BONE MYOREGULATION REFLEX: A POSSIBLE NEW MECHANISM

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ABSTRACT

• ***Objective:*** *A bi-directional interaction between muscle and bone functions may be assumed. However effects of muscle activity on bone structure and function have been investigated till today. Aim of this study was to determine whether bone mineral density (BMD) affected muscle strength gain.*

• ***Material and Method:*** *Twenty three young-adult healthy males were included in this double-blind prospective study. These volunteers were randomized into two groups. In Electrical Muscle Stimulation (EMS group, electrical muscle stimulation of the right wrist flexor muscles was applied; in healthy controls, transcutaneous electrical nerve stimulation was applied. Electrodes were placed over the flexor aspect of the right forearm in both groups. Electrical stimulation was applied for six weeks in both groups. Before trail, BMD of the rigth distal radius were measured in all participants.*

• ***Results:*** *Isokinetic muscle torque measurements was revealed that increase in the wrist extensors strength was 67.2% in EMS group, and was 18.1% in controls (p=0.001). Strong correlation between baseline ultradistal radius BMD and muscle strength gain of the wrist extensors were found in EMS group. Regression analysis revealed that ultradistal radius BMD may be an important determinant of the muscle strength gain of the wrist extensors.*

• ***Conclusion:*** *Current study suggests that bone can regulate muscle activity, based on its BMD. This result implies that there may exist a mechanism that bone sensing mechanical stimuli can send the signals to central nervous system and neuronally regulate muscle activity. It is well known that bone subjected to loading neuronally regulates bone formation.*

Taken together, a possible new mechanism, bone reflex, may be defined that bone subjected to loading can neuronally regulate bone formation and muscle activity.

• ***Key Words:*** *Bone, muscle strength, exercise, electrical muscle stimulation, bone mineral density.* ***Nobel Med 2009; 5(3): 9-17***

ÖZET

KEMİK MİYOREGÜLASYON REFLEKSİ: OLASI YENİ BİR MEKANİZMA

• **Amaç:** Kas ve kemik fonksiyonları arasında çift yönlü etkileşim olabileceği düşünülebilir. Fakat, günümüze dek kas aktivitesinin kemik yapı ve fonksiyonları üzerine etkisi incelenmiştir. Bu çalışmanın amacı kemik mineral yoğunluğunun (KMY) kas kuvvet artışı üzerine etkisi olup olmadığını incelemekti.

• **Materyal ve Metod:** Bu çift-kör prospektif çalışmaya 23 sağlıklı genç erişkin gönüllü erkek dahil edildi. Olgular iki gruba randomize edildi. Elektriksel kas stimülasyonu (EKS) grubunda, sağ el bileği fleksör kaslarına elektriksel kas stimülasyonu; sağlıklı kontrol grubunda, transkütan elektriksel sinir stimulasyonu uygulandı. Elektrodlar her iki grupta sağ önkolun fleksör yüzüne yerleştirildi. Elektriksel stimulasyon her iki grupta 6 hafta uygulandı. Deney öncesi, tüm olguların sağ distal radius KMY ölçümü yapıldı.

• **Bulgular:** İzokinetik kas kuvveti ölçümleri el bileği ekstansör kas kuvvetinde, EKS grubunda %67,2, Kontrol grubunda %18,1 artış olduğunu göstermiştir (p=0,001). EKS grubunda, ultradistal radius KMY ile elbilek ekstansör kas kuvveti artışı arasında güçlü korelasyon saptandı. Regresyon analizi el bileği ekstansör kas kuvveti artışı açısından ultradistal radius KMY'nin önemli bir faktör olabileceğini göstermiştir.

• **Sonuç:** Bu çalışma, kemiğin, KMY'ne bağlı olarak kas aktivitesini düzenleyebileceğini öne sürmektedir. Bu bulgu, mekanik uyarıları algılayan kemiğin, bu uyarıları merkezi sinir sistemine gönderdiği ve kas aktivitesini nöronal olarak düzenlediği bir mekanizmanın var olabileceğini düşündürmektedir.

Mekanik yüklenmeye maruz kalan kemikte, kemik yapımının nöronal olarak düzenlendiği bilinmektedir. Her iki mekanizma birlikte dikkate alındığında, mekanik yüke maruz kalan kemiğin, kas aktivitesini ve kemik yapımını nöronal olarak düzenlediği düşüncesi kemik refleksi olarak adlandırılarak muhtemel yeni bir mekanizma olarak tanımlanabilir.

• **Anahtar Kelimeler:** Kemik, kas kuvveti, egzersiz, elektriksel kas stimülasyonu, kemik mineral yoğunluğu

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INTRODUCTION

The human musculoskeletal system consists of bones, cartilage, ligaments, tendons and muscles. A functional integrity exists between bones and skeletal muscles.

