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Bone Formation and the Wnt Signaling Pathway

TO THE EDITOR: Simsek Kiper et al. (June 30 issue)[1] link Pyle's disease to a deficiency of secreted frizzled-related protein 4 (sFRP4), a soluble Wnt inhibitor, and demonstrate its specific effects on cortical bone (which is unusually thin in persons with Pyle's disease) versus trabecular bone (which is increased in persons with Pyle's disease). In sFrp4-deficient mice, the inhibition of cortical bone formation, which determines bone strength at large, was shown to be mediated through bone morphogenetic protein (BMP)–dependent induction of sclerostin, a key Wnt inhibitor in bone. Given the small amount of trabecular bone in the mouse femur, are bone marrow–derived osteoblasts that are obtained from the femur indeed representative of trabecular bone? Second, did the authors assay levels of dickkopf 1 (Dkk1)? Dkk1 also inhibits Wnt and — like sclerostin — is a downstream target of BMP signaling. Therefore, Dkk1, in addition to sclerostin, may contribute to the suppression of bone formation.[2] Moreover, blocking sclerostin increases the expression of Dkk1 in bone, which partially limits the bone-forming effects of sclerostin inhibition.[3] Thus, Wnt signaling has multiple redundant safeguards to fine-tune bone formation. Therapeutically, this complexity may require the use of bispecific antibodies against more than one Wnt inhibitor to fully restore Wnt signaling, bone formation, and ultimately bone strength.

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THE AUTHORS REPLY: We isolated bone marrow–derived osteoblasts from the femora and tibiae of mice that were 10 weeks old, an age at which both the femur and the tibia contain trabecular bone. It is well established that enhancement of canonical Wnt signaling is associated with increases in bone mass.[1] Our studies clearly show that sFrp4 deficiency has a marked anabolic effect on trabecular bone in humans and mice. Given that trabecular bone resides in the marrow and that the properties of sFrp4-deficient bone marrow–derived osteoblasts (e.g., the Wnt canonical pathway — but not the noncanonical pathway — is activated in these cells) are consistent with the changes observed in trabecular bone (increased bone mass), we concluded that these cells better reflect the cellular activities in the trabecular bone compartment than do calvarial cortical osteoblasts. With regard to the second point, sFrp4 deficiency was associated with increased *Dkk1* expression in both bone marrow–derived and calvarial osteoblasts (Fig. 1). This is not surprising: *Dkk1* is a well-known canonical

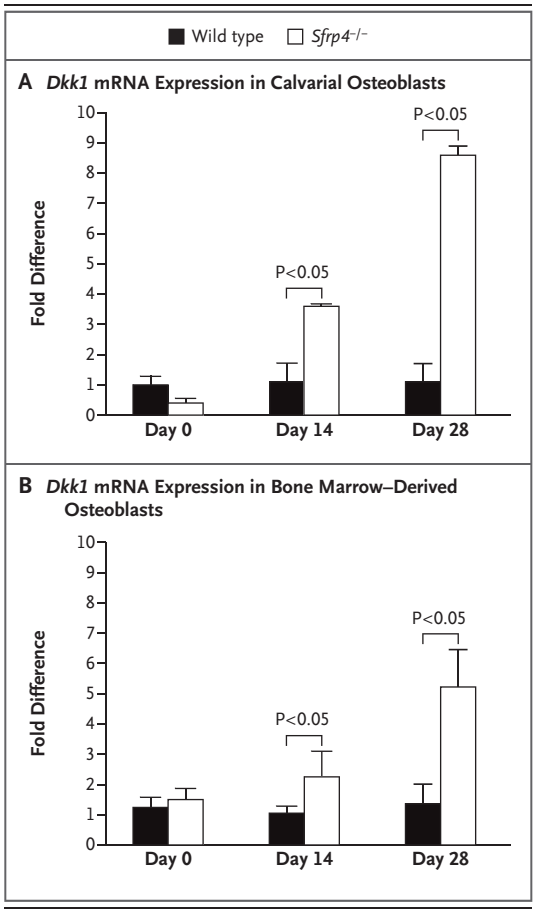

Figure 1. Effect of *Sfrp4* Deletion on *Dkk1* Messenger RNA (mRNA) Expression.

Dkk1 mRNA expression in calvarial osteoblasts and bone marrow–derived osteoblasts of wild-type and *Sfrp4*−/− mice after 0, 14, and 28 days of osteogenic differentiation is shown. Fold differences in mRNA expression relative to that in wild-type cells were calculated as described by Livak and Schmittgen.[2] The bars show mean values; T bars indicate standard deviations. Three independent experiments were performed at each time point.

Wnt signaling target gene. We agree with Rauner and colleagues: bispecific antibodies against sclerostin and Dkk1[3] could have a stronger effect on the maintenance of cortical bone homeostasis than do antibodies to only sclerostin.

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Fire-Related Inhalation Injury

TO THE EDITOR: In his proposed algorithm for the early management of fire-related inhalation injury, Sheridan (Aug. 4 issue)[1] excluded bronchoscopy from the recommendations listed as standards of care because of the lack of "high-level proof" of its efficacy. That stance raises concern because there are reports that favor the use of bronchoscopy in this context. The degree of inhalation injury identified on bronchoscopy has been reported as a determinant of an inflammatory response to smoke inhalation,[2] and bronchoscopic findings have been positively correlated with mortality.[3] Our experience also supports the use of bronchoscopy in this situation. In providing medical care for the victims of a nightclub fire in Brazil, we found that serial, flexible bronchoscopy provided us with information that was crucial to the decision-making process with regard to treatment, allowing us to identify the extent of burns in the airways and to remove large amounts of debris (Fig. 1). No complications were observed with the use of this procedure. Among 18 patients who underwent bronchoscopy at our hospital, 16 are still receiving follow-up care and have had good clinical outcomes. Thus, the limited data available on bronchoscopy can