



## ■ REVIEW ARTICLE

# The anabolic and catabolic responses in bone repair

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**The literature on fracture repair has been reviewed. The traditional concepts of delayed and nonunion have been examined in terms of the phased and balanced anabolic and catabolic responses in bone repair. The role of medical manipulation of these inter-related responses in the fracture healing have been considered.**

Biological treatments are beginning to make an impact on clinical orthopaedic practice. However, there is no acceptably robust system for classifying either failure of treatment or intervention in biological terms. We believe that the outcome in bone repair is determined by the magnitude and interaction of the anabolic and catabolic responses. The fields of osteoporosis and metabolic bone disease have recently experienced a similar shift towards anabolic and catabolic concepts.<sup>1</sup>

The processes of bone and fracture repair can be considered as consisting of anabolic (bone forming) and catabolic (bone resorbing) responses. As the anabolic response produces the sequence of steps that results in the bridging of the fracture by new bone, it has received most attention. Catabolic action is an essential component of remodelling of bone during the later stages of repair, although excessive or dysregulated catabolism may impede union. Controlling catabolism in such circumstances can be as important as anabolic stimulation. This concept does not specify the various mechanical,<sup>2</sup> biological<sup>3</sup> or pharmacological<sup>4</sup> stimuli known to influence bone repair, only the responses. Cellular responses are related to the summation of relevant stimuli, but the activation of complex pathways is required for their transformation into a response. It is the end response that determines outcome. An example of this concept might be that whereas mechanical stimulation would normally be expected to increase bone healing, the presence of non-steroidal anti-inflammatory drugs or corticosteroids could block the production of prostaglandins required to produce an anabolic response. Likewise, stimuli that we deem

to be undesirable can be blocked, thus allowing a more favourable response.

**The physiology of fracture healing and bone repair.** Three forms of bone repair bring about fracture union, namely endochondral ossification, intramembranous ossification and appositional bone formation. Closed to the fracture site, cellular responses lead to the production of cartilaginous tissue, which undergoes endochondral ossification. At more peripheral sites, direct intramembranous ossification occurs through a collagenous framework and areas of appositional bone formation reinforce the entire callus. Varying mixes of these processes are apparent in different circumstances of repair. These mechanisms primarily produce woven bone, which is later remodelled into lamellar bone. Eventually, in an ideal situation, the entire external callus is removed to restore the original cortical and trabecular configuration.

The process of endochondral ossification in bone repair has been likened to prenatal embryonic processes and those that occur post-natally at the growth plate. Here a multitude of cells and tissues behave in a co-ordinated and orderly fashion. First, chondrocytes proliferate and produce a non-mineralised cartilage scaffold. Hypertrophic chondrocytes then mineralise the vertical, but not the transverse, septa of the matrix. Matric metalloproteinase (MMP)-expressing cells, including the vascular endothelial cells themselves, facilitate vascular invasion as well as the removal of the transverse septa and any remnants of the apoptotic chondrocytes.<sup>5</sup> Osteoblastic cells then lay down new bone on the mineralised chondral remnants to produce the primary spongiosa or trabecular bone. At this stage, remodelling

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©2007 British Editorial Society  
of Bone and Joint Surgery  
doi:10.1302/0301-620X.89B4.  
18301 \$2.00

*J Bone Joint Surg [Br]*  
2007;89-B:425-33.

