

The Bone remodelling profile through bone thickness analysis after salmon calcitonin administration

by Gadis Meinar Sari

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PROSIDING

**"The Role of Physiology
to Increase the Quality of Life
Through One Health Concept:
Health Care for Human, Animals,
Plants and Environment"**

 Gadjah Mada University Press





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**International Symposium on
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25th The Indonesian Physiological Society
(IPS/IAIFI) Annual Meeting**

**"The Role of Physiology
to Increase the Quality of Life
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Health Care for Human, Animals,
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WELCOMING SPEECH

Welcome to Jogja!!! On behalf of the committee, we are welcoming all of the guest speakers and participants to Yogyakarta. Indonesian Physiology Society (IPS) or Ikatan Ahli Ilmu Faal Indonesia (IAIFI) Yogyakarta collaborate with Universitas Gadjah Mada and Universitas Muhammadiyah Yogyakarta host the International Meeting, entitled International Symposium on Global Scientific Meeting of IAIFI for 2 days at 21-22 Oktober 2016. This event is in a series of the Faculty of Veterinary Medicine's Anniversary in collaboration with IPS/IAIFI.

The concept of One Health is a global concept of health that it contains the multidisciplinary area which is, medical science, biology, environment, agriculture etc. World issues related to the concept will be discussed thoroughly in this international symposium. Physiology as the backbone and the chief knowledge of health sciences that study the health condition of the living creature has a very important role in the implementation of the one-health concept.

In this international symposium and annual meeting we invite experts from abroad and also from Indonesia. This meeting also conducts oral and poster presentation about the physiology of many researchers from various universities.

Initiate this symposium and annual meeting we conduct 3 pre-symposium events, which are The Basic short course of cell culture, a workshop on animal laboratory and workshop on sports.

Furthermore, we would like to remind about the uniqueness of the Yogyakarta which is known as the city of education, also a city of culture and tourism with various tourist destinations that are very fascinating, like Sultan's palace and the temples. Moreover various unique and distinctive culinary of Yogyakarta and various well-known souvenirs, i.e batik, will be unforgettable memories while you are in Yogyakarta. Enjoy Yogyakarta...!!!

Yogyakarta, 21st September 2016

Dr. dr. Denny Agustiningsih, M.Kes

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THE BONE REMODELLING PROFILE THROUGH BONE THICKNESS ANALYSIS AFTER SALMON CALCITONIN ADMINISTRATION

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ABSTRACT

Bone is a metabolically active organ that undergoes continuous remodelling throughout life. Remodelling process involves resorption and formation that eventually affect the bone mass and bone density. The increasing of bone density can be affected by many factors, such as calcitonin hormone which inhibit bone resorption. Recombinan calcitonin or salmon calcitonin is proposed to have influence in bone remodelling process through inhibition of bone resorption so that the bone density increased. This study was conducted to analyzed the bone thickness after salmon calcitonin treatment. This experimental study used the post test only control group design and was carried out in Faculty of Medicine, Universitas Airlangga. Twenty eight healthy male Wistar rats (*Rattus norvegicus*) were randomized to one of the following groups: control, calcitonin treatment group, exercise group and combination group. The treatment group was treated for 8 weeks, and bone thickness analysis was done afterward. The trabecular thickness of femur showed significant difference between control and calcitonin salmon treatment ($p=0.043$). This study concluded that salmon calcitonin treatment increases bone thickness through inhibition of bone resorption process.

Keywords : bone remodelling, bone thickness, salmon calcitonin

INTRODUCTION

Bone is a complex tissue consisting of cells and matrix. Bone matrix is formed by fibre and basic substance which contain mineral salt. The bone's mass and thickness always undergoes increase and reduction through remodeling process in which bone matrix is resorption and formation. Cells which play role in bone formation is osteoblast; while cell playing role in resorption process is osteoclast. Because of the formation and resorption processes, people have to maintain bone's density since in the early age. Having high density bone means having strong and healthy bone, hence bones will not easily get loss and fragile, as a result, early osteoporosis can

be avoided (Junqueira, 2007; Ganong, 2008). The number of osteoporosis sufferer in Indonesia is increasing. It can be seen the fact that the number of femur fracture incidents increases significantly because of osteoporosis, from 20.000 in 2007 to 43.000 in 2010 (Depkes, 2010).