The main function of the muscles is to provide the mobilization and the locomotion. Bones work together with muscles as simple mechanical lever system to produce body movement. The bone also supports the body against the pull of gravity. In order to fulfill their mechanical functions, bones need to have considerable resistance to deformation under load.[1]

It is well known that exercise improves the resistance of bone to mechanical loading and is important for treating and preventing osteoporosis. Resistance and impact training have been shown to induce bone formation and/or prevent bone resorption.[2,3]

Scientific observations indicate that the structure - functions of bones and muscles are usually changed in the same direction. Osteoporosis and sarcopenia frequently are seen together.[4] In disuse situations, muscle atrophy and weakness accompany to bone loss.[5] Theoretically it may be expected that a bi-directional interaction between bone structure-functions and muscle structure-functions exist. All researches in the matter of bone have focused on the effects of muscle activity (i.e. exercises) on bone structure and function. However, the effect of bone (structure and function) on the muscle (structure and function) is not investigated yet. The osteocytes are thought to be the primary mechanosensors in bone.[6,7]

Osteocytes embedded in bone matrix, are interconnected by numerous dendritic processes to form a wide mechan osensitive cellular network.[1] It was revealed that bone subjected to mechanical loading can send the mechanical input to central nervous system (CNS).[8]

As the bones have the ability to receive the mechanical input and send these to the CNS, it may be said that a proper physiological and anatomic basis for hypothetical effects of bone on muscle function exists. Muscle activity is regulated by CNS.[1] In this study, we tested the hypothesis that bone mineral density (BMD) affects an increase in muscle strength which can be provided by exercises in healthy young adult males.

MATERIAL and METHOD

The current study was a prospective, randomized, controlled, double-blind, parallel group, unicenter clinical trial. →

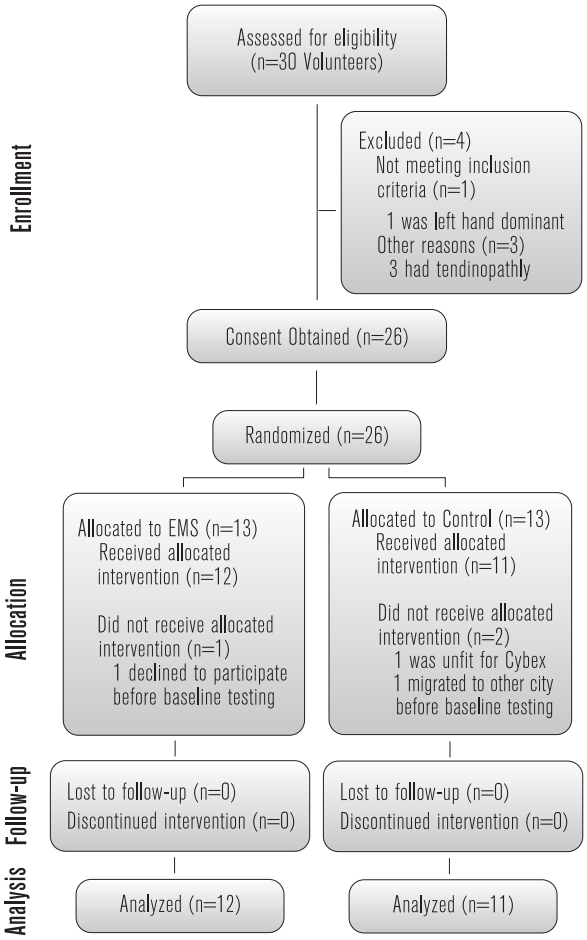

Figure 1. Flow chart of participants considered for inclusion

Participants

Ethical approval was obtained from Institutional Review Board. All participants were volunteers and provided written informed consent. Among young adult males working in our hospital, 30 subjects who voluntarily accepted to participate in this study were assessed for eligibility. Participants had to meet the following criteria: young-adult healthy volunteer, male, righthand dominant. Hand dominance was determined by the preferred hand for writing.

We excluded subjects who had a chronic disease such as metabolic/endocrine bone disease (osteoporosis, osteomalasia, Paget's disease etc), myopathy, tendinopathy, neurologic disorders (hypoesthesia / anesthesia, epilepsy, paralysis), dermatologic disease, peripheral vascular disease, joint disease; had cardiac pacemaker; was noncooperative; was professional sportsman; engaged in regular sportive activity such as tennis, volleyball; was heavy worker.

The participants meeting the criteria were randomized into two groups: electrical muscle stimulation (EMS) group and the control group. This study report followed the guidelines of the CONSORT statements for individual randomized, controlled trials of non pharmacologic treatment.[9] (Fig 1).

Randomization

Only one investigator was involved in the randomization process, which employed the random number generator. Methods for generating random result was coin flipping.

Procedure

Subjects were in a sitting position with 90° flexion at the elbow and supination of the hand during electrical stimulation. Electrical stimulation for muscle strength was applied in the EMS group; Transcutaneous Electrical Nerve Stimulation (TENS) was applied in the control group. Rectangle (4x8 cm), self-adhering, pregelled skin electrodes were used for stimulation. Two large electrodes were placed over the flexor aspect of the right forearm in both groups (Fig 2). Electrical stimulation was applied for thirty sessions (one session a day, five days a week for six weeks) in both groups by the same researcher. Compex2 (Medicompex SA, Switzerland) was used for electrical stimulation. Subjects were requested not to voluntarily contract their wrist flexor muscles during electrical stimulation.