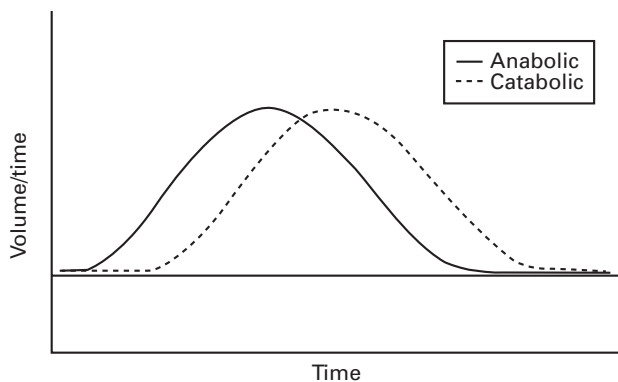


Fig. 1a

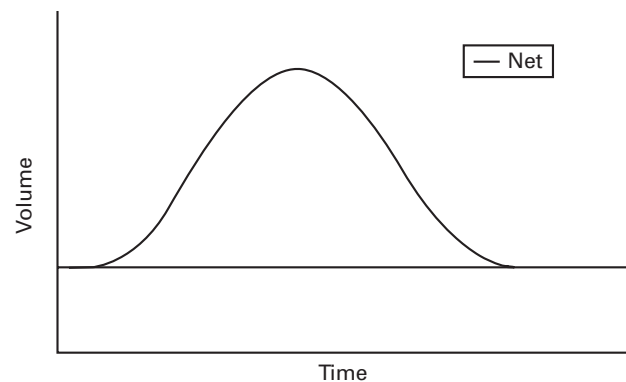


Fig. 1b

Model of anabolic and catabolic responses. These graphs model the underlying anabolic and catabolic responses in a normal healing fracture. Figure 1a – The rates of anabolism and catabolism, assuming a symmetrical increase and decrease for each effect. The y-axis represents the rate of bone accumulation (solid) or bone loss (dashed) in volume/time. The x-axis represents the healing time, with anabolism preceding catabolism. Figure 1b – The summation of anabolic and catabolic responses gives the net accumulation of bone over time. This corresponds to what is observed on radiographs. Bone accumulates while the rate of anabolism dominates over the rate of catabolism, and initial union usually occurs when callus size is maximal. In the remodelling phase, resorption of callus followed by lamellar bone formation results in diminution in the size of the callus, with catabolism dominating over anabolism. A steady state is reached such that the initial bone is restored and the callus disappears.

starts to occur, with osteoclastic resorption followed by the formation of new lamellar bone.

The interface of the soft cartilaginous callus and bony hard callus at the site of bone repair resembles the growth plate, but with several key differences. First, the process of ossification in fracture repair is less orderly, with some areas of the callus undergoing remodelling while others are still in the cartilaginous phase. Second, whereas the anabolic activity of the growth plate is constantly replenished until growth ceases, in fracture repair there is a burst of expression of anabolic genes after injury, the response to which must produce the soft and hard callus.<sup>6</sup>

Unlike the highly organised process in the growth plate of normal individuals, endochondral ossification in bone repair can fail. This may result from the differing requirements for achieving initial union as opposed to the subsequent remodelling. We define initial union as the bridging of the fracture with bone in sufficient quantity for the restoration of major mechanical function. Remodelling ensures that other features, such as durability and resistance to future injury, are produced in the long term.

The conversion of soft to hard callus that occurs during initial union is not the same process as the remodelling of hard callus. The exact role of the osteoclast in initial union is still uncertain. Although osteoclasts may contribute to vascular invasion and early endochondral ossification, these processes are not inherently dependent on osteoclasts.<sup>5</sup> Our findings when inhibiting osteoclasts with bisphosphonates similarly indicate that osteoclasts are not essential during the initial stages of endochondral fracture repair.<sup>7</sup>

It is important to note also that bone remodelling is not a requirement for initial fracture union. The primary spongiosa that forms during the initial process of fracture heal-

ing, both intramembranous and endochondral, does so without prior need for bone resorption.

**The relationship of anabolic and catabolic responses during fracture healing.** While repair is proceeding the net volume of new bone produced can be observed macroscopically on plain radiographs. An increased production of bony callus is usually observed, leading to union, followed by a progressive reduction in size and a change in structure as the bone remodels. Eventually, in an ideal situation, the original form and function of the bone are restored. However, the magnitude of this net response is the product of the competing anabolic and catabolic responses, which cannot be readily appreciated at the macroscopic level.

Prior to injury, the anabolic and catabolic responses run at low levels in a state of homeostasis, such that the ongoing bone turnover and remodelling continue. This turnover replenishes the skeleton and repairs accumulated microdamage. When a fracture occurs, there is an appropriate inflammatory response in the bone and surrounding tissues, followed by cellular recruitment and proliferation. The cell differentiation and the production of organised connective tissue matrices are co-ordinated with the revascularisation of the injured region. The anabolic phase dominates and precedes the catabolic removal of unwanted tissue and bone resorption associated with subsequent remodelling. Normally, these anabolic and catabolic responses are coordinated such that the mineralised callus is sufficiently robust to restore functional mechanical integrity before significant remodelling occurs.

The rates of anabolism and catabolism and their summation during bone healing can be represented schematically. Figure 1 depicts an idealised version of the rates of anabolism and catabolism in a normally healing fracture, and the net callus formation at any given time.

**Table I.** Proposed classification for failure of bone repair

Classification	Cause of delayed union or nonunion
Anabolic deficiency	Insufficient new bone formation
Catabolic excess	Premature and/or excessive resorption of callus or original bone
Combined anabolic/catabolic dysfunction	Both insufficient bone formation and excessive resorption

**The anabolic/catabolic classification system for the failure of bone repair.** Descriptive terms such as delayed union, hypertrophic nonunion and atrophic nonunion are in common use. However, these terms fall short of constituting a diagnosis or specifying the underlying processes that are abnormal. These may be classed as 'mechanical failure' or 'biological failure', but clearly the two may be linked. We consider that the failure of initial bone union may be better classified based on the underlying anabolic and/or catabolic derangement as shown in Table I.