Some hormones influence bone tissue are calcitonin, parathyroid, growth hormone, androgen, and estrogen. Calcitonin is polypeptide which has the role to reduce plasma calcium. During its development, the synthesis or the recombination from different species is developed from salmon's calcitonin which is used for medical purposes. So far, salmon's calcitonin which is often used in clinical practice due to the fact that it has intrinsic potential 40-50 times higher than human's calcitonin as well as it has better analgesic properties. Calcitonin in human beings is used to cure post-menopause diseases, osteoporosis, paget disease of bone, and hypercalcemia (Novartis, 2009). The role of Salmon's calcitonin in the normal bone physiology of human has not been clearly understood.

One of the efforts to increase bone's thickness and density is through physical exercises. Previous research have proven that regular physical exercises which is done in a certain dosage result an increase in the bone's density, bone's size, and bone's shape (Ide, 2012). Physical exercise is one of physical stressors which can affect the composition of bone. Physical exercise is repeated physical activity and aims to maintain, improve, and express fitness (Bompa, 1994). Nevertheless, the impact of submaximum intensity physical exercise on bone density is still unclear.

This research is aimed to investigate the potential of salmon's calcitonin to increase bone density by doing an examination on bone thickness through remodeling process. The result is expected to be an alternative way to prevent early osteoporosis in order to reduce the number of osteoporosis cases in Indonesia.

MATERIAL AND METHODS

Subject. This research is experimental research by the Posttest-only control group design. The sample were male white rats (*rattus norvegicus*) in their growing period with the weight between 160 and 180 gram, at the age of 6 to 8 weeks, in healthy condition, which were taken from the unit of animal experiment development, biochemical laboratory, medical faculty of Universitas Airlangga. The sampling technique used in this research

was simple random sampling. The number of rats used was 28 which were divided randomly into 4 groups. Thus, each group consisted of 7 rats. The four groups were group 1 as control group, group 2 as the group which is given salmon's calcitonin, group 3 as the group which experienced submaximum intensity physical exercise, and group 4 as the group which was given salmon's calcitonin and experienced submaximum intensity physical exercise.

Procedure. After a week of acclimatization period, every group was given appropriate equal treatment for 8 weeks. Then, the samples were sacrificed and their femur bone was taken to be demineralized and to be used as histological preparations with hematoxylin-eosin painting. The examination of bone thickness is measured by using Image Raster 3 software with micrometer unit (μm).

RESULT AND DISCUSSION

The result of this research is the measurement data obtained from the research which covers the data of all variables, i.e. independent and dependent variables. The data obtained was the thickness of femur bone (μm), which was tested with the significance level of 5%.

The data which met the normality requirements were then analyzed by using difference test, i.e. anova test. This test has a purpose of seeing the effect of the treatment among groups on dependent variables. The result of anova test shows that the value is $p > 0.05$. The value of $p = 0.04$ means that there is significant difference on the means among the groups which is shown in following table 1.

Table 1. Comparison of bone thickness between groups

Group	Mean	SD	p
Control	187137.1	29322.06	0.04
Calcitonin	238045.7	41970.59	
Physical exercise	196624.8	31156.29	
Calcitonin+exercise	205728.7	23584.11	

Post-anova test is carried out if $p < 0.05$. If it happens, homogeneity requirements among the members of the four groups must also be fulfilled ($p > 0.05$), which is done through Barlet test. This test can be carried out

whenever the four groups have the same variant. Homogeneity test is done by using Barlet test. The result is $p=0.58$ which means that the four groups have similar variant. Therefore, post Anova Bonferroni test can be conducted.