Electrical muscle stimulation (EMS)

Electrical stimulation of the right wrist flexor muscles (M. flexor carpi radialis, M. palmaris longus) and passive extension motion of the right wrist joint was simultaneously applied in the EMS group. Before the trial, all participants completed familiarization protocol consisting of muscle stimulation for one minute in EMS group. Maximum current intensity tolerated was applied for familiarization protocol. Full flexion of the right wrist joint was obtained during electrical muscle stimulation of the familiarization protocol.

A software program for muscle strength of the stimulator (Compex2) was used for EMS group. This program consisted of two consecutive stimulation periods: (tetanic) contraction period and relaxation period. The electrical parameters for contraction period: a high frequency pulsed current (frequency 85 pps, pulse width: 250 µsec, pulse rhythm: monopolar; current rise time: 1.5 sec, steady time 4 sec, and fall time: 0.75 sec) was used for tetanic contraction. The electrical parameters for relaxation period: a low frequency pulsed current (frequency 4 pps, pulse width: 250 µsec, pulse rhythm: monopolar; current rise time: 0.5 sec, steady time 24 sec and, fall time: 0.5 sec) was used for →

recovery. Recovery between contraction periods is Electrical muscle stimulation was applied for 20 minutes. Before this muscle stimulation, a warm-up program (frequency 5 pps, pulse width: 200 µsec; current rise time: 1.5 sec and fall time: 1.5 sec) was applied for five minutes. After the muscle stimulation, a cool-down program (frequency 3 pps, pulse width: 200 µsec; current rise time: 1.5 sec and fall time: 1.5 sec) was applied for ten minutes. Maximum current intensity tolerated was used so as to stimulate the highest possible number of motor unit. The stimulation intensity increased every five minutes during a session.

Passive wrist extension

Passive extension of the wrist joint was applied to obtain passive stretching of the wrist flexor muscles. A full passive wrist extension motion was done during each tetanic muscle stimulation. The wrist extension motion was about 80 degrees. In this way, angular velocity of this motion calculated was 20°/sec. Both electrical stimulation and passive stretching of the right wrist flexor muscles was simultaneously applied by the same researcher in all EMS subjects (Fig 2).

Transcutaneous electrical nerve stimulation (TENS)

Conventional mode of TENS was applied for the control subjects. The conventional mode was characterized by a low amplitude and high frequency (frequency: 100 pps, pulse width: 50 µsec, pulse rhythm: bipolar; current rise time: 1.5 sec and fall time: 1.5 sec). Transcutaneous electrical nerve stimulation was applied for 20 minutes. The stimulus intensity was adjusted as the lowest current at which the subject felt only a slight tickling of the impulses. A visible, and palpable muscle contraction was not provided during TENS stimulation. The stimulus intensity was not changed during the first session. Subsequently, TENS was applied at same intensity in all sessions.

Measurements

Before the trial, baseline distal radius (ultradistal radius (UD), mid radius and total radius) bone mineral density (BMD) was measured by dual energy X-ray absorptiometry (GE-LUNAR DPX PRO Lunar Corporation, Madison, WI, USA) in all participants. The coefficient of variation (CV) for all distal radius BMD measurements was below 1.41%. Isokinetic torque was measured in the right forearm with the Cybex (Humac 2004/Norm) extremity-testing system. The muscles tested included the right wrist flexors and extensors. Subjects were in a sitting position with 90° flexion at the elbow and supination of the hand. The right forearm was placed on a lateral splint. Fixating straps were placed