**Anabolic deficiency.** The most common cause of anabolic deficiency is disruption of local bone and soft tissue, as in high-energy fractures or extensive surgical procedures. Such injury will compromise the vascular supply of the bone and surrounding tissues. The return of the vasculature is necessary for final repair, and the magnitude of the initial vascular injury determines the level of damage to potential local osteoprogenitor cells. It is known that vascularity returns even in established nonunion in both animals and humans.<sup>8,9</sup> A recent model of soft-tissue trauma and fracture showed only a transient diminution of blood flow, with later hypervascularity.<sup>10</sup> Furthermore, the initial events in endochondral ossification are cartilaginous, and hence avascular.

Damage to local osteoprogenitor cells may be more important, as infarcted soft tissues may provide insufficient responder cells for recruitment by the inflammatory cascade to form the required quantity of tissue for initial repair. Cells that do respond may not be stimulated to differentiate down the appropriate chondrogenic or osteogenic lineages in the unfavourable microenvironment, and the presence of cytokines and pro-osteogenic signals released by the initial injury may have waned by the time sufficient new mesenchymal cells have migrated to the site.

Other systemic or local host factors, including advancing age, diabetes, smoking, and infection, can also increase the likelihood of anabolic deficiency.

**Catabolic excess.** We consider that either anabolic failure or a relative excess of catabolism could be responsible for the formation of insufficient callus during bone repair, especially in rigidly-fixed fractures and other situations with relative stress shielding. Rigid fixation of fractures enhances soft-tissue recovery and ensures optimal alignment for future function, but comes at the price of a smaller amount of callus. Traditionally, rigid fixation and the

resultant stress shielding have been thought to inhibit callus formation. In an extreme example, absolutely rigid fixation in the mouse tibia prevented the stimulation of chondrogenic pathways, resulting in the formation of a small, mostly intramembranous callus.<sup>11</sup> However, the size of the callus was increased threefold when fractures were left completely unfixed and unstable, suggesting differences in the translation of mechanical signals into an anabolic response in the two situations. These same mechanical stimuli also influence the catabolic response. The reduced loading associated with microgravity induces osteoblasts to upregulate their secretion of interleukin (IL)-6, macrophage-colony stimulating factor (M-CSF) and tumour necrosis factor (TNF)- $\alpha$  and to significantly increase the receptor activator for nuclear factor Kappa-B Ligand (RANKL), osteoprotegerin (OPG) (RANKL/OPG) ratio, leading to an increase in osteoclast production.<sup>12</sup> Likewise, the stress shielding that occurs in rigidly-fixed fractures also modulates bone turnover in favour of catabolism, so that some of the primary trabeculae are rapidly resorbed and not replaced. This can be seen clinically when a cloud of fracture callus is observed on early radiographs, but then disappears with resultant nonunion. We consider that retaining the primitive scaffolding of the primary trabeculae for longer could increase the volume of callus and provide a more robust early repair, even when the mechanical conditions are unfavourable. We have used several model systems where bone repair was modulated by anti-catabolic agents to test this view.

**The use of anabolic and anti-catabolic agents in orthopaedics.** Boosting anabolism, reducing early catabolism, or influencing both the responses can influence outcome positively. It is critical to match treatment to the underlying anabolic or catabolic state. For example, stem cell therapy may in future provide important gains when anabolic deficiency is due to a lack of local cells. However, it may not be helpful when the anabolic response is already adequate but the uncontrolled variable is excessive catabolism. In these circumstances, anti-catabolic agents may prove more efficacious.

**Anabolic therapies.** These aim to enhance the number of differentiated osteogenic cells at the fracture site and increase the production of bone. This could involve promoting the proliferation and/or differentiation of endogenous osteoprogenitors, increasing the migration, retention and support of these cells, or the transplantation of additional osteocompetent cells. Anabolic treatments can be mechanical (e.g. distraction osteogenesis, ultrasound), biological or pharmacological (e.g. bone morphogenetic proteins, parathyroid hormone), graft based (autologous bone graft, allograft) and cell based (e.g. bone marrow or mesenchymal stem cells, platelets, gene therapy).

The use of such means of treating an anabolic deficiency can be illustrated graphically. If the anabolic response is deficient, the normal forces of catabolism will lead to an

insufficient overall response (Fig. 2a). Decreasing catabolism in this circumstance can have a small positive effect (Fig. 2b), but restoration of the anabolic response is more effective in restoring the net amount of callus formation (Fig. 2c). **Anti-catabolic treatment.** Anti-catabolic treatments are usually pharmacological, for example the administration of nitrogen-containing bisphosphonates (N-BPs) to inhibit resorption of osteoclasts. Novel pharmacological approaches to alter catabolism are being explored using compounds that reduce osteoclast formation (e.g. inhibitors of RANKL, such as denosumab); agents that disrupt osteoclast adhesion (e.g. inhibitors of  $\alpha\text{v}\beta 3$  integrin); others that reduce resorption of the organic phase of bone (e.g. cathepsin K inhibitors); and molecules that target acid production by osteoclasts and thus reduce resorption of the mineralised phase of bone (e.g. ClC7 chloride channels and vacuolar- $\text{H}^+$ ATP-ase inhibitors).<sup>13</sup> However, mechanical stimuli may also decrease catabolism by reducing stress shielding, as with the dynamisation of external fixators.

