Optimal exercise protocol for osteogenic response

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Received: November 18, 2015 / Accepted: November 30, 2015

Abstract Mechanical loads on the skeleton imposed by exercise increase bone mass and strength. The sensor in the osteocyte that detects mechanical stress, the mechano-sensor, responds to bone strain caused by mechanical loading. Greater magnitude and rate of strain increases osteogenic response, making high-impact exercise, which imposes large and dynamic strain on the skeleton, an effective mode of exercise. However, the sensitivity of the mechano-sensor (mechano-sensitivity) drops after a large number of repetitions performed within an exercise session, which has diminishing returns. It takes several hours or several days to reestablish mechano-sensitivity after the last loading session. It is important to consider the time to recovery of mechano-sensitivity when determining optimal exercise frequency.

Keywords: mechanical stress, mechanical sensitivity, exercise frequency, high-impact exercise

Introduction

It is well known that the mechanical stress generated by exercise increases bone mass and strength. However, the optimal exercise protocol for osteogenic response is not yet known. With regard to exercise mode, it is reported that high-impact exercise, which imposes dynamic skeletal loading, is desirable for osteogenic response. With regard to exercise intensity, osteogenic response has been shown to increase in proportion to the size of the load, within physiological limits. However, the optimal exercise frequency for osteogenic response is still unclear, although several studies have focused on this issue. It is assumed that mechano-sensors in the osteocytes respond to mechanical stress. The sensitivity of the sensor may drop after a large number of cycles of repeated loading; therefore, the time to recovery of the mechano-sensor must be considered when determining optimal exercise frequency. The optimal exercise protocol, particularly with regard to exercise frequency, is discussed in this review.

Bone adaptation to mechanical-stress

Bones increase in mass and strength when they undergo mechanical stress. This adaptation to mechanical stress appears to be quite localized; while mechanical stress on the bones of the lower limbs results in increased mass and strength, the bones of the rest of the body remain unchanged. Moreover, within the same bone, the adaptation is limited to the loading site. This phenomenon strongly suggests that osteocytes play an important role in this adaptation because they exist everywhere in a given bone.

In the mechanostat theory proposed by Frost, bone mass increases or decreases according to the magnitude of strain generated locally by mechanical stress. When bones undergo mechanical stress greater than that normally experienced, they are placed under greater strain, and the mechanism-transduction system is stimulated to increase bone mass. However, once the bones adapt to extended periods of increased mechanical stress and their mass is increased, further increases do not occur because the acquired bone mass diminishes the magnitude of strain. Conversely, when bones are loaded with less mechanical-stress than that normally experienced, the reduction in strain leads to decreased mass. However, once the bones lose some degree of mass, they stop decreasing in mass because bone loss enlarges the magnitude of strain generated by the new normal load. Thus, the mechanostat theory provides a rational explanation of bone adaptations to mechanical stress.

Another important factor in bone mechano-sensor stimulation is strain rate. Strain rate, the change in magnitude of strain over time, relates to the speed of mechanical loading. In their study of the avian ulna, Lanyon and Rubin demonstrated that dynamic loading was more effective than static loading, or fixed pressure to the bone with the same magnitude of strain, for increasing bone mass. Rate of strain is therefore considered an independent factor in stimulating bone mechano-sensors. High-impact exercise is effective for gaining bone mass because a high-impact load can produce a high degree of strain magnitude and rate in bone. In particular, exercise with a large ground-reaction force caused by body weight is considered effective for bone development.
Stimulation of mechano-sensors with repeated loading

In animal studies, many kinds of exercise training, including treadmill-running\(^{1,12}\), voluntary wheel-running\(^{13}\), resistance training\(^{14,15}\), and climbing\(^{16,17}\), have been reported to be beneficial for osteogenic response. Jump training has also been shown to be effective in increasing bone mass or bone mineral content (BMC)\(^{6,18-21}\). In jump training, rats jump from the bottom to the top of a 40- or 45-cm-high wooden box and are then placed at the bottom for the next jump. The bones of the lower limbs receive greater loads during takeoff than during landing. The number of daily repetitions of loading for osteogenic response during 8 weeks of jump training were studied, and a relationship shown between increased bone mass and number of daily repetitions of loading\(^{21}\). Five jumps per day resulted in a significant increase in bone mass compared with no jumps per day. However, the loading effect did not increase in proportion to the number of repetitions, and a diminishing return was seen (Fig. 1). Following this, a review by Turner\(^{22}\) used our data and data from a study by Rubin and Lanyon\(^{23}\) to demonstrate that the loading effect could be approximated by a logarithmic curve as a function of number of repetitions. In that review, our data were characterized mathematically as follows:

\[
\text{Tibial bone mass (\% of control)} = 100.1 + 11.0 \log (1 + N),
\]

where \(N\) is the number of repetitions per day.

