論　文

Relationship between Serum Leptin and Calcaneus Bone Assessment-Related Indices in Females

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Key words : Serum leptin, Calcaneus bone assessment-related indices, Sympathetic nerve system, RANKL, CART

Ⅰ. Introduction

The activity level in the daily living, exercise habits[1-3], eating habits[4～6], shapes (height and weight)[7,8], percentage of body fat and body fat mass[9,10], menses state[11,12], smoking[13],drinking[3], stress[14], heredity[5,15], sex hormone[16], level of solar radiation exposure[17] , and medicine[18] etc. have a huge influence on the onset of osteoporosis. Early detection and settlement are the primary means of prevention. Furthermore, it is necessary for people to have their bone strength tested and to make effort to increase their bone strength during adolescence[3,19].

In recent years, as the factors influencing on the bone strength, many researchers have paid deep attention to serum leptin which is secreted from fat cells, and sympathetic nerve system[20-26]. But it is not known sufficiently about the potential degree of the relationship between the bone mineral density or the bone strength of the human body and serum leptin. Further study will make it possible to gain new knowledge about the relationship between obesity, increased sympathetic nerve activity induced by the stress or physical exercise and osteoporosis from the other point of view.

The aim of this study is to elucidate the relationship between the bone assessment- related indices measured by the ultrasonic equipment and serum leptin with females.

Ⅱ. Methods

A. Subjects

Fifty-seven healthy females aged 23-69 years participated in this study as a subject. Their age, height, weight, BMI, percentage of body fat, and body fat mass were 52.8±9.4 years (mean±standard deviation, it was the same in the following), 153.7±5.3cm, 22.6±2.7kg/m^2, 26.2±7.3%, and 14.3±5.5kg respectively.

B. Measurement items

SOS (which is speed of sound when the ultra sound penetrates through the calcaneus bone, and is thought to reflect the density of the spongy bone in the calcaneus bone), TI (which is transmission index when ultra sound penetrates through the calcaneus bone, and is thought to reflect the mass of the spongy bone in the calcaneus bone), and OSI (which is osteo-sono assessment index, and is calculated in TI×OSI^2 ,and is thought to reflect the elasticity of the bone) were measured using a ultrasonic bone assessment equipment AOS-100 made by Hitachi Aloka Medical, Ltd. as calcaneus bone assessment-related indices. The median was made by measuring the right calcaneus bone for each individual three times. On the identical day, the venous blood was collected and serum leptin was assayed (the analysis was provided by Cosmic Corporation). This study was conducted at Hokuriku Institute of Wellness and Sports Sciences (Komatsu city, Ishikawa prefecture), and the aim of this study was explained sufficiently to each subject and informed consents were obtained from all the subjects before

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the measurements.

C. Statistical analysis

Pearson’s product-moment correlation coefficient and partial correalation coefficient were calculated by using the statistical software SPSS15.0J for Windows. A p value of less than 0.05 was considered to indicate statistically significant.

Ⅲ. Results

The value of leptin was 7.41 ± 4.15 ng/ml. Table 1 revealed the correlation coefficients of serum leptin with each calcaneus bone assessment-related indices. Each correlation coefficient was negative but was below the significant level.

Table 1. Correlation coefficients between serum leptin and calcaneus bone assessment-related indices

Items	r
Serum leptin vs. SOS	−0.095
Serum lptin vs. TI	−0.141
Serum leptin vs. OSI	−0.134

Table 2 revealed the partial correlation coefficients of serum leptin with each calcaneus bone assessment-related indices independent of age, weight and body fat mass.

Table 2. Partial correlation coefficient between serum leptin and calcaneus bone assessment-related indices

Items	r
Serum leptin vs. SOS	−0.157
Serum leptin vs. TI	−0.286 *
Serun leptin vs. OSI	−0.256

*：p<0.05

The partial correlation coefficient of serum leptin with SOS was negative value was below the significant level. The partial correlation coefficient of serum leptin with TI was negative and was above the significant level. Consequently, the partial correlation coefficient of serum leptin with OSI was negative and had statistical risk of less than 10% which was below the significant level.

Ⅳ. Discussion

Serum leptin produced by the stimulus of insulin is the obese gene-derived hormone which was found during the study of the cause on the disease of the hereditary obese mouse in 1994, and is secreted from the fat cell. It brings the strong eating restraint and the acceleration of the energy consumption mainly through the receptor of hypothalamus. Therefore, it is thought that the lack of leptin’s action plays the important role to the origin of obesity. Serum leptin has sex difference in the amount, has positive correlation with percentage of the body fat, is different in individual, and is dependent on the age roughly[27)].

When serum leptin acts on hypothalamus, sympathetic nerve system is activated and inhibits the bone formation by the osteoblast through the medium of noradrenalin and β-2 adrenergic receptor, and besides that, promotes the formation of the osteoclast by producing the RANKL (Recetor Activator of NK-kBligand), so that both simultaneous actions decrease the bone mass. On the other hand, at the same time when serum leptin acts on hypothalamus, CART (Cocaine Amphetamine Regulated Transcript, which is regulated in hypothalamus) of one of the neuropeptide promotes the action of the osteoblast and results in the promotion of the bone formation through the humoral pathway[20-22,25)]. Therefore, serum leptin is thought to have reciprocal influences of both positive and negative directions on the bone mass.