Anti-catabolic therapies can also be represented graphically. As with an anabolic deficiency, premature or excessive catabolism may lead to a reduction in net bone (Figs 3a and 3b). If the excess catabolism is managed by an anti-catabolic therapy such as a bisphosphonate, a much larger amount of bone is retained (Fig. 3c).

### Categorising existing pharmaceutical therapies

**Bone morphogenetic proteins are local anabolic agents.** Interest in bone morphogenetic proteins (BMPs) as mediators of bone healing began in the 1960s,<sup>3</sup> but the efficacy of treatment with BMPs in fracture healing has only been proven in the last decade. They are naturally occurring proteins in the TGF- $\beta$  superfamily, but only some are truly osteogenic, inducing the formation of bone as an isolated stimulus. In pharmacological doses they stimulate the recruitment, proliferation and differentiation of osteoblast progenitors, leading to increases in the net production of new bone.<sup>14</sup> BMP-2 and osteogenic protein 1 (OP-1/BMP-7), both of which are involved in skeletogenesis and bone homeostasis, have been successfully marketed commercially in their recombinant human forms.

Both BMP-2 and OP-1 can induce healing in animal models.<sup>15-19</sup> In clinical studies, BMP-2 has been shown to be effective in the treatment of open tibial fractures, with 74% proceeding to union without secondary intervention, compared with 54% of untreated controls.<sup>20</sup> A recent sub-analysis showed a prominent effect in grade III open fractures.<sup>21</sup> In a clinical trial in tibial nonunion OP-1 was shown to be as effective as autologous bone graft in most respects.<sup>22</sup> Radiological union was achieved in 75% of cases.

Despite clearly being a useful, even a potent, anabolic stimulus, such pharmacological doses of BMP do not achieve union in all cases, either because the stimulus was not sufficient to bring about union owing to a lack of responder cells, or because catabolism altered the net effect

on bone production. There may be a concomitant BMP-mediated increase in bone resorption.<sup>23-25</sup>

**Parathyroid hormone is a systemic anabolic therapy.** Parathyroid hormone (PTH) is an 84 amino acid polypeptide which, among other actions, liberates calcium from the skeleton in response to systemic needs. It acts on cells that express PTH receptor, which include osteoblasts. Osteoclastic activity can be indirectly activated by the effects of PTH on osteoblasts.<sup>26</sup> It has been shown in animals and humans that continuous exposure to PTH or PTH1-34 leads to an increase in osteoclast density and activity, whereas intermittent exposure stimulates osteoblasts and results in increased bone formation.<sup>27-29</sup> Therefore, PTH/PTH<sub>1-34</sub> can increase both anabolism and catabolism, but when given in an intermittent dosing schedule its net effects are predominantly anabolic.

Daily administration of PTH<sub>1-34</sub> in doses ranging from 10  $\mu\text{g}/\text{kg}$  to 200  $\mu\text{g}/\text{kg}$  in rat models of closed fracture healing has an anabolic effect on fracture repair, associated with substantially-increased mechanical and histological properties.<sup>30-32</sup> It has also been shown to be effective in a rat model of distraction osteogenesis.<sup>33</sup> Although these animal results are encouraging, clinical trials of the effect of PTH<sub>1-34</sub> on bone repair in humans are yet to be published. Also whereas PTH<sub>1-34</sub> exerts an anabolic response only in an established bone microenvironment, its administration may not enhance the recruitment of cells to a fracture site, as do BMPs and other growth factors.

**Nitrogen-containing bisphosphonates (N-BPs) are anti-catabolic drugs.** These have been successfully applied as adjunctive agents in animal models of distraction osteogenesis and fracture repair. Distraction osteogenesis is one of the most potent anabolic processes known. However, failures do occur, and in our clinical experience most are due to catabolic excess.<sup>34</sup> In a model of distraction osteogenesis in New Zealand White rabbits, one or two doses of zoledronic acid, a potent N-BP, increased the bone mineral content, the volume of new bone and the strength of delaying remodelling, a catabolic effect.<sup>35,36</sup> Chondrocyte removal was normal in these animals, but the remnants of calcified chondral matrix in primary trabeculae were retained for longer. This gave an increase in the size and strength of the callus at the time of union. These findings have recently been validated and expanded by Takahashi et al.<sup>37</sup> Using an improved model of distraction osteogenesis in the rabbit, they examined both the osteosclerotic and the osteopenic zones of the regenerate and showed that high doses of the N-BP YM529 improved the homogeneity and strength of the regenerate by eliminating excessive new bone resorption intrinsic to the process of distraction.

