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Comparison Between Physical Exercise and Alendronate Against Bone Calcium Levels and Body Weight In Wistar Rats Model Glucocorticoid-Induce Osteoporosis

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ABSTRACT

Glucocorticoid-induce osteoporosis (GIO) is a bone condition with osteoporosis due to taking long-term glucocorticoid drugs which is the most common cause of increasing the number of fracture cases which is a health problem. GIO is one of the most common forms of osteoporosis in men. Sodium alendronate is a biphosponate drug that is approved for prevention and management of GIO but has serious side effects on long-term use. Doing physical exercise "weight-bearing exercise" such as running is known to increase BMD (Bone Mineral Density) and can reduce osteoponia and the risk of osteoporosis. This study was a study with experimental studies, using male Wistar rats aged 8 weeks divided randomly into 4 groups, namely 1) positive control group (given oral prednisolone 0.54 mg/200g/day), 2) negative control group (not given oral prednisolone), 3) physical exercise group and 4) oral administration group of sodium alendronate (0.09 mg / 200g / day). Bone density will be measured by measuring the calcium level of the tibia bone using the AAS (Atomic Absorptions Spectrophotometer) method and the body weight of mice using scales. The results showed that physical exercise and sodium alendronate significantly affected p = 0.029 with (p <0.05) increasing calcium levels in rats induced by glucocorticoids and obtained p = 0.064 with (p <0.05) in this study there was no difference significant body weight difference between research groups

Keywords : Bisphosphonate; Bone Mineral Density; Glucocorticoid; Treadmill.

INTRODUCTION

Glucocorticoids have an immunosuppressive effect that is useful for use as a drug to cure various inflammatory conditition (Sherwood L., 2011). The use of glucocorticoid pharmacological therapy is very broad, especially in the fields of rheumatology, respirology, neurology, hematology, dermatology, gastroenterology, and transplantation (Permadi A, 2007). Generally the use of

glucocorticoid therapy is used in the long run and its use above physiological doses will have a number of side effects of the drug. The most common and potentially serious side effect is the onset of osteopenia which can then lead to secondary osteoporosis (Adachi J D, 2005; Permana Hikmat, 2013). From some causes of secondary osteoporosis, long-term use of glucocorticoid therapy is the most common cause and increases the number of fracture cases which is a health problem. Osteoporosis not only causes pain in the form of fractures but can increase the limitations of quality of life

Glucocorticoids have an effect on bone cells that cause changes in the number of bone cells and function for bone loss. Glucocorticoids besides increasing the number and lifetime of osteoclasts, glucocorticoids affect osteocytes that are responsible for sensing physical stimuli and also for osteoblasts that play a role in the matrix and its calcification process (Adachi J D, 2005) 7 In a study conducted by Kanis et al (in Adachi, Papaioannou, 2005), showed glucocorticoid exposure resulting in an increased risk of fracture characterized by changes in bone mineral density (BMD) and decreased osteoblast activity.

Several studies have shown that many patients with glucocorticoid therapy do not receive prevention efforts for secondary osteoporosis from long-term use of glucocorticoids due to lack of information about the benefits and importance of prevention in treatment strategies (Permana Hikmat, 2013). Recommended GIO (glucocorticoid-induced osteoporosis) therapy is lifestyle modification, weight training and therapy with antiresorptive agents (Davis S, et. al., 2010; Lloyd T, et. al., 2004)

Of the various types of antiresorptive agents FDA approved one of them is a class of bisphosphonates such as sodium alendronate as a therapy for the choice of first-line drugs approved for the prevention and management of GIO (Davis S, et. al, 2010; Merck S & Dohme, 2012; Marques CMG, et. al., 2001). In a 3-year study of postmenopausal women with osteoporosis, the risk of a vertebral fracture decreased by 70%, and the risk of hip fracture by 41% with bisphosphonate use.

Problems occur when the cost of treatment using bisphosphonates is relatively expensive so that it becomes one of the factors of disobedience patients in long-term therapy. Nearly 50% of patients with osteoporosis are disobedient in taking bisphosphonate as an adjunctive therapy (Swenson K K, et. al., 2009). There are also serious side effects such as esophageal malignancy, low blood calcium levels (hypocalcemia), pain in bones, joints, muscles and osteonecrosis of the jaw (Nurhadi FM., 2012).

One strategy to prevent osteoporosis is to increase bone mass by doing physical exercise. Ertem, Karakoc, Duzova, Kekilli, Emre, and Kilinc showed that exercise performed by male Wistar rats by performing moderate intensity treadmills every 5 days a week for 30 minutes would increase BMD in rats during 13 weeks of exercise. done in humans by Rizzoli et al, most physical exercise

with types of exercise with the impact such as jumping, running and gymnastics have a significant effect on increasing bone mass so that it is expected to improve bone mass and bone formation for bone health in the long run (Bonnet N , Ferrari L., 2010)

METHODS

Subjects: Male Wistar rats were divided randomly into 4 groups, namely 1) positive control group / KP (given oral prednisolone 0.54 mg / 200g / day), 2) negative control group / KN (not given oral prednisolone), 3) exercise group physical / T and 4) oral administration group of sodium alendronate / NA (0.09 mg / 200g / day). The number of samples in each group was determined using Mead's Formula, each of which was 4 animals per group.

