease transmission quotient' has been questioned with the discovery of bovine spongiform encephalopathy (BSE) and porcine endogenous retroviruses (PERVs).<sup>3</sup>

Xenotransplantation may allow such organisms to infect xenograft recipients, who may, consequently, contract previously unknown diseases.<sup>4</sup> There is also a risk that the infectious organisms might cause disease and destroy the transplanted organ, even if they do not harm the human recipient. Even if not infected with disease-causing organisms when transplanted, the xenografted organ may remain susceptible to infectious organisms of animals.<sup>4</sup> Also, if a xenograft recipient is infected, there is a possibility that the resultant disease might then be passed on to the public. In this way, xenografting may pose a risk to public health as well as to individual health.<sup>4</sup>

*Anorganic bovine-derived bone xenograft (BDX):* The BDX is a xenograft consisting of deproteinized, sterilized bovine bone with 75 to 80% porosity and a crystal size of approximately 10 mm in the form of cortical granules.<sup>5,6</sup> The advantage of BDX is that it has osteoconductive properties and according to Cohen et al and Callan et al<sup>1,7</sup> use of this graft material is considered safe since all the proteins are removed and is 100% crystalline hydroxyapatite grafting material. Yet, there are reported cases of BSE.

Infectious particles cause BSE in cattle, when these are accidentally transplanted in humans through bone grafts they cause Creutzfeldt-Jakob disease (CJD) and a variant of Creutzfeldt-Jakob disease (vCJD).<sup>8</sup> CJD is a rare, fatal neurodegenerative disorder<sup>8,9</sup> of old age, but its variant vCJD can occur at any age. The occurrence of CJD is rare

**Table 1:** Various types of Creutzfeldt-Jakob disease

Disease	Mechanism of pathogenesis
<i>Human diseases</i>	
Kuru (Fore people)	Infection through ritualistic cannibalism
Iatrogenic Creutzfeldt-Jakob disease	Infection through prion-contaminated HGH, dura mater grafts, and so forth
Variant Creutzfeldt-Jakob disease	Infection through bovine prions?
Familial Creutzfeldt-Jakob disease	Germline mutations in PrP gene
Gerstmann-Straussler-Scheinker disease	Germline mutations in PrP gene
Fatal familial insomnia	Germline mutations in PrP gene (D178N and M129)
Sporadic Creutzfeldt-Jakob disease	Somatic mutation or spontaneous conversion of PrPC into PrPSC?

approximately one case per million populations. The disease is caused by prions, which are considered to be composed mainly of an altered normal protein (prion protein).<sup>8</sup>

It is also known as the prion disease. It was first discovered by Stanley B Prusiner, and he defined prions as infectious, transmissible proteinaceous particles that lack nucleic acid and are composed exclusively of a modified isoform of the noninfectious cellular prion protein (PrPC). The pathogenic (also called scrapie or PrPSc) form of the prion protein (PrP) has the same amino acid content but a higher  $\beta$ -sheet content than PrPC.<sup>10</sup> These prions get deposited in cerebrum and cerebellum causing sponge-like degenerative changes in the brain. Clinical features include psychiatric symptoms such as depression, anxiety, apathy, withdrawal, delusions; there is persistent painful sensory symptoms pain and/or dysesthesia, ataxia, chorea/dystonia or myoclonus, dementia. Oral manifestations include pseudobulbar palsy which may cause dysphagia and dysarthria in patients with transmissible spongiform encephalopathies (TSEs), orofacial dysesthesia or paresthesia, as well as loss of taste and smell.<sup>11,12</sup>

There are various types of CJD. Table 1 below describes those types.<sup>13</sup>

There are many reported case of transmission of BSE, although the risk of transmission of CJD through dentistry is unclear, the theoretical risk of transmission through any contaminated instruments or contaminated bovine bone graft can take place. Incidence of transmission of BSE with bovine xenograft is estimated to be far less than the incidence of being hit by lightning.<sup>14</sup> Therefore, the risk of getting disease transmission from allograft and xenograft is relatively low as long as the disinfection/sterilization protocols are followed by the suppliers. World Health Organization stated that bone is labeled as type IV (no transmission) for proteinaceous infectious particles (prions) diseases. All current available bone graft materials are safe and reliable instead of disease transmission potential. According to Sogal and Tofe<sup>15</sup> the risk of TSE transmission from a commercially available bovine-derived xenogenic bone substitute was insignificant.

In animal studies, Adams and Edgar<sup>16</sup> assessed the possibility of transmission of scrapie through dental burs. They found no clinical or histological findings of scrapie when the healthy mice were killed and examined 15 months later. Ingrosso et al<sup>17</sup> conducted a study on the possibility of prion infection through dental procedures. They found a significant level of infectivity in the trigeminal ganglia and in the gingival and pulpal tissues of scrapie-affected hamsters after intraperitoneal inoculation, suggesting

possible transmission from the central nervous system through trigeminal nerves toward the oral cavity.