Early clinical trials of this approach have begun in the hope that treatment with N-BP will sustain distraction-induced regenerate such that it will be better able to resist deformation and fracture at the time of removal of the frame.<sup>34</sup> The anti-catabolic effects of N-BPs diminish with

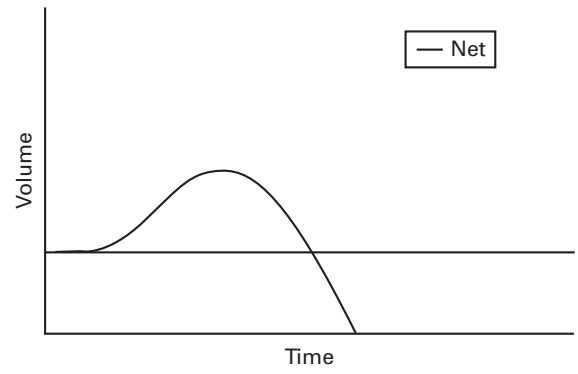
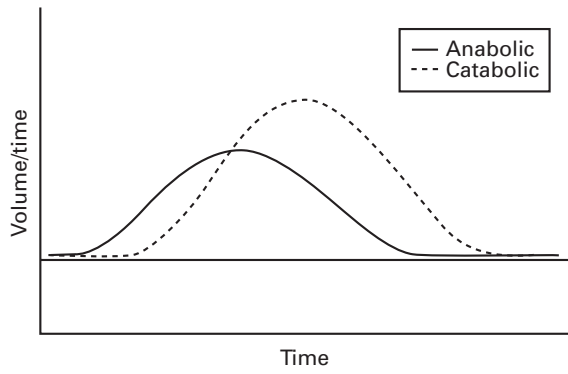


Fig. 2a

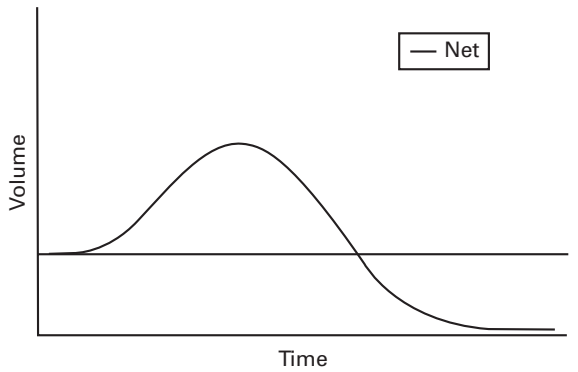
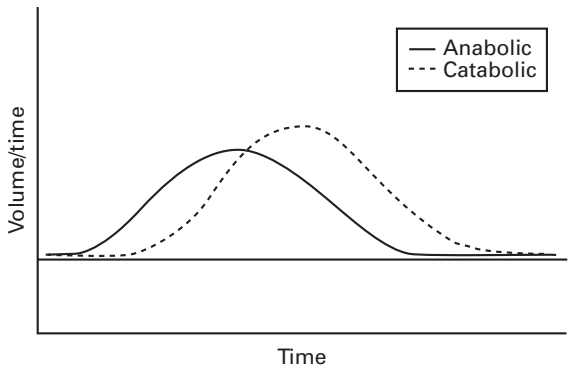


Fig. 2b

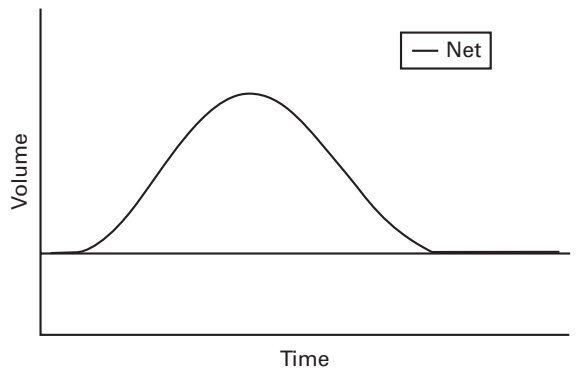
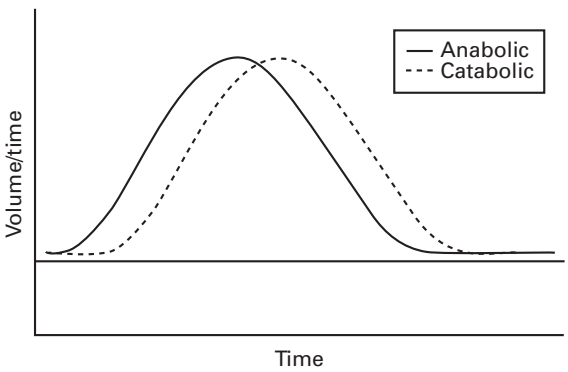


Fig. 2c

Model of anabolic deficiency. Rates of anabolism/catabolism are shown in the left-hand panels and the net bone formed in the right-hand panels. Figure 2a – Decreased anabolism leads to a net decrease in bone production. Note the similarity in resultant net bone formation to Figure 3b. Figure 2b – Anti-catabolic treatment has some effect in anabolic deficiency, but does not restore the full net response. Figure 2c – Restoration of the anabolic response with an anabolic treatment. Owing to receptor activator for nuclear factor Kappa-B ligand (RANKL)-induced osteoclastogenesis, catabolism is usually concomitantly increased. Net bone production is restored, but the rate of bone turnover may be increased.