The partial correlation coefficients of serum leptin with the bone assessment-related indices of SOS, TI and OSI independent of age, weight and body fat mass were obtained along the above-mentioned results and the close relationship of the bone strength with weight[7,8]. They were higher than the correlation coefficients of serum leptin with the bone assessment-related indices in the negative direction as a self-evidence.

Furthermore, weak but significant and negative correlation coefficient was admitted between serum leptin and TI which reflected the bone mass. Weak, negative and nearly significant level of correlation coefficient was admitted between serum leptin and OSI which reflected the bone elasticity. When considered the negative influence of sympathetic nerve activity induced by serum leptin on the bone metabolism (including RANKL) and the humoral, direct and positive influence of CART on the bone, it was thought to be natural that the partial correlation coefficients were low, and it was suggested that the negative values of the partial correlation coefficients were attributed to the stronger action of the bone resorption than the one of the bone formation caused by serum leptin. But the reason why only the TI showed the significant partial correlation coefficient was unknown. Further study to analyze the more premenopausal and postmenopausal females separately is needed.

Sato[28] reported that there was a low and negative but significant correlation coefficient ($r=-0.210$, $p<0.01$) between the bone mineral density (measured by single photon absorptiometry) and serum leptin after adjustment for weight with 221 females (their age, height, weight and BMI were 52.1±8.7 years, 167.5±5.8cm, 66.4±9.2kg and 23.6 ±2.8kg/m^2 ,respectively). In that study, it was suggested that serum leptin was possible negative regulatory factor to the bone mineral density. The correlation coefficient of that study was roughly the same as the partial correlation coefficient of present study.

The previous study[29] in which the relationship of the autonomic nerve activity with bone mineral density was examined showed no significant correlation coefficient between them. But the subjects of that study were only diabetics and not healthy people. In addition, the author of that study had made a vital mistake in regards to the integral value of the frequency range 0.04-0.15Hz of the power spectrum density (Lo) when analyzing the heart rate variability by using fast Fourier transformation as the index of sympathetic nerve activity because Lo was the frequency band which contained both sympathetic nerve activity and parasympathetic nerve activity[30]. Consequently, Lo/Hi (in which Hi is the integral value of the high frequency range 0.15-0.40Hz of the power spectrum density) should be used as the index of sympathetic nerve activity[30]. Even more, that study emphasized the necessity to examine the relationship of the bone mineral density with muscle sympathetic nerve activity which is presumed to resemble the bone-controlled sympathetic nerve activity, however, muscle sympathetic nerve activity has already been reported to be correlated with cardiac sympathetic nerve activity and renal sympathetic nerve activity even from the results of animal experiments[31], so that it seems to be valid that the relationship of the bone mineral density with cardiac sympathetic nerve activity using the spectrum analysis of the heart rate variability will be examined.

Hereafter further study to examine the relationship of bone mineral density with sympathetic nerve activity using Lo/Hi or the other index containing only the component of sympathetic nerve activity with healthy subjects will be needed. In addition, it has been reported that adiponectin has a direct influence on the differentiation of the osteoblast[32] and serum homocysteine relates closely with the bone quality and bone fracture[34], so additional study to elucidate these mechanisms is needed .

The bone formation is accelerated through the activation of the osteoblast induced by the increasing blood flow into the bone marrow and accompanying increased bone metabolism turnover rate by exercise. Piezoelectric occurs to the loaded bone by the exercise and calcium ion gets fixed here (Wolff's law[34]), so that the bone mass increases. But sympathetic nerve is activated simultaneously by exercise, so the way in which the acceleration of sympathetic nerve activity associates with the phenomenon of the increased bone mass and the movement of the RANKL and CART during exercise will have to be reconfirmed.

Obese persons are thought to have the chance to increase the bone mass due to the piezoelectric effect induced by being overweight, however, they possess a high value of serum leptin which has a negative influence on their bone mass. Contrary to it, the obese persons are known to show the depressed action of their sympathetic nerve activity as the obesity-derived term MONA LIZA (Most Obesity Known are Low in Sympathetic Activity) hypothesis[35] is usually used. And a few papers[19,36] reported that there was no relationship between body fat mass and bone mass. The need to elucidate these topics in further detail is indicated.

In summary, this study suggests that sum total of the action to bone induced by serum leptin tends to result in strengthening the state of the bone resorption.

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女性における血清レプチンと踵骨骨強度指標との関連性

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要旨：本研究の目的は血清レプチンと踵骨骨強度指標（SOS,TI,OSI）の関連性を追究することである。被検者は 23～69 歳（52.8±9.4 歳）の女性 57 名であった。血清レプチンと TI の間には年齢と体重の影響を除いた有意な負の偏相関係数が認められた。血清レプチンと OSI の間にも負の偏相関係数が認められたが有意な水準はなかった。これらの結果から、血清レプチンを介した交感神経系の活性化および RANKL の産生に基づく骨吸収の促進作用と、同じく血清レプチンを介した CART による体液性の直接的な骨形成促進作用の総和は、骨吸収の促進作用により大きく傾いていることが示唆された。