*Porcine bone grafts:* The pig has a number of advantages as a renewable source of donor tissue including a vast experience in its husbandry and health care, as well as the advancing technologies to engineer transgenic animals<sup>18</sup> thus, porcine bone grafts are widely used in dentistry, selective breeding and screening of the pig can reduce the risk of animal-human infections, from xenotransplantation. However, pigs harbor many viruses or ghosts of viruses, some active, some latent and others represented only by a partial genetic sequence embedded in the pig genome<sup>19</sup> such as endogenous retroviruses PERV, which are encoded in their genomic DNA<sup>20,21</sup> and are thus in every cell of every pig, and are therefore less susceptible to exclusion by careful breeding. There are at least three variants of PERVs (A, B, B1 and C) in native pig cells.<sup>4-6</sup> PERV-A and PERV-B can infect several species including humans, while PERV-C tropism is limited to pig cells.<sup>22,23</sup> However, recombination between PERV-A and PERV-C occurs frequently producing a high titer, human tropic PERVA/C,<sup>23-25</sup> these are considered to be most problematic as they use the same cell receptor as PERV-A and are the forms derived from cocultivation of porcine primary cells and human cells.<sup>26</sup>

PERVs infect human cells *in vitro* and have been cloned.<sup>27,28</sup> Recent data suggest that despite the presence of many fragmentary copies of virus sequences, there are relatively few,<sup>22,27</sup> full length copies of the viral DNA in each cell that are capable of producing infective virus. In addition, some genomic sites produce incomplete viral transcripts, which are not thought to be infective.<sup>28</sup> This small number of intact genes might allow inactivation of proviruses of PERVs through genetic manipulation.<sup>29</sup>

Gammaretrovirus particles are released by pig cell lines,<sup>30</sup> yet only recently have investigators looked into the potential risk of human infection by PERV. Two of the three identified receptor classes of PERV, distinguished by their envelope sequence and tropism, have been shown to be capable of replicating in human cells *in vitro*. *In vivo* they may cause infection and may give rise to two possible effects: mutagenesis and immunosuppression.<sup>31</sup> The first may induce cancer. The second will damage the human immune system and in analogy to HIV and SIV, high titer virus replication may cause an AIDS-like disease in the immunosuppressed human transplant recipient. Pig cells can survive for many years in the human body and microchimerism has been detected. In microchimerism, the pig cells in the human body contain PERV but—if no infection has occurred—no virus particles have been incorporated rated in the human genome. This however does

not decrease the risk that PERV may cause. Whether one can really distinguish between microchimerism and an infection is not clear.<sup>32</sup>

Another infection that humans can acquire from pigs is Ebola virus (EBOV). EBOV causes extremely severe disease in humans and in nonhuman primates in the form of viral hemorrhagic fever. EBOV is a select agent, World Health Organization Risk Group 4 Pathogen (requiring Biosafety Level 4-equivalent containment). EBOV was first described in 1976 by David Finkes.<sup>33-35</sup> Today, the virus is the single member of the species Zaire ebolavirus, which is included into the genus Ebolavirus, family Filoviridae, order Mononegavirales. The name EBOV is derived from the Ebola River (a river that was at first thought to be in close proximity to the area in Zaire where the first recorded EBOV disease outbreak occurred) and the taxonomic suffix viruses. It causes a fulminating hemorrhagic fever syndrome resulting in the death of most patients within a few days. Human immune responses have as yet been poorly investigated, mainly due to the fact that most outbreaks occur in remote areas of central Africa. In infected humans there is fatal outcome in humans and is associated with aberrant innate immunity characterized by a 'cytokine storm,' with hypersecretion of numerous proinflammatory mediators and by the noteworthy absence of antiviral interferon. The adaptive response is globally suppressed, showing a massive loss of CD4 and CD8 lymphocytes and the immune mediators they produce.

*Equine derived bone graft:* There is always search for better bone grafts resembling human bone matrix and capable of osteoconductive properties. With discovery of PERV through porcine bone grafts and CJD through bovine bone grafts, use of equine bone grafts has become popular. However, research on risk on disease transmission through equine is still being investigated. El-Sabban et al<sup>36</sup> stated that there are no studies on bone substitutes of equine origin, apart from few papers on an equine bone protein extract, which was capable of inducing osteoblastic differentiation of human bone marrow-derived mesenchymal stem cells and ectopic bone formation in a rat model.<sup>37</sup> According to Stefano et al equine graft material is biocompatible, and its usage is associated with new blood vessels ingrowth during healing, which has been found to be extremely important in bone formation. The status still remains the same. There is rapid increase in use of equine bone grafts; however, research disease transmission through this material needs more attention.

*Human dura matter:* Allografts have been successfully used for intraosseous defects, most common being decalcified freeze dried bone allograft (DFDBA), however, controversy

exists with respect to the osteoinductive potential of these materials.<sup>38</sup> It has been shown that inductive capacity varies from bone bank to bone bank and also from different batches of the same bone bank. The bioactivity is also dependent on the age of the donor, the younger the donor, the more osteoinductive graft material will be.<sup>38</sup> Also there are chances of disease transmission, the most common being Creutzfeldt-Jakob disease, which can be transferred from an infected donor. The main disadvantage is that this disease transcripts as a preclinical state in which it can lie dormant in the individual for decades (1-40 years), also it cannot be detected in human blood. These factors increase the chances of transmission as it goes undetectable on screening. According to Gajdusek et al another subacute spongiform encephalopathy, survived room temperature in 10% formalin for 7 months in the form of a brain suspension.

## CONCLUSION

With various bone grafts in has now become possible to reach the goal of bone regeneration and achieving ultimate results providing both function and esthetics. However with the use of xenografts the risk of disease transmission increases. Although till now no case of infection from xenotransplantation in dentistry has been reported, but there is a risk. And to avoid certain precautions can be taken by the dentist.

Patients with confirmed prion disease should be scheduled at the end of the day to permit more extensive cleaning and decontamination.<sup>28</sup> It is preferable to avoid activating waterlines because of the risk of retraction of prions in oral fluids. Also, a stand-alone suction unit with disposable reservoir, rather than the suction component of the dental unit, and a disposable bowl instead of the dental unit spittoon should be used.<sup>22</sup> To avoid environmental contamination, dental equipment should be adequately shielded using disposable, impermeable cover sheets.<sup>28</sup>

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