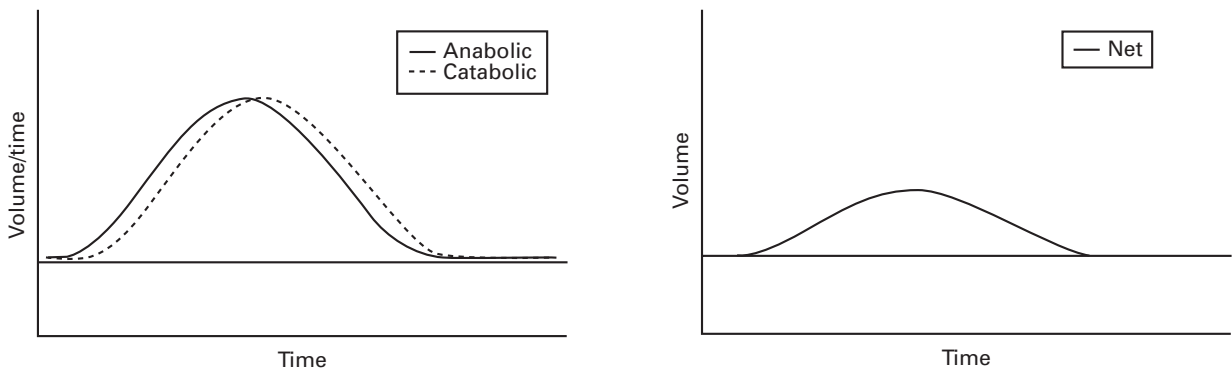


Fig. 3a

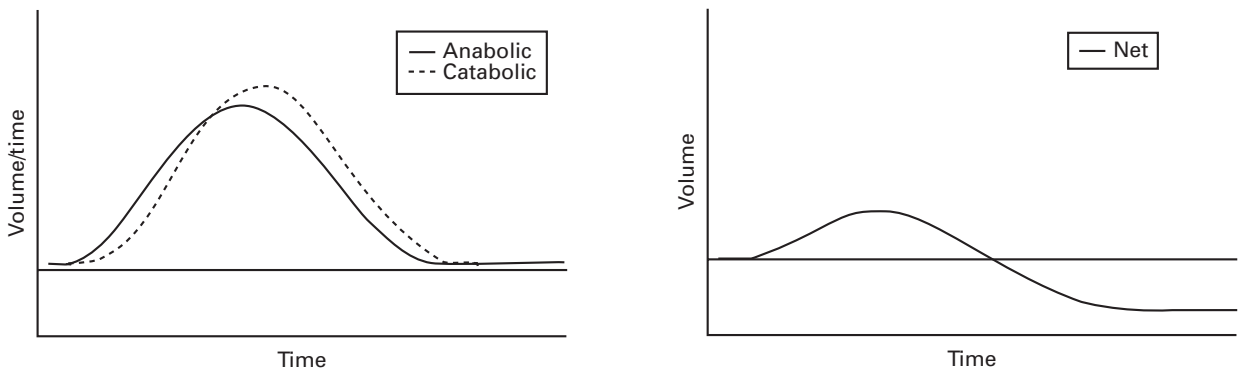


Fig. 3b

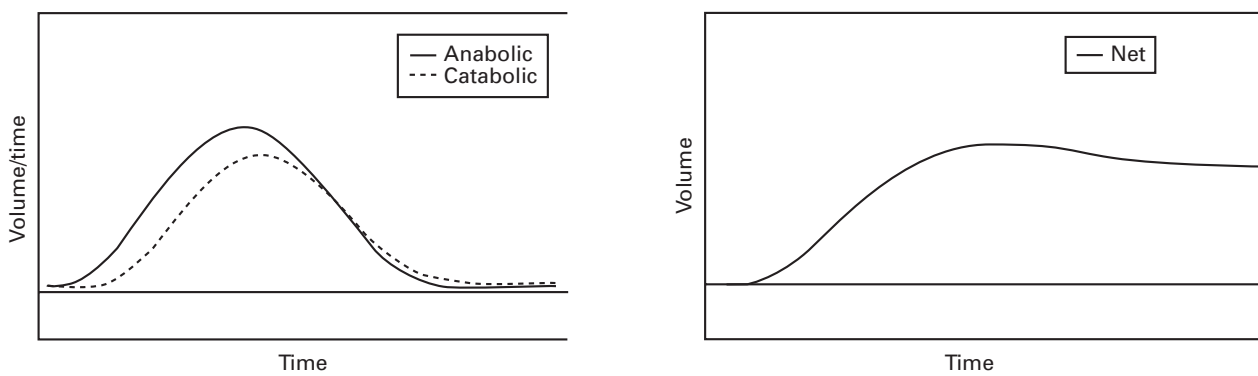


Fig. 3c

Model of catabolic excess. Rates of anabolism/catabolism over time are shown in the left-hand panels and the net bone formed is shown in the right-hand panels. Figure 3a – Normal anabolism with premature catabolism. Figure 3b – Normal anabolism with premature and excessive catabolism. In both situations the net bone production is severely impaired. Figure 3c – Anti-catabolic treatment increases the net amount of bone at the site of injury and prolongs its retention.