Exercise procedure: In the first week to the end of the 5th week, all groups of research rats were given oral prednisolone therapy to make the condition of osteopenia rats except in the KN group. Then at 6 weeks until the end of the 13th week, continued oral administration of prednisolone accompanied by treadmill physical exercise treatment in rats in group T and in the NA group given oral sodium alendronate (0.09 mg / 200 gBB/day). Physical exercise given to group T is carried out with a frequency of 5 times a week (Monday-Tuesday-Wednesday-Thursday-Friday) with a duration of exercise for 30 minutes/day. Previously at the beginning of the 5th week, group T was adapted first using a treadmill with a speed of 10 cm/second for 30 minutes to get to know the condition of the treadmill for 1 week. Entering the end of the 13th week, all groups of rats were decapitated using ether and isolation tibia bone. Bone density will be measured by measuring the value of bone calcium levels. Examination of calcium levels was carried out using the Atomic Absorptions Spectrophotometer (AAS).

Data analysis: The data obtained were statistically analyzed using descriptive test, normality distribution test, initial data homogeneity test on weight variables, ANOVA test to prove group differences and Mann-Whitney test to distinguish between treatment groups.

RESULTS AND DISCUSSION

Subjective characteristics assessed were the difference in body weight from initial body weight when starting the study and body weight at the end of the study. The results of the mean difference in body weight of Wistar rats in each group can be seen in Figure 3.1

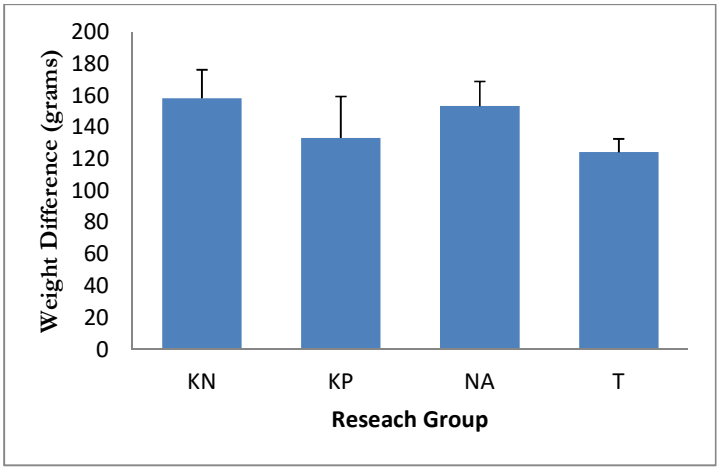

Figure 3.1 Average graph of body group weight gain. The treadmill physical exercise group had the lowest weight difference compared to the other study groups but found p = 0.064 there was no significant difference in body weight difference between the study groups. Negative group (KN), positive group (KP), sodium alendronate (NA) and physical exercise group (T). Data in mean values, error bars indicate standard intersections.

Description: * p <0.05

Based on the results of the ANOVA statistical test, it was obtained p = 0.064 with (p> 0.05). Thus it can be concluded that there is no significant difference in body weight difference between the study groups.

Effect of Physical Exercise and Sodium Alendronate on Calcium Levels

The average results of the tibia bone calcium level were obtained from the measurement results with the AAS method, each group can be seen in Figure 3.2

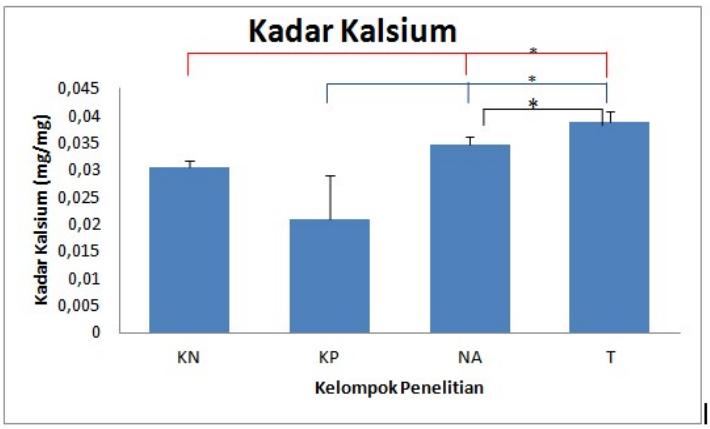

Figure 3.2 Graph of average calcium levels in each research group. The T group had the highest calcium levels compared to other research groups where the T group and NA group had significant differences in calcium levels (p = 0.029). Data in mean values, error bars indicate standard intersections.