Moreover, Turner and Robling\(^{24}\) proposed an osteogenic index (OI), which shows the loading effect from daily exercise as a logarithmic function, as

\[
\text{OI} = \text{intensity} \times \ln (N + 1),
\]

where intensity equals the load applied to the bone. They proposed that, because the magnitude of force on the skeleton in many human exercises is usually proportional to the ground-reaction force, intensity is represented by the ground-reaction force divided by body weight. Using this formula, the OI of 10 repetitions of jump exercise with a ground-reaction force 3.0 times the body weight is calculated as follows:

\[
\text{OI} = 3.0 \times \ln (11) = 7.2.
\]

Another example shows that the OI of 100 repetitions of jump exercise with a ground-reaction force 3.0 times the body weight is

\[
\text{OI} = 3.0 \times \ln (101) = 13.9.
\]

As seen in these examples, even if the number of repetitions increases 10-fold, the effect on bone increases by less than a factor of 2.
Using the same formula, the OI of 1,000 steps of walking exercise with a ground-reaction force 1.1 times the body weight is calculated as follows:

\[ OI = 1.1 \times \ln (1,001) = 7.6 \]

This shows that 10 repetitions of moderate-intensity jump exercise has an OI approximately equal to that of 1,000 steps walked in about 20 minutes.

In the rat-jumping studies\(^6,18-20\), the rats were usually only jumped 10 or 20 times daily for 8 weeks, and an increase of about 10% was observed in bone mass compared with non-jumped rats. The rats in the studies were easily trained and took less than 1 minute to complete a ten-jump exercise. Ten-jump exercise training has some other advantages as well, for example, 1-hour running exercise in rats affects the respiratory and circulatory systems and may have aerobic and anabolic components. It is assumed that these factors in running exercise indirectly influence bone mineral metabolism as well as mechanical loading. Moreover, running exercise in rats generally influences their body weight, and bone mechanical stress is sensitive to body weight. However, 10-jump exercise training in rats generally does not affect their body weight and has little aerobic effect, making jump training a useful training mode for studies on the effects of mechanical stress.

Some human studies have also demonstrated that high-impact, low-frequency jump training had the potential to increase bone mineral density (BMD). Kato et al.\(^25\) assigned 36 young women to an exercise-training group or a non-exercise-training group. The exercise-training group performed only 10 maximal jumps per day 3 times per week for 6 months. The BMD of the lumbar spine and femoral neck significantly increased compared to baseline in the exercise-training group, whereas no significant change in BMD was observed in the control group. The areas of bone in which BMD increased were the points mechanically stressed by the jump exercise because those areas sustained the body weight. The authors therefore concluded that the effects of jump exercise on bones are obvious even with low-frequency loading. Of note in this study was that the subjects were asked to jump with maximal effort, which presumably exposed their bones to unusually large loads. When mechanical stress greater than the bone-formation threshold in Frost’s mechanostat theory is applied, the bones will respond to the strain even if the frequency of stress is very low.

MacDonald et al.\(^26\) also reported the positive effects of low-frequency jump exercise on the bones of children. In their school-based study, each child jumped 10 times at the beginning of the school day, 10 times during the lunch break, and 10 times at the end of the school day. After 14 months of training, the authors observed positive effects on bone development, especially in boys. These studies highlighted the usefulness of low-frequency jump exercise, although the physiological adaptations require more time in humans than in rats.

**Decline and recovery of mechano-sensitivity after a large number of cycles of repeated loading**

The relationship between the number of repetitions and increases in bone mass can be represented by a logarithmic curve, as seen in the above formulas. Progressive loading decreases mechanical sensitivity, so that, for 100 repetitions, the initial 10 repetitions will have a greater effect on bone mass than the final 10. An effective exercise program must account for recovery of mechano-sensitivity.

For example, in a daily exercise program consisting of some number of repetitions of loading, dividing the repetitions into several sessions separated by several hours may have a greater effect on bones than one session consisting of the total number of repetitions. Robling et al.\(^27\) examined 16-week loading programs in which they artificially compressed the ulnas of anesthetized rats longitudinally. The program consisted of 90 repetitions per session four times daily (90 \times 4), performed at 3-hour intervals. After 16 weeks, this program led to increases in the BMD and BMC of the rat ulnae that were significantly greater than those achieved with a single daily session of 360 repetitions (360 \times 1). They concluded that the 3-hour intervals between sessions allowed for recovery of mechano-sensitivity to some extent, and that the divided program had a better effect.