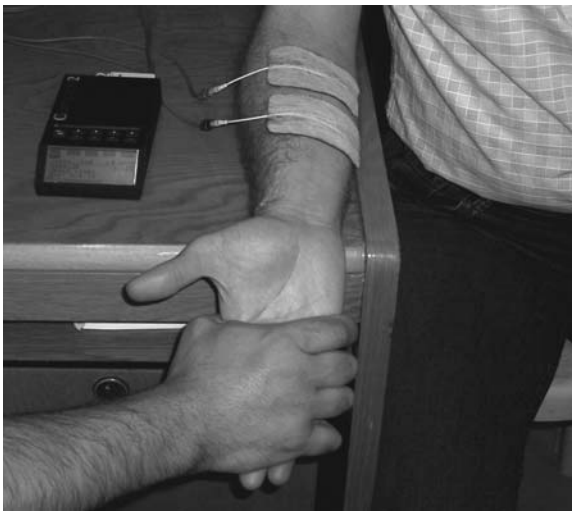

Figure 2. Location of electrodes and passive wrist extension

Figure 3. Forearm position during isokinetic muscle testing

over the right forearm. The machine's axis of rotation was aligned with that of the right wrist joint (Fig 3). Subjects were instructed to pull and push as hard as possible throughout the whole range of motion. Before testing, the participants warmed up for five minutes on a cycle ergometry (Cybex) at 90 revolutions per minute. After a resting period of two minutes, the cases performed the next set of four trial repetitions and three maximal repetitions at 30°/s. One minute of rest between each testing velocity was provided to reduce the likelihood of fatigue. During the tests participants were guided and encouraged to perform maximal muscle performance by standardized auditory feedback, on every repetition. The peak torque obtained in each testing velocity measured in Newton meter (Nm) was normalized to body weight. The isokinetic dynamometer reported the data as mean peak torque.Data were accepted if the CV for torque values did not exceed 14%. This was done to discard results from subjects who did not s how maximal effort. All measurements were performed at baseline and in→

the five days after trial in both groups by the same laboratory assistant.

Blinding

All participants were informed on the effects of electrical stimulation on muscle strength gain investigated in this study. Electrical stimulation was applied to all participants. However, subjects had no knowledge about characteristics of electrical current used for the muscle strength enhancement. All measurements were made by an independent assessor (DXA laboratory assistant and Isokinetic test laboratory assistant) blinded to the trial allocation.

Statistical analysis

The Kolmogorov-Smirnov test was used to confirm that data (age, body height, body mass index (BMI), baseline wrist flexor and extensor muscles strength, final wrist flexor and extensor muscles strength, rate of the increase in muscle strength [=(muscle strength after trial-muscle strength at baseline) 100/muscle strength at baseline], baseline distal radius BMD) were normally distributed in both groups. Continuous variables were summarized as arithmetic mean and standard deviation (SD). The Independent-Samples T test was used to analyze the statistical difference in the forearm BMD, the wrist muscle strength between EMS group and control group. Measured values of the wrist muscles strength at baseline and after experiment were compared with Paired-Samples T test.

In the EMS group, a multiple linear regression analysis was performed to detect independent predictors for the occurrence of the increase in the muscle strength and to find confounding effects between potentially independent predictors (age, baseline muscle strength, baseline BMD). A variable was entered into the model if the probability of its score statistic was less than the Entry value (0.05) and was removed if the probability was greater than the Removal value (0.1). A stepwise method was used to construct multiple linear regression models. A p value of less than 0.05 was considered statistically significant. The Pearson test was used to analyze the correlation between the increase in the muscle strength and the distal radius BMD. A correlation coefficient (R) value of more than 0.30 and a p value of less than 0.05 were considered statistically significant. The data management software package used was SPSS for Windows.

RESULTS

The mean age of participants was 29.6 (22-40) years in the EMS group (n=12) and 34.1 (27-41) years in the control group (n=11) (p=0.054). The mean body mass index (BMI) was 25.4 (20.3-29.4) kg/m^2 in the EMS group and 26.1(22.6-29.7) kg/m^2 in the control group (p=0.495).

Table 1: Baseline distal radius BMD (g/cm2) in both groups

Region of interest	EMS group	Control group	p value
Ultradistal radius	0.546 ± 0.032	0.581 ± 0.085	0.224
Mid radius	0.901 ± 0.071	0.935 ± 0.075	0.279
Total radius	0.737 ± 0.048	0.774 ± 0.069	0.154

Table 2: The wrist muscles peak torque (N.m) at baseline and after 6 weeks

Wrist Muscle		EMS group	Control group
Flexors	at baseline	35.7 ± 8.3	39.5 ± 8.4
	after trial	52.5 ± 11.3	40.6 ± 6.8
	p value	0.0001	0.697
Extensors	at baseline	25.2 ± 5.0	30.9 ± 9.6
	after trial	41.7 ± 8.3	35.1 ± 10.3
	p value	0.0001	0.120

Table 3: Correlations between the increase in the extensor muscle strength and baseline BMDs [correlation coefficient (p value)]

Groups	Distal Radius BMD		
	UD Radius	Mid Radius	Total Radius
EMS group	-0.602 (0.038)	-0.407 (0.189)	-0.503 (0.095)
Control group	0.382 (0.246)	-0.076 (0.824)	0.270 (0.422)

Table 4: Results of multiple linear regression for the increase in the muscle strength of the wrist extensors at in EMS group

	Unstandardized Coefficients		Standardized Coefficients	t	p value
	B	Std Error	Beta		
Constant	345.9	117.1		2.953	0.014
UD radius BMD	-510.2	214.1	-0.602	-2.382	0.038

There were no statistically significant differences in distal radius BMDs between the groups at baseline (Table 1). The right wrist muscles strength significantly increased in the EMS group but not in the control group (Table 2). The increase in the extensor muscle strength was 67.2% in the EMS group and was 18.1% in the control group.