Description: * p <0.05

Based on the results of the Mann-Whitney statistical test, the KN and NA groups were obtained p = 0.029, KN groups and T groups p = 0.029, KP groups and NA groups p = 0.029, KP groups and groups T p = 0.029, NA groups and T groups p = 0.029 with (p <0.05). Thus it can be concluded that all research groups have significant differences in calcium levels.

Based on the results of the ANOVA statistical test to determine whether there are differences in weight difference when compared to each study group, it was obtained p = 0.064 with (p <0.05) which means it can be concluded that in this study there was no significant difference in body weight difference between groups research. However, there are differences in weight differences in each study group. The lowest mean weight difference was in the treadmill physical exercise group (124.25 mg), and the group with the highest average weight difference was in the negative control group (158.25 grams).

Marques, Lawford, Cochrane (Marques CMG, 2001) showed that the group of male Wistar rats with treadmill physical exercise significantly decreased weight compared to the control group who did not do physical exercise. This occurs because the effects of physical exercise cause weight loss because there has been an increase in energy consumption used. According to Lynne B in Nurhadi,[11] that doing aerobic physical exercise done at low intensity to moderate intensity for 30 minutes would burn about 250 calories in the human body. The energy source used is to use carbohydrates and fats in a balanced manner. Aerobic exercise at moderate intensity will reduce body fat more optimally because aerobic exercise can increase fat oxidation.

In the KP group, weight loss also occurred when compared to the KN group. This study is in line with the research conducted by Fang, DuBois, He, Almon, Jusko in normal male Wistar rats

given an infusion of methylprednisolone for 1 month showed a significant effect on decreasing food consumption and weight loss It is known that glucocorticoids can cause changes in glucose plasma, insulin and FFA concentration. Reducing food intake in animals at glucocorticoid administration (De Vos P. et. al., 1995) was associated with induction of leptin expression and reduced production of neuropeptide Y (NPY), which is a stimulator of food intake. In the same study conducted by Fang J et al. (Fang j, et. al., 2011) in the gastrocnemius muscle in Wistar rats compared with the control group there was a significant reduction in gastrocnemius muscle weight and body weight observed in all dose groups given methylprednisolon. This indicates that the catabolic effect of corticosteroids and muscle wasting is one of the main side effects of chronic steroid therapy and a decrease in muscle weight can be a major cause of weight loss.

In this study, the tibia bone was chosen as a parameter of bone density because weight-bearing in the tibia bone had a higher sensitivity to treadmill training than the lumbar bone in mice. , iron (Fe), Copper (Cu), and Zinc (Zn) (Iwamoto J, et. al., 1999) Osteopenia is a condition where bone density (density) is said to be less than normal bone and will show a decrease in BMD accompanied by a decrease in bone calcium mineral levels.

Based on the results of the Mann-Whitney statistical test with (sig.p <0.05), it can be concluded that all groups in this study had significant differences in bone calcium levels. Figure 3.2 shows that the average calcium level of Wistar rats for 13 weeks of treatment showed that the calcium level in the KP control (0.0209 mg/mg) had a lower average number than the KN group and other research groups. While the calcium level in group T (0.0387 mg/mg) was higher than the calcium level in the NA group and in other research groups

Calcium levels in the KP group that have received glucocorticoid prednisolone induction in the long term will have a very low amount of calcium. This is known because glucocorticoid therapy in addition to causing secondary hyperparathyroidism, will also have an effect on the decreased absorption of calcium in the intestine because glucocorticoids inhibit calcium transport through the intestinal barrier and increase calcium excretion in the tubular kidneys. Whereas group T who have done treadmill physical exercise can increase bone calcium levels. This is in line with research conducted by Shiga K, using Sprague-Dawley male rat. The results show that physical exercise not only increases tibia bone calcium levels but can also increase calcium absorption compared to mice that do not do physical exercise (Shiga K, et. al., 2003). Physical exercise with moderate intensity is known to stimulate osteocytes and osteoblasts so it will have a positive impact on bone and also against calcium metabolism. Physical exercise can increase the concentration of calcium ions in the plasma, so that the bone does not need to release calcium ions from the bone so that the concentration of calcium ions in the bone can be maintained and bone mass is maintained. In contrast to the research conducted by Ip, Peterson, Byrner, Tou, in his research to find out the effect on intensity exercise using treadmills in mice reported not showing

significant results in differences in bone calcium levels in mice given physical exercise with treadmill compared to mice that not doing physical exercise.

In the administration of sodium alendronate when compared with treadmill physical exercise, the mean tibia bone calcium levels were higher in the T group than in the NA group. This is possible in this study can be caused by absorption factors in sodium alendronate by oral is not as good as through the intravenous pathway so that the potential effect of anti-resorption potential is less than optimal for osteoclasts and osteoblasts.

CONCLUSION

Physical exercise with impact and oral sodium alendronate exercise has an effect on increasing calcium levels. Calcium levels at physical exercise were higher than those of oral alendronate sodium in glucocorticoid-induced osteoponia. The mean difference in body weight in the physical exercise group compared to other treatment groups was lower.

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