In another study, Robling et al.\(^28\) used a loading model of rat tibias to determine the time course of recovery of mechano-sensitivity after mechanical loading. They manipulated the recovery times (0, 0.5, 1, 2, 4, or 8 hours) among four identical, daily, 90-repetition loading sessions (4 \times 90, or 360 repetitions total) and performed histomorphometric measurements using fluorescent labels from the endocortical surfaces of the tibias. The authors found that the bone formation rate in the 8-h recovery group was 100% greater than that in the 0- or 0.5-h recovery group. They concluded that approximately 8 h of recovery was sufficient to restore full mechano-sensitivity to the cells.

Turner and Robling\(^29\) then proposed a formula for OI when bones are loaded during two exercise sessions in one day, as follows:

\[ OI = (\text{intensity}_1) \times \ln (N1 + 1) + (\text{intensity}_2) \times \ln (N2 + 1) \times (1 - e^{-t/\tau}) \]

where \( t \) is the interval between sessions and \( \tau \) is a time constant. They suggested that \( \tau \) is approximately equal to 6 h by the data from Robling et al.\(^29\).

According to the formula for OI, continuous 20-jump exercise with a ground-reaction force 3.0 times the body weight is calculated as follows:
OI = 3.0 × ln (11) = 9.1

However, the OI of 20-jump exercise split into two 10-jump exercise sessions (2 × 10) at the same intensity and divided by a 6-h interval, is

\[ OI = 3.0 \times \ln (11) + 3.0 \times \ln (11) \times (1 – e^{-1}) = 11.7 \]

OI increases by approximately 30% when the repetitions are divided into two sessions.

However, our results in the rat-jumping model were not consistent with those of Turner and Robling24. We compared 10 jumps once daily (1 × 10) with two daily sessions of 10 jumps each (2 × 10) separated by more than 6 h and observed similar effects on tibial weight gain6 (Fig. 2A). This showed that 6 h was not sufficient to recover the decrease in mechano-sensitivity caused by 10 jumps. Using the same rat-jumping model, Sogo et al.29 reported that mechano-sensitivity did not recover completely within 24 hours. These results suggested that a program consisting of multiple loading sessions daily is not always effective for increases in bone mass.

One reason for the discrepancy between our results and those of Robling et al.27 is a difference in the size of the load. Judging from the increases in BMC in the two loading models, the load exerted by jumping is considered greater than the artificial loading used by Robling et al. It is assumed that recovery of the decreased mechano-sensitivity after prolonged repeated loading depends on the size of the load and is delayed under large loads. More studies are needed on this subject.

Another study investigated the optimal number of training sessions per week for osteogenic response using a rat-jumping model9. It was found that 10 jumps once daily for 8 weeks had the greatest potency, although 10 jumps once per week for 8 weeks (80 jumps total for the entire experimental period) significantly increased tibial bone mass (Fig. 2B) and strength. This demonstrated that even a low-frequency exercise protocol was effective for osteogenic response.

In addition to these session-interval studies, there are individual loading-interval studies. In our rat-jumping model, the rats were usually jumped about every 3 s. However, significantly greater potency was seen in the jump-exercise protocol with 30 s between jumps than in the protocol with 3 s between jumps20. Similarly, greater potency has been reported for loading protocols with 10 to 30 s between each repetition than for loading protocols without rest intervals27,30,31. This may mean that there is a slight recovery of mechano-sensitivity within a few seconds after application of a single load; but at least several hours are required for complete recovery after prolonged repeated loading.

The effect of mechano-stress on bones is manifested as bone strength rather than bone mass. Robling et al.32 reported that 16 weeks of artificial loading of rat ulnas increased bone strength by about 80% compared to controls, but that bone mass increased only 8%, suggesting that mechanical stress is essential for bone strength. Moreover, recent studies have suggested that the exercise effect on bones acquired when subjects are young is retained for a long period to some extent33-37. These results

![Fig. 2](image-url)
demonstrate the importance of exercise for the prevention of osteoporosis. Further studies of the exercise protocol and mode that provide the greatest osteogenic response, and that consider mechano-sensitive activation of the mechano-sensor, are needed.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this article.

Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (26350916).

References