There were strong correlations between baseline UD

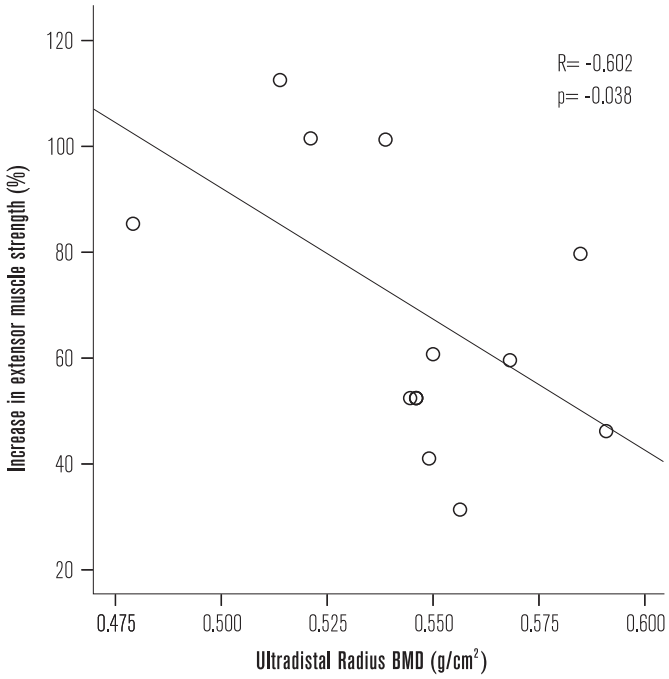

Figure 4. Relationship between increase in muscle strength of wrist extensors and baseline UD radius BMD in EMS group

radius BMD and the increase in the muscles strength of the wrist extensors, in the EMS group (Table 3) (Fig 4).

There was no correlation between UD radius BMD and the wrist extensor muscle strength at baseline, in the EMS group (R=-0.110 p=0.733).

Multiple linear regression analysis revealed that UD radius BMD but not age and baseline muscle strength of wrist extensors was an independent predictor for the increase in the muscle strength, in the EMS group (Stepwise Linear Reg Analysis; R=-0.602, Adjusted R square=0.298 F=5.6 p=0.038) (Table 4). This analysis also indicated that UD radius BMD accounted for 29.8% of the increase in the wrist extensor muscle strength.

Power analysis

Electrical muscle stimulation efficacy was evaluated by comparing the change on primary outcome measures (changes in the muscle strength) between groups. The mean increase in the extensor muscle strength was 16.5±6.4 Nm in EMS group and 4.2±8.3 Nm in control group. For the given effect size (population means of 16.5 vs 4.2), SD (6.4 vs 8.3), sample sizes (12 and 11), and alpha (0.050, two-tailed), the power was 0.965.

DISCUSSION

Weight bearing or strength-training exercise has been shown to produce a beneficial effect on BMD[2]. It is also reported that muscle strength of the paretic forearm is an important predictor of its bone mass[10]. The present study revealed that BMD could be a significant determinant of the muscle strength gain in strength training. Based on the current scientific knowledge, electrical muscle stimulation effectively prevents acute atrophy of muscle fibers.[11] and improves muscle strength.[12] Present study showed that electrical stimulation of the wrist flexor muscle provided an increase in the muscle strength of the wrist flexors in healthy young adult males. It is interesting that the muscle strength gain was determined in the right wrist extensor, although electrical stimulation was not applied to those muscles. Because, Sherington's law of reciprocal inhibition: tight muscles will inhibit it's functional antagonist. Nerve impulses in large muscle spindle (Ia) afferents cause a monosynaptic excitation of motoneurones innervating the homonymous and synergic muscles and a concomitant disynaptic inhibition of motoneurones to antagonists.[13] Electrical stimulation with superimposing a passive stretching of the right wrist flexor muscles may excite muscle spindles in those muscles.

Present study also showed that the muscle strength gain of the wrist extensors were negatively correlated with UD radius BMD in healthy young adult males. This study suggests two important results that is firstly bone can affect the muscle function, and secondly this effect is inversely associated with BMD.

Electrical stimulation of the right wrist flexor muscles with superimposing a passive wrist extension were applied so as to obtain maximum mechanical loading tolerated in variable directions on the distal radius.

According to results of this study conducted in healthy young adult males, muscle strength gain may be higher in subjects with relatively low BMD. It might be thought that muscle strength gain might be higher in subjects with a relatively low BMD, perhaps due to the relatively low baseline muscle strength. However, no correlation between baseline wrist muscles strength and UD radius BMD was found. The baseline UD radius BMD, but not baseline muscle strength, was also found to be an independent determinant for the extensor muscle strength gain. According to our results, UD radius BMD accounted for about 29.8% of the extensor muscle strength gain. As a result, it is suggested that bone subjected mechanical loading has an effect on muscle strength gain.