The result of post-anova test indicates that the groups which show significant difference are between group K1 (control) and K2 (calcitonin) with $p=0.043$, as seen in table 2 below:

Tabel 2. The result of post-Anova Bonferroni Test

	K1	K2	K3
K2	0,043	-	-
K3	1,000	0,182	-
K4	1,000	0,441	1,000

The bone thickness of the groups is depicted in the following diagram (figure 1)

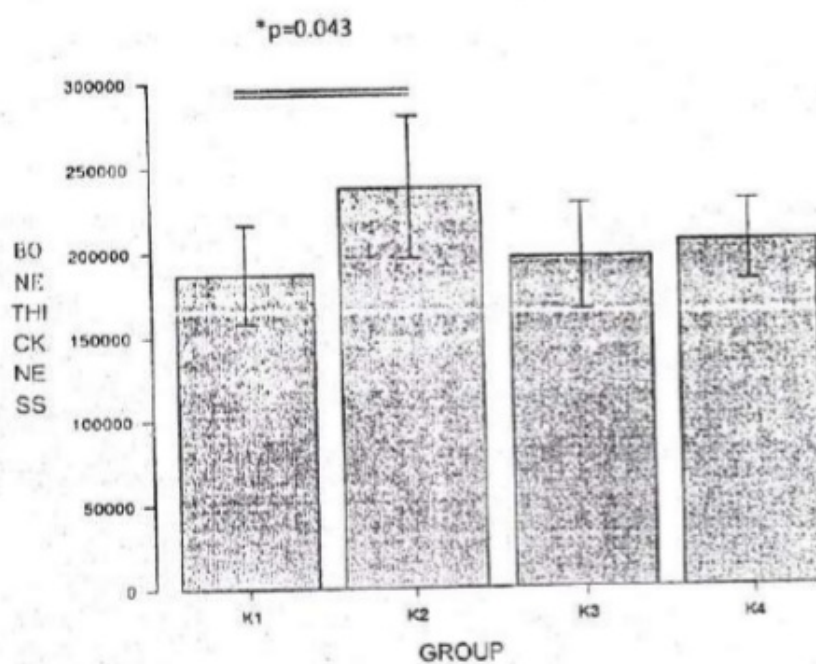


Figure 1. Trabecular bone thickness among the groups

Result of the measurement of trabecular bone thickness of control group through histological examination, with 40 times dilation, can be seen in figure 2.

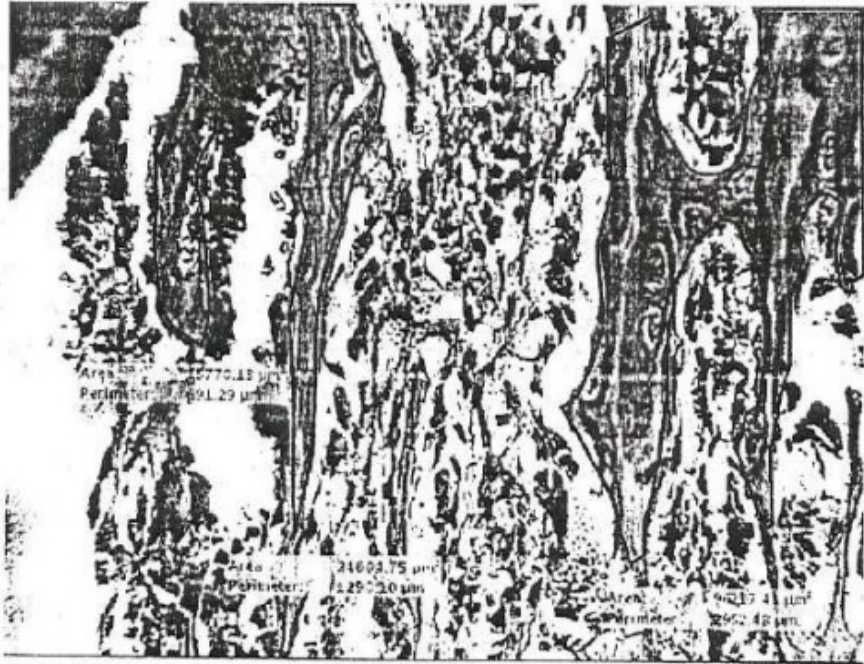


Figure 2. Bone thickness of control group (40x).