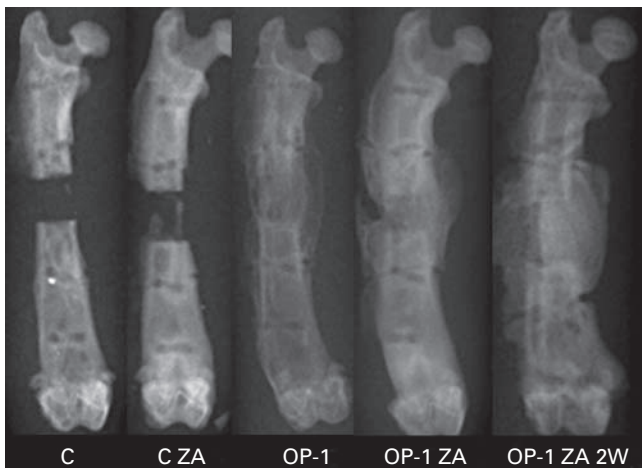


Fig. 4a

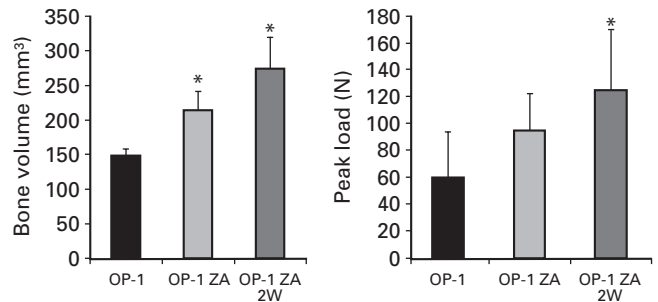


Fig. 4b

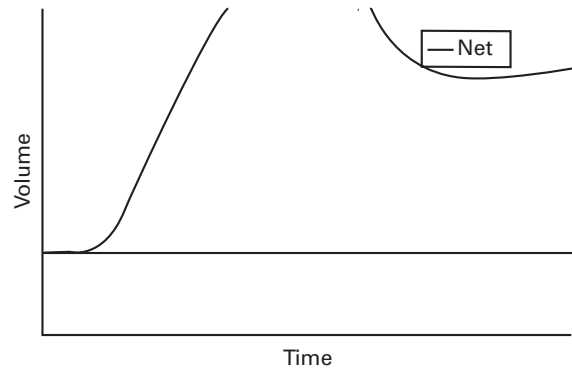
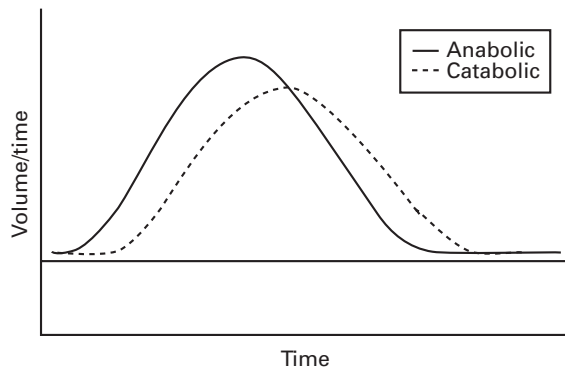


Fig. 4c

Synergy using anabolic and anti-catabolic combination therapy. Experimental results using a rat critical-size defect model. Figure 4a – Only groups treated with osteogenic protein-1 (OP-1) as an anabolic agent went on to unite (C, saline control; CZA, saline + post-operative zoledronic acid; OP-1, local OP-1; OP-1ZA, local OP-1 + post-operative zoledronic acid; OP-1ZA2W, local OP-1 + zoledronic acid given two weeks post-operatively). Figure 4b – Addition of zoledronic acid to the OP-1-treated groups increased bone volume by up to 86% and strength by up to 107% (From Little et al<sup>4</sup>). Figure 4c – Graphical representation showing that anabolic and anti-catabolic therapy gives the biggest net result in terms of callus formation.

time, thus allowing remodelling of bone in response to the normal mechanical environment of free weight-bearing.