The current knowledge in the fields of anatomy and physiology of the bone and muscle may help explain the result of this study theoretically: →

1- Bone is sensitive to mechanical loading
2- Sensitivity of bone to mechanical loading is inversely related to BMD
3- Bone subjected to mechanical loading can send the mechanical input to CNS
4- Central nervous system regulates the muscle function and activity

According to Wolff's law and Frost's mechanostat proposal, bone is sensitive to mechanical loading.[1, 14] Osteocytes make up over 90% of all bone cells and interconnected by numerous dendritic processes to form a complex cellular network. They are thought to be the primary mechanosensors in bone that mediate the effects of bone loading through their extensive communication network. Osteocytes can transduce musculoskeletally derived mechanical input signals into biological output.[6, 7]

The osteocytic lacuna acts as a strain concentrator effectively amplifying the macroscopic strain applied to the whole bone and this amplification factor is a function of the local peri-lacunar bone tissue material properties. The stiff peri-lacunar bone tissue may attenuate the strain signal acting on embedded osteocytes. Conversely, the less mineralized bone region around each osteocyte may serve as an important strain amplifier. In subjects having relatively low BMD, the peri-lacunar tissue should exhibit a lower peri-lacunar tissue modulus so that the available skeletal loads are converted to higher tissue strains at the lacuna. Thus in subject having relatively low BMD, the less mineralized peri-lacunar bone may enhance the mechanical signal sensed by osteocytes.[6, 7] There should be a communication between the bone and the muscle so that bone will have an effect on muscle activities. This may hypothetically be provided via nervous system. First of all, bone should be able to send mechanical input signals to CNS. It was shown that cyclic mechanical loading of the right ulna had significant effects on adaptive bone modeling, and that modeling responses to loading of the right ulna developed in multiple thoracic limb bones, and also that temporary blockade of neuronal signaling between the loaded limb and the spinal cord abolished any significant bone modeling effects in the contralateral (left) ulna in rats.[8]

Consequently, these reports support the existence of a communication between the bone and CNS, and sending mechanical input signals to CNS Skeletal muscle is supplied by alpha motor neurons located in the spinal cord. Function and activity of these muscles are regulated by CNS.[1]

The present study suggests the existence of a functional integrity among four main physiological mechanisms mentioned above. In this way, a new mechanism may be defined that osteocytes can send mechanical input signals to CNS and so neuronally regulate muscle activity. This proposed mechanism may be defined as "bone myoregulation reflex" In this way, it may be understood why the muscle strength gain was higher in subjects having relatively low baseline BMD. Because the mechanical signal sensed by osteocytes may be higher in subjects with relatively low baseline BMD, a facilitatory effect of bone on the muscle contraction may be higher through the proposed the myoregulation reflex. Facilitation of muscle contraction is reported to result in muscle strength gain.[15]

Bone myoregulation reflex and bone reflex

According to neuronal regulation mechanism of load-induced bone formation, mechanical stimulations are sended to the CNS.[8] Present study suggests that bone subjected to mechanical loading could regulate the muscle activity and this effect was inversely related to BMD. Based on these two fundamental mechanism, "bone reflex" as a possible physiological mechanism may be described. Bone reflex may be defined as a hypothetical mechanism that mechanical loading is perceived by mechano-sensitive network constructed by osteocytes and that based on strain distribution throughout the cross-sectional area of bone, muscle activity and bone formation are regulated by CNS.

Bone reflex may consist of five components: mechano-sensitive network constructed by osteocytes as a receptor; the sensory neurons transmitting afferent impulses to the CNS; the control/integration center within the CNS; the motor neurons transmitting efferent impulses away from the CNS; bone cells (osteoblast, osteoclast) and skeletal muscle cells as effector organs.

It is well known that osteocytes have a mechano-receptor function.[6, 7] There are afferent and efferent nerve fibers terminating in the vicinity of bone cells.[16, 17] These nerve fibers release neuropeptides such as calcitonin gene-related peptide, substance P, neuropeptide Y, vasoactive intestinal polypeptide and glutamate. The neuropeptides regulate activities of osteoblast and osteoclast.[8, 17-23] On the other hand, alpha motor neurons regulate skeletal muscle activity.[1]

For validity of the bone reflex mechanism, it is important to show that a connection between mechanosensitive network constructed by osteocytes and afferent nerves innervates bone. However, there is no synaptic connection between osteocytes and the afferent nerve fibers.

The structural and functional organization of osteocytes is similar to those of smooth muscles. Smooth muscle→

cells, similar to osteocytes, are interconnected by gap junction to form a wide cellular network.[1, 24] Smooth muscle, similar to bone, is innervated by autonomic nerves.[17, 24] Nerve fibers are shown to terminate in the vicinity of bone cells.[16, 17] Similarly, autonomic afferent and efferent axons terminate in the vicinity of smooth muscle cell.[24] There is no fixed junction with well defined pre- and postjunctional specializations in smooth muscle. It is probable that neurotransmitter diffuse the gap to the adjacent muscle cells.[24,25] Similar neurotransmission mechanism may be supposed to exist between bone cells and autonomic axons terminating in the vicinity of these cells.