The following figure depicts the result of the measurement of trabecular bone thickness of calcitonin group through histological examination, with 40 times dilation

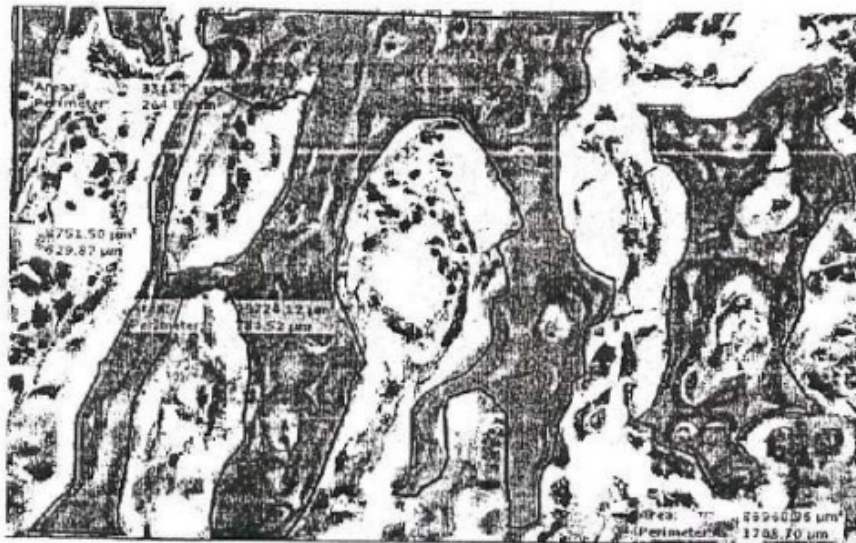


Figure 3. Trabecular bone thickness of calcitonin group (40x)

Figure 4 shows the result of the measurement of trabecular bone thickness of sub-maximum physical exercise group through histological examination. From the figure, it can be seen that the trabecular bone of sub-

maximum physical exercise group is thicker than the one of control group, yet it is not thicker than the one of calcitonin group and of combination of calcitonin and sub-maximum physical exercise group.

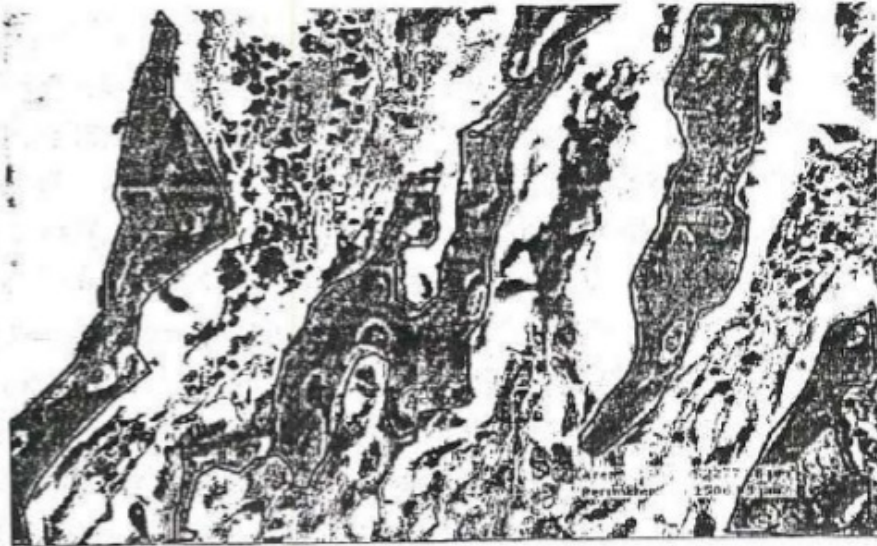


Figure 4. Bone thickness of submaximum physical exercise group (40x).

