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Osteonecrosis ONJ (Session Summary)

Osteonecrosis and osteonecrosis of the jaw (ONJ)

H.K.W. Kim

Shriners Hospital for Children, University of South Florida, Tampa, FL, USA

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The anatomical site that is most often affected by osteonecrosis is the femoral head, but a recent increased incidence of osteonecrosis of the jaw (ONJ) has heightened interest in this clinical entity. Whereas bisphosphonate therapy has emerged as a potential new biological treatment to decrease the development of femoral head deformity following osteonecrosis, bisphosphonates have been implicated as a possible contributory agent in jaw osteonecrosis. This suggests that the two entities, although related by name, are perhaps distinct pathophysiologically. Various disease processes, such as infection, infiltration, and thromboembolic processes, can cause osteonecrosis. One of the most common causes of osteonecrosis in the pre-antibiotic era was osteomyelitis. The term *septic necrosis* is used to denote bone necrosis secondary to infection. The term *aseptic necrosis* is used to denote osteonecrosis that occurs in the absence of infection; the most common cause being ischemic necrosis secondary to fracture or dislocation. The term *avascular necrosis* reflects the common etiological nature of the condition, however, since not all bone death occurs from ischemia or avascularity, the term *osteonecrosis* is preferred.

Because bisphosphonate therapy is emerging as a potential new biological treatment to decrease the development of femoral head deformity following osteonecrosis, the rationale behind this treatment was reviewed. There is mounting evidence from animal and early clinical studies that inhibition of osteoclast-mediated bone resorption during repair of the infarcted femoral heads can decrease the femoral head deformity. Long-term studies on large animal models of ischemic osteonecrosis and patients treated with bisphosphonates for femoral head osteonecrosis are lacking and

should be considered prior to applying this form of treatment widely. Local intraosseous administration instead of oral or systemic administration for this localized condition is appealing and should be further investigated.

Comparison between femoral head osteonecrosis and ONJ is difficult to make as ONJ is still in the discovery phase in which etiology, natural history, and the pathophysiology of the condition remains largely unknown. Although many case reports and institutional reviews have been published since 2003, only a few studies have reported on the histopathological and radiographic changes observed in ONJ. Based on these studies it is difficult to make any conclusive statements about the pathogenesis of this condition. Given that the condition is relatively uncommon, developing animal models of ONJ which incorporate bisphosphonate therapy coupled to tooth extraction or induced infections are reasonable approaches to gaining further pathophysiological insight into this condition.

The recent ASBMR Task Force on Bisphosphonate-Associated ONJ defined BP-associated ONJ, and reviewed its epidemiology. It reviewed the value of different diagnostic imaging modalities, and provided recommendations for clinical management. Improved reporting of cases of ONJ along with more standardized data collection will be useful in defining the true incidence and the risk factors associated with this condition. There was concern that imaging could provide many false-positives, and that the use of diagnostic imaging prior to the presence of exposed bone be used with caution. The full report of the Task Force can be found on the ASBMR website (www.asbmr.org).

Laurie McCauley, DDS, PhD discussed the unique developmental, anatomical, histological, bone remodeling, and microbial features relating to the jaw. Possible explanations as to why certain regions of the jaw would be predisposed to developing bisphosphonate-related ONJ were outlined. Wound healing following tooth extraction was discussed along with the potential effects of inhibition of osteoclastic function on the healing process. Since osteoclastic resorption is required to remodel the residual bone and newly-

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Corresponding author: Dr. Harry K.W. Kim, Shriners Hospital for Children,
12502 Pine Drive, Tampa, FL 33564, USA
E-mail: hkim@shrinenet.org

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formed woven bone in the extraction socket, a compromise in osteoclast function may hinder the healing process and contribute to a non-healing wound. Another important consideration is the potential inhibitory effect of bisphosphonates on angiogenesis, which is important for vascular granulation tissue formation and invasion of the extraction socket. Designing and carrying out studies to understand the effects of bisphosphonates on wound healing following dental procedures and how it affects bone remodeling and angiogenesis would be useful in elucidating the pathophysiology of ONJ.

Finally, Matt Allen, PhD reported on his work pertaining to the development of animal models of ONJ. Findings from pilot studies on dogs treated with alendronate for 1 or 3 years were reported. Some of the alendronate-treated dogs showed regions in the mandible devoid of basic fuchsin staining, suggesting osteocyte death, without evidence of vascular compromise in the Haversian canal to suggest that the cell death was due to ischemia. Furthermore, the extent of osteocyte

death was regional or patchy in nature. These histological findings are quite different from those found with femoral head osteonecrosis due to the absence of changes consistent with ischemic osteonecrosis where cell death tends to be extensive and affect all cells in the marrow and bone. These findings suggest that the pathophysiology of the two conditions are different. The patchy nature of cell death without involvement of cells in the marrow or Haversian canal suggests a non-ischemic mechanism of injury. Since the rate of bone turnover in the mandible is thought to be important to the etiology of BP-associated ONJ, development of animal models should take into consideration remodeling at this anatomical site. This may reduce the utility of mouse models, although it was mentioned that the C3H mouse does have remodeling in its long bones and may therefore be developed as a potential small animal model. It is apparent that the development of reliable and reproducible animal models of ONJ is essential for elucidating the pathophysiology of bisphosphonate-related ONJ.