Osteocytes subjected to mechanical loading are hypothetically possible to stimulate afferent nerve fibers via mediators released to intercellular milieu by osteocytes. Future studies are needed to confirm these explanation and further investigation should be focused on the neurotransmission mechanisms between bone cells and afferent nerve fibers.

The main function of bone reflex may be to protect the bone from the destroying effects of the mechanical loadings. This protecting effect may appear like "fast response" or "delayed response" that is given to the mechanical loadings. When there is a mechanical loading unsuitable for distributing to the bone cross-sectional area, optimal distribution of this load can be provided by muscle contractions. So the vectorial direction of mechanical load can be optimized by changing of its location. This mechanism defined as "fast response or bone myoregulation reflex" may prevent structural damages such as micro-fracture.

Electrical stimulation with superimposing a passive stretching of the right wrist flexor muscles may led a mechanical loading on flexors side of distal radius cross-sectional area. Suitable distribution of this mechanical loading to the bone cross-sectional area is achieved by the wrist extensor muscle contractions.

The vectorial direction of mechanical loading obtaining electrical stimulation with superimposing a passive stretching of the right wrist flexor may be changed toward extensors aspect of the distal radius by the extensors contraction. This study showed that ultradistal radius BMD may be an important determinant of the muscle strength gain of the wrist extensors.

According to bone myoregulation mechanism, mechanical loading obtaining electrical stimulation with superimposing a passive stretching of the right wrist flexor may stimulate osteocytes at flexor side of the distal radius cross-sectional area so that these osteocytes may excite motor neurons of the wrist extensor muscles and may facilitate the wrist extensors contraction.

As a response to the mechanical loading, release of neuropeptide and increase in osteoblastic activity can be seen.[8] Modelling period is completed in 2-3 months .[26] So, neuronal regulation of bone formation induced-by mechanical loading can be described as a "delayed response or bone osteoregulation reflex". Both "fast response" by changing the vectorial features (force direction, magnitude) of the mechanical load applied on the bone, and "delayed response" by changing the structural features of bone (microarchitecture, mineral density) may protect bone against abnormal mechanical loads and enable facing of mechanical load.Whole-body vibration can effectively enhance muscle strength and power.[27]

Bone reflex may help explain how the muscle strength gain. Bone reflex may also help explain the muscle atrophy and weakness known to be associated with osteoporosis. According to the current study conducted in healthy young adult males, in subjects with relatively low BMD, muscle strength gain is higher. The less mineralized perilacunar bone may enhance the mechanical signal sensed by osteocytes.[6,7] So, intensity of signals arising from an osteocyte may increase. In patient with osteoporosis, however, total signals arising from bone may be reduced, because pathological and progressive loss of both osteocytes and bone mass occur.[19, 28-30]

Consequently, reduced total signals may contribute to developing muscle weakness. To make this subject clear, the association between muscle strength gain induced by exercise and baseline BMD should be investigated in future studies in patients with osteoporosis.

CONCLUSION

This is the first study evaluating effect of BMD on muscle strength gain. According to results of current study conducted in healthy young adult males, it may be suggested that bone can regulate muscle activity, based on its BMD. These results also imply that there may exist a mechanism that bone sensing mechanical stimuli can send the signals to CNS and neuronally regulate muscle activity (bone myoregulation reflex).

It is well known that load-induced adaptive bone formation is neuronally regulated. Taken together, a mechanism, bone reflex, may be defined that bone subjected to loading can neuronally regulate bone formation and muscle activity. Future studies are needed for a full delineation of the bone reflex.

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REFERENCES

1 Standring S. Functional anatomy of the musculoskeletal system. Standring S editor-in-chief. Gray's Anatomy: The Anatomical Basis of Clinical Practice. Elsevier Churchill Livingstone 2005: 83-136.

2 de Villiers TJ. Bone health and osteoporosis in postmenopausal women. Best Pract Res Clin Obstet Gynaecol 2009; 23: 73-85

3 Schwab P, Klein RF. Nonpharmacological approaches to improve bone health and reduce osteoporosis. Curr Opin Rheumatol 2008; 20: 213-217.

4 Walsh MC, Hunter GR, Livingstone MB. Sarcopenia in premenopausal and postmenopausal women with osteopenia, osteoporosis and normal bone mineral density. Osteoporos Int 2006; 17: 61-67.

5 Lam H, Qin YX. The effects of frequency-dependent dynamic muscle stimulation on inhibition of trabecular bone loss in a disuse model. Bone 2008; 43: 1093-100.

6 Bonivtch AR, Bonewald LF, Nicolella DP. Tissue strain amplification at the osteocyte lacuna: a microstructural finite element analysis. J Biomech 2007; 40: 2199-2206.

7 Nicolella DP, Feng JQ, Moravits DE, et al. Effects of nanomechanical bone tissue properties on bone tissue strain: Implications for osteocyte mechanotransduction. J Musculoskelet Neuronal Interact 2008; 8: 330-331.