The following figure is the result of the measurement of trabecular bone thickness of combination of calcitonin and sub-maximum physical exercise group through histological examination, with 40 times dilation. The figure shows that the trabecular bone of combination of calcitonin and sub-maximum physical exercise group indicates having more thickness than the one of control group, but it is not thicker than of calcitonin group (figure 5)



Figure 5. Bone thickness of combination group (40x).

This research is laboratory experimental research by *The Posttest-Only Control Group*. The sample was collected from rats in the growing period at the age of 6 to 8 weeks, which is the early period of rats' puberty (Kusumawati, 2004). Using rats in the growing period as samples was based on the consideration that according to Mackovic (1994), 90% of the bone mass is formed at the age of 12 to 14 years; that is during pre-puberty and puberty periods (Yuliati, 2002). The maximum bone mass is achieved when someone is around the age of 30 years. After that, bone mass is reduced because remodeling process imbalance begins to happen (Ide, 2012).

The treatment given to experiment animal in this research was by giving salmon calcitonin and by giving submaximum intensity physical exercise. Salmon calcitonin was obtained from miacalcic preparat. The contents in its each millilitre are salmon calcitonin 100 IU, acetic acid 2.25mg, phenol 5 mg, sodium chloride 7.5 mg, and water for injection (Novartis, 2009). Calcitonin contains 32-amino acid peptide as well as N-corner ring structure which is composed of six amino acid joined to each other through disulfide bridge and one amide group, proline amide, on C-corner. Like parathyroid hormone, calcitonin works through cAMP mechanism. Both corners of the molecules contain species which is invariant residue needed for tying G-protein. G-protein is the receptor in osteoclast. Ligand specificity of calcitonin's isoform receptor causes the receptor to modify protein (RAMPs) forming heterodimer which has the role in preventing cell recycle (Zaidi *et al*, 2002).

Submaximum intensity physical exercise was swimming with the intensity of 85% of the maximum swimming ability of the experiment animal (Kragel *et al*, 2006). Submaximum intensity is the intensity whose burden level is between medium and high. Submaximum intensity physical exercise is a physical exercise which is close to high intensity. This exercise resulted a change on cardiovascular system like the increase of stroke volume, the heart rate reduction, and a slight reduction in cardiac output (Fox, 1993). However, the effect of submaximum intensity physical exercise on bone thickness remains unclear.

The measurement of bone thickness was conducted after 8-week treatment. It is in line with the time needed by osteoclast to fill the resorption cavity (Raisz, 1988 *cit* Sunoto, 2001). Trabecular bone thickness measurement was carried out by using software *Image Raster 3*, with 2-dimension bone thickness image in micrometer unit (μm).

The measurement was conducted in femur metaphysic bone due to the fact that it provides sufficient clue about mineralization and the condition of the structure of bone tissue (Dalen, 1993). Through macroscopic observation, it appears that bone consists of cortical bone (compact) and trabecular (spongiosa). Trabecular and cortical bone exist in every bone, yet with very different number and distribution. Trabecular bone often undergoes mineral changes because of its wider surface shape. In long bones, the metaphysic area has more trabecular bone tissues than cortical bone (Borer, 2005). Bone remodeling begins with lining cell activity and bone mineral removal by protein enzyme (proteolytic) that coat bone surface. Bone resorption begins with multinucleated osteoclast adhering to trabecular bone surface or to Haversian interior unit. Osteoclast membrane is equipped with proton pump that produces acid dissolving bone mineral. Afterward, osteoclast resorps bone mineral and matrix through acid and proteolytic enzyme release. After the resorption occurs, the resorpted cavity will be occupied by lining cell and osteoblast that form new bone through hydroxyapatite deposition (Borer, 2005).