The effect of treatment with zoledronic acid on the healing of closed fractures has been examined using the model of Bonnarens and Einhorn.<sup>38</sup> In this model the fractures heal by the formation of a cartilage intermediate, with calcification, vascular invasion and endochondral ossification leading to union by six weeks. Regimens of treatment included a bolus dose at one week after fracture, or weekly in weeks one to five using a total dose of 0.1 mg/kg. Healing fractures showed no significant difference in the percentage of callus made up of vascular bone *versus* cartilage, indicating that endochondral repair progressed normally using these regimens.<sup>7</sup> In a further study using the same model, animals treated with a single dose of 0.1 mg/kg at one or two weeks after injury showed significant increases in bone mineral content, volume of callus and mechanical strength compared with animals treated with saline.<sup>39</sup> Thus, by delaying resorption of the peripheral bony callus with anti-catabolic therapy, a callus was formed that was more resist-

ant to re-fracture. There was a trend towards a further increase in strength when zoledronic acid treatment was delayed by one to two weeks, suggesting that the optimal timing for anti-catabolic therapies may be after bone formation has commenced.

In a recent study using a model of an open fracture in osteoporotic rats, only 42% of control animals healed.<sup>40</sup> Treatment with alendronate increased union to 78% and animals pre-treated with alendronate followed by anabolic treatment with PTH had an almost identical rate of union of 82%. In this experiment both anabolic and anti-catabolic approaches were successful.

It is important to note that these positive studies are in animals given relatively short-term treatment with bisphosphonate. However, several reports of inhibition of fracture repair have emerged in patients on very long-term bisphosphonate therapy.<sup>41,42</sup> Long-term treatment may have reduced turnover to a point where both anabolic and catabolic responses are compromised.

**Synergism with BMPs and N-BPs combined anabolic and anti-catabolic therapy.** BMPs provide a potent anabolic stimulus in the presence of responder cells. However, they can also directly stimulate osteoclastogenesis and induce mature osteoclasts to increase bone resorption.<sup>23-25</sup> They can also stimulate osteoclastogenesis indirectly through osteoblasts via the RANK/RANKL pathway.<sup>43</sup> Hence their use could be limited, as both anabolic and catabolic stimulation occur simultaneously, inducing a high bone turnover. This may be why large doses of BMP are required in clinical practice.

Using a model of a critical-sized defect in the rat, we applied a fixed anabolic stimulus (50 µg OP-1) and by controlling catabolism with zoledronic acid were able to increase the volume and strength of bone tissue that formed in eight weeks.<sup>44</sup> Untreated defects, defects with a carrier alone and defects with the carrier alone plus systemic zoledronic acid did not show a significant anabolic response and did not unite. This illustrates that an adequate anabolic response is required for anti-catabolic therapies to be effective. When OP-1 was present as an anabolic stimulus, co-treatment with zoledronic acid led to an increase in the volume and mechanical strength of the callus. Again, an improved outcome could be obtained by delaying zoledronic acid treatment by two weeks in an OP-1/zoledronic acid combined approach (Fig. 4).

Histological examination showed that in this rigidly-fixed environment the BMP-induced bone had formed primarily through intramembranous pathways. Retaining this framework allowed for increased callus formation, much of which appeared to be appositional bone, as seen by the presence of multiple osteoid seams. Dynamic histomorphometry revealed no differences in the bone formation rate between the OP-1 alone and the OP-1/zoledronic acid groups, indicating that the increases in callus volume were not due to differences in anabolism. This study strongly supports the hypothesis that the anabolic response can be enhanced by delaying catabolism.

### Application of the anabolic/catabolic model in assessing new treatments

The anabolic/catabolic model provides an intuitive way of assessing new biological treatments for bone repair. The following factors should be taken into account:

1. What is the effect on the anabolic response?
  - (a) Does treatment increase cellular recruitment or provide additional cells?
  - (b) Does it increase osteogenic commitment and differentiation?
  - (c) Does it increase the production of bone matrix?
  - (d) Is the anabolic effect modulated via a supporting mechanism such as the vasculature?
2. What is the effect on the catabolic response?
3. For how long will these effects be needed for an optimal result?

4. Are there local environmental conditions that might influence the transduction of anabolic and catabolic stimuli?

The sum of these factors will determine how much bone is formed at the site of injury and at what speed it is removed. If we only take into account pro-anabolic characteristics and ignore possible catabolic effects of either the treatment or the underlying bony environment, the desired effect is unlikely to be realised.

Modulation of the anabolic and catabolic responses can generate profound changes in bone repair. However, as anabolism and catabolism are intrinsically linked, targeting only one response may not always be optimal. The ideal model in bone repair is to promote a robust anabolic response with control of catabolism until union is achieved.

We would like to acknowledge the work of members of the Orthopaedic Research and Biotechnology Laboratory at the Children's Hospital at Westmead. This review draws heavily on the postgraduate work of Michelle McDonald, Negin Amanat and Elisabeth Smith. We would also acknowledge funding from NHMRC grant 352391 and the philanthropic support of Ingham Enterprises Pty Ltd. Dr Little has received consultancy fees from Novartis Pharma AG. Some research funding was also provided by Novartis Pharma AG. Stryker Corporation kindly provided the OP-1 used in some of our studies.

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