8 Sample SJ, Behan M, Smith L, et al. Functional adaptation to loading of a single bone is neuronally regulated and involves multiple bones. J Bone Miner Res 2008; 23: 1372-1381.

9 Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. Ann Intern Med 2008; 148: 295-309.

10 Pang MYC, Eng JJ. Muscle strength is a determinant of bone mineral content in the hemiparetic upper extremity: Implications for stroke rehabilitation. Bone 2005; 37: 103-111.

11 Misawa A, Shimada Y, Matsunaga T, Sato K. The effects of the rapeutic electric stimulation on acute muscle atrophy in rats after spinal cord injury. Arch Phys Med Rehab 2001; 82: 1596-1603.

12 Gremeaux V, Renault J, Pardon L, et al. Low-Frequency Electric Muscle Stimulation Combined With Physical Therapy After Total Hip Arthroplasty for Hip Osteoarthritis in Elderly Patients: A Randomized Controlled Trial. Arch Phys Med Rehab 2008; 89: 2265-2273.

13 Fu TC, Hultborn H, Larsson R, Lundberg A. Reciprocal inhibition during the tonic stretch reflex in the decerebrate cat. J Physiol 1978; 284: 345-369.

14 Frost HM. From Wolff's law to the mechanostat: a new "face" of physiology. J Orthop Sci 1998; 3: 282-286.

15 Rees SS, Murphy AJ, Watsford ML, McLachlan KA, Coutts AJ. Effects of proprioceptive neuromuscular facilitation stretching on stiffness and force-producing characteristics of the ankle in active women. J Strength Cond Res 2007; 21: 572-577.

16 Imai S, Rauvala H, Konttinen YT, et al. Efferent targets of osseous CGRP-immunoreactive nerve fiber before and after bone destruction in adjuvant arthritic rat: an ultramorphological study on their terminal-target relations. J Bone Miner Res 1997; 12: 1018-1027.

17 Irie K, Hara-Irie F, Ozawa H, Yajima T. Calcitonin gene-related peptide (CGRP)-containing nerve fibers in bone tissue and their involvement in bone remodeling. Microsc Res Tech 2002; 15; 58: 85-90.

18 Cherruau M, Morvan FO, Schirar A, Saffar JL. Chemical sympathectomy-induced changes in TH-, VIP-, and CGRP-immunoreactive fibers in the rat mandible periosteum: influence on bone resorption. J Cell Physiol 2003; 194: 341-348.

19 Hill EL, Elde R. Calcitonin gene-related peptide-immunoreactive nerve fibers in mandibular periosteum of rat: evidence for primary afferent origin. Neurosci Lett 1988; 29; 85: 172-178.

20 Hill EL, Elde R. Distribution of CGRP-, VIP-, D beta H-, SP-, and NPY-immunoreactive nerves in the periosteum of the rat. Cell Tissue Res 1991; 264: 469-480.

21 Huebner AK, Keller J, Catala-Lehnen P, et al. The role of calcitonin and alpha-calcitonin gene-related peptide in bone formation. Arch Biochem Biophys 2008; 15; 473: 210-217.

22 Juarranz Y, Abad C, Martinez C, et al. Protective effect of vasoactive intestinal peptide on bone destruction in the collagen-induced arthritis model of rheumatoid arthritis. Arthritis Res Ther 2005; 7: R1034-1045.

23 Liu D, Jiang LS, Dai LY. Substance P and its receptors in bone metabolism. Neuropeptides 2007; 41: 271-283.

24 Standring S. Smooth muscle and the cardiovascular and lymphatic systems. Standring S editor-in-chief. Gray's Anatomy: The Anatomical Basis of Clinical Practice. Elsevier Churchill Livingstone 2005; 138-155.

25 Standring S. Nervous System. Standring S editor-in-chief. Gray's Anatomy: The Anatomical Basis of Clinical Practice. Elsevier Churchill Livingstone 2005; 43-67.

26 Martin TJ, Seeman E. Bone remodelling: its local regulation and the emergence of bone fragility. Best Pract Res Clin Endocrinol Metab 2008; 22: 701-722.

27 Rees SS, Murphy AJ, Watsford ML. Effects of whole-body vibration exercise on lower-extremity muscle strength and power in an older population: a randomized clinical trial. Phys Ther 2008; 88: 462-470.

28 Dai R, Ma Y, Sheng Z, et al. Effects of genistein on vertebral trabecular bone microstructure, bone mineral density, microcracks, osteocyte density, and bone strength in ovariectomized rats. J Bone Miner Metab 2008; 26: 342-349.

29 Kaufman JM, Goemaere S. Osteoporosis in men. Best Pract Res Clin Endocrinol Metab 2008; 22: 787-812.

30 Lane NI, Yao W, Balooch M, et al. Glucocorticoidtreated mice have localized changes in trabecular bone material properties and osteocyte lacunar size that are not observed in placebo-treated or estrogen-deficient mice. J Bone Miner Res 2006; 21: 466-476.

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