Salmon calcitonin is single chain polypeptide hormone containing 32 amino acids which are used in long term therapy for metabolic diseases characterized by high bone turnover, such as osteoporosis. Salmon calcitonin inhibits or slows down bone resorption process mediated by osteoclast (Bhandari, 2012). Research on work mechanism of calcitonin in bone show that calcitonin binding to receptor causes morphological change in osteoclast which results bone resorption inhibition. Calcitonin combats osteoclast motility causing immobility through cAMP-dependent mechanism. Moreover, calcitonin induces the change of intracellular calcium causing osteoclast retraction. The result of *in vitro* and *in vivo* experiments proves that calcitonin inhibits osteoclastogenesis. Consequently, the bone resorption is inhibited as well. In addition, it does not influence osteoblast proliferation significantly (Naot *et al*, 2008). It is in line with the result of the research which shows that calcitonin administration will increase bone thickness.

Calcitonin receptor is surface protein-G receptor expressed more in osteoclast, kidney, and nerve cells which bind calcitonin with high affinity. Calcitonin endogen is mainly secreted by C cell of the tyroid to face the changes of serum calcium level. The main role of calcitonin in calcium

homeostatic is to inhibit bone resorption to reduce tubular reabsorption and to regulate the production of 1.25-dihydroxy vitamin D3 in the kidneys (Sexton PM, 1999; Shinki T, 1999; Turner AG, 2011)

Even though calcitonin has been used as bone disease therapy, its long term use is often limited by the development of antibody and inhibition function of calcitonin in reducing osteoclast which is proven in vitro and in vivo, depending on the dosage and time. There have been many research conducted by using pharmacological calcitonin dosage which is originated from salmon and other low vertebrata. The physiological role of endogen calcitonin through receptor calcitonin still becomes controversy and remains unclear (Ikegame, 2004; Turner AG, 2011).

This research shows that salmon calcitonin administration increases trabecular bone thickness. The other two groups show an increase in bone thickness as well, even though it is not as much as the one of the group of calcitonin administration.

Neuropeptide like *vasoactive intestinal peptide* (VIP) dan *Calcitonin gene-related peptide* (CGRP) exists in nerve fiber of bone tissue and regulates bone remodeling. *Oscillatory fluid flow* (OFF)-*induced shear stress* is an important signal on mechanotransduction that regulates anabolic and catabolic bone remodeling. However, the interaction between neuropeptide and mechanic induction in bone remodeling process has not been clearly understood (Kim CH, 2006). A research conducted by Yoo (2014) recognized the effect of the combination of neuropeptide and mechanic stimuli on the expression of protein related with bone resorption. It counted the neuropeptide protein content and/or *shear stress* which was influenced by OFF applied in pre-osteoblast MC3T3-E1 cell and the change on receptor activator of nuclear factor kappa B (NF- κ B) ligand (RANKL) and mRNA osteoprotegerin (OPG). Neuropeptide and sheer stress influenced by OFF also reduced RANKL and increased OPG content compared to control. There was no further change on the combination of neuropeptide and sheer stress influenced by OFF. The result shows that neuropeptide CGRP and VIP play important role pressing the bone resorption activity through RANKL/OPG track, similar to mechanical loading (Yoo YM, 2014)

According to Nielsen RH, 2011, salmon calcitonin administration is against osteoarthritis pathology in cartilage and bone and might give curative

effect on clinical experiment. It is in line with the result of this research that salmon calcitonin administration also increase trabecular bone thickness.

Calcitonin causes a meaningful inhibition in bone resorption process. A long term administration decreases the rate of bone resorption process. It is hystologically related with a decrease in the number of osteoclast and significantly followed by the decrease of osteocytic resorption. Some cases indicate that in the beginning of bone formation, it is influenced by calcitonin through the increase of osteoblast activity. Calcitonin may not influence bone formation in long term (Novartis, 2009). Hence, in this research, it proves why combination group did not show an increase in bone thickness more than calcitonin administration group.

CONCLUSION

The result of this research, shows that salmon calcitonin administration can increase trabecular bone thickness through a bone remodeling process which becomes the basis of bone metabolism process. The increase of bone thickness of the salmon calcitonin administration group is higher than the one of submaximum physical exercise group as well as the one of calcitonin group and submaximum physical exercise combination group.

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GRADEMARK REPORT

FINAL GRADE

GENERAL COMMENTS

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