Adipose tissue – A new window of insight into bone remodelling?

Fat grafts transplanted into surgically created bone defects inhibit local bone regeneration. This phenomenon is employed to good effect by surgeons. In neurosurgery, fat grafts prevent constriction of the spinal cord by laminectomy membrane composed of scar tissue and bony callus. Also, following the resection of a segment of ulnar diaphysis or a transphyseal bone bridge in growing dogs and children, the insertion of a fat graft prevents the local regeneration of bone; effectively producing a localised atrophic non-union and allowing continued bone growth (1,2). Since fat grafts are composed mainly of adipocytes embedded in a sparse fibrous stroma, it has been assumed that a piece of fat filling a bony void simply prevents the ingrowth of fibrovascular tissue and subsequent bone callus formation.

As orthopaedic surgeons, this appreciation for the value of fat has been about the limit of our interest in this apparently unprepossessing tissue, aside from the obvious difficulties it creates when performing surgery on obese animals. However some very interesting research, largely driven by the epidemic of obesity, has revealed some quite surprising findings. It seems that adipose tissue also has some systemic effects on the homeostasis of various skeletal elements, including bones and synovial joints.

Adipose tissue is the largest endocrine gland of the body. Adipocytes produce some 20 different hormones, cytokines and bioactive molecules; one of the more important adipokines is leptin, which is a 16 kDa protein hormone. Serum leptin levels normally rise following food intake and consequently suppress appetite. Although leptin levels are also elevated in obese patients, its normal functions become dysregulated with obesity in a manner that is analogous to 'insulin resistance' of type II diabetes. In a review article on obesity and osteoarthritis by Marshall and his colleagues in this issue of the Journal, you can read much more about how leptin contributes to the development of osteoarthritis in obese animals and people (3). Apart from its effects on synovial joints, leptin also has effects on skeletal bone.

Mechanical loading is a very major factor regulating bone remodelling in skeletally mature animals, but leptin also has some role in regulating bone mass. Leptin acts directly on bone cells and bone marrow stem cells, and indirectly via the hypothalamic-sympathetic nervous system to alter bone mass (4). Leptin receptors are present in the hypothalamus, and receptor-bound leptin blocks sympathetic innervation of bone. Sympathetic nerve fibres are widely and non-uniformly distributed over bone surfaces, and normally the release of noradrenaline from sympathetic fibres projecting onto bone inhibits bone formation. Thus elevated levels of leptin may act centrally, and indirectly result in bone proliferation. Although these interactions are quite complex, a growing body of knowledge provides us with a whole new window of insight into the understanding the 'non-loading' mechanisms that control bone remodelling. These neuro-endocrine mechanisms are probably important in regulating normal bone remodelling in 'non-loaded' limb bones such as the upper limb in bipedal animals. Also, they might be involved in the development of certain idiopathic bone diseases. For example, animals and people suffering from secondary hypertrophic osteopathy (Marie's Disease) have bilaterally symmetrical periosteal bone formed along the diaphyses of the limb bones, in conjunction with intra-thoracic pathology. Often the bone proliferation on the limbs will inexplicably regress after resection of the intra-thoracic lesion, suggesting that some type of neuro-endocrine mechanism is responsible for the bone proliferation. Certainly it is gratifying to appreciate how research into the growing epidemic of obesity has serendipitously revealed so much new knowledge about the regulation of bone remodelling.

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References

1. Vanderwater A, Olmstead ML, Stevenson S. Partial ulnar ostectomy with free autogenous fat grafting for treatment of radius curvus in the dog. Vet Surgery 1982; 11: 92–99.
2. Langenskiöld A. Surgical treatment of partial closure of the growth plate. J Pediatric Orthopedics 1981; 1: 3–11.
3. Marshall WG, Bockstahler BA, Hulse DA et al. Osteoarthritis and obesity – a review: Current understanding of the relationship and benefit of obesity treatment and prevention in the dog. Vet Comp Orthop Traumatol 2009; 22: 339-345.
4. Hamrick WM, Ferrari SL. Leptin and the sympathetic connection of fat to bone. Osteoporos Int 2008; 19: 905–912.