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Original Research

Bone adaptation process on post-menopausal women after Speed Play Walking Exercise with medium & high increased cadence

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Abstract

Background: Postmenopausal period is usually marked by dominancy of osteoclast activity, which leads to a decrease in bone mass. Speed Play Walking Exercise (SPWE) could be an important mechanical strategy for maintaining bone cell activity in postmenopausal women.
Aim(s): This study evaluated the rate of increased cadence in SPWE, which can reduce bone resorption and increase bone formation activities, associated with body mass index.
Material and methods: This was four group pre-post intervention design randomized clinical trial, included 32 postmenopausal women in normal-weight (NW) vs. overweight (OW) groups, divided into 2 groups of different walking speeds. The intervention is SPWE method with increased 15-35% or 50-80% from initial cadence as intervention target cadence, alternated with usual cadence, 3 times a week, for 4 weeks duration. Variables are baseline CTx and NMid osteocalcin serum taken on pre and post 4 weeks exercise.
Result: sNMid osteocalcin was increased in groups walked with 15-35% increased cadence compared to group walked with 50-80% increased cadence ($p=0.002$ for NW group and $p=0.042$ for OW group, respectively). NW group walked with 50-80% increased cadence showed the most decreased bone formation marker ($p=0.019$). CTx/NMid ratio is reduced in NW group walked with 15-35% increased cadence, on the other hand, OW group walked with 50-80% increased cadence showed the most increased trend of CTx/NMid ratio.
Conclusions: To maintain bone formation activity, SPWE with a rate of 15-35% increased from initial cadence is suggested for postmenopausal women; however, the benefit is more visible in women with normal-weight.

Keywords: *CTx, NMid osteocalcin, Postmenopausal women, Play Speed Walking Exercise, Weight.*

INTRODUCTION

Following estrogen cessation in the rat and human, there is an increase in the rate of both apoptosis and remodeling, results in increased skeletal fragility. The first five years postmenopausal period also become a bone window period, that show the rapid bone loss, dominancy of osteoclast activity and can lead to reduce bone mass at the end of this period. A logical therapeutic approach to restoring bone mass following the menopause would therefore be to enhance the adaptive process.[1] A systematic review and metanalysis from some studies have shown exercise therapy was an important management strategy for maintaining bone mineral density (BMD), with preference to high intensity resistance and impact training for maintaining lumbar spine BMD.[2] BMD evaluation needs a longer time to give a valid measurement. Serum bone turnover biomarkers have been developed to estimate the status of bone formation (N-Mid osteocalcin) and bone resorption (CTx), which are more stable. non-invasive, cost-effective and could evaluate the change of bone adaptation state earlier.[3] They are good bone biomarkers for detecting the changes after exercise earlier.

Walking is the ambulation process which includes stance phase (heel strike, foot flat, toe off and push off) and swing phase (acceleration, mid-swing and deceleration), which has mechanical implication to the musculoskeletal system. It is an affordable and attainable form of weight-bearing exercise that has a low risk of injury, so that it may be a safe exercise for postmenopausal women.[4] The principal of axial loading results in changes at the cellular level according to strain principals on the bone adaptation process. Walking also affects the body composition, cardiovascular fitness, flexibility, muscular endurance and muscular strength. According to Yue, longer duration of daily outdoor walking is correlated with a reduced risk of osteoporosis, but is also affected by osteoporotic genetic risk score.[5] The primary mechanical function of bones is to provide rigid levers for muscles to pull against, and to remain as light as possible to allow efficient locomotion.[6] Bone adapts to altered mechanical stimuli. Exercise, generally, helps to maintain bone mass and counter osteoporosis, but highly strenuous exercise can also have detrimental effects on bone. Mechanical stimuli have potent influences on skeletal health and function.[7] Three rules that govern bone adaptation are dynamic strain stimulus, case of diminishing returns and bone cells accommodating to routine loading.[6] Functional adaptation refers to adaptation controlled principally through mechanics, typically coordinated by the osteocyte via a biological set point theory termed the mechanostat. Adaptation is separated into modeling (motion of the periosteal and endosteal surfaces through surface drifts) and remodeling (changes in cortical and trabecular bone through coordinated cell action).[8] It is well-established that cyclic, but not static, mechanical loading has anabolic effects on bone. The relationship between the loading frequency and the amount of bone adaptation suggests that trabecular bone adaptation is regulated by mechanical signals in the local in vivo environment and furthermore, that mechano-regulation is logarithmically dependent on loading frequency with frequencies below a certain threshold having catabolic effects, and those above anabolic effects.[9]

This research is directed to answer the question whether increased rate of cadence can affect the bone resorption (reflected by serum CTx) and formation (reflected by serum NMid osteocalcin) activities on the postmenopausal women. We hypothesized that the rate of increased cadence in walking exercise can reduce bone resorption and increase bone formation activities, associated by body mass index. We compare these bone activities between groups with increased rate of cadence 15-35% vs 50-80% from the initial cadence, on Normal vs Overweight BMI groups.

MATERIAL AND METHODS

This study was four groups pre-post intervention design randomized clinical trial, consisted of two groups of body mass index (Normal vs Overweight BMI), divided in two groups of different percentage of increased cadence (15-35% and 50-80% increased cadence). Cadence is a number of steps per minute. Outcome measurements were biochemical bone marker (serum N-Mid osteocalcin (N-Mid) for detecting bone turnover activity as bone formation marker and serum C-telopeptide (β-CrossLaps/CTx) for detecting osteoclast activity as bone resorption marker). Confounding variables are age, menopause period and physical activity. **Figure 1** below shows an overview of the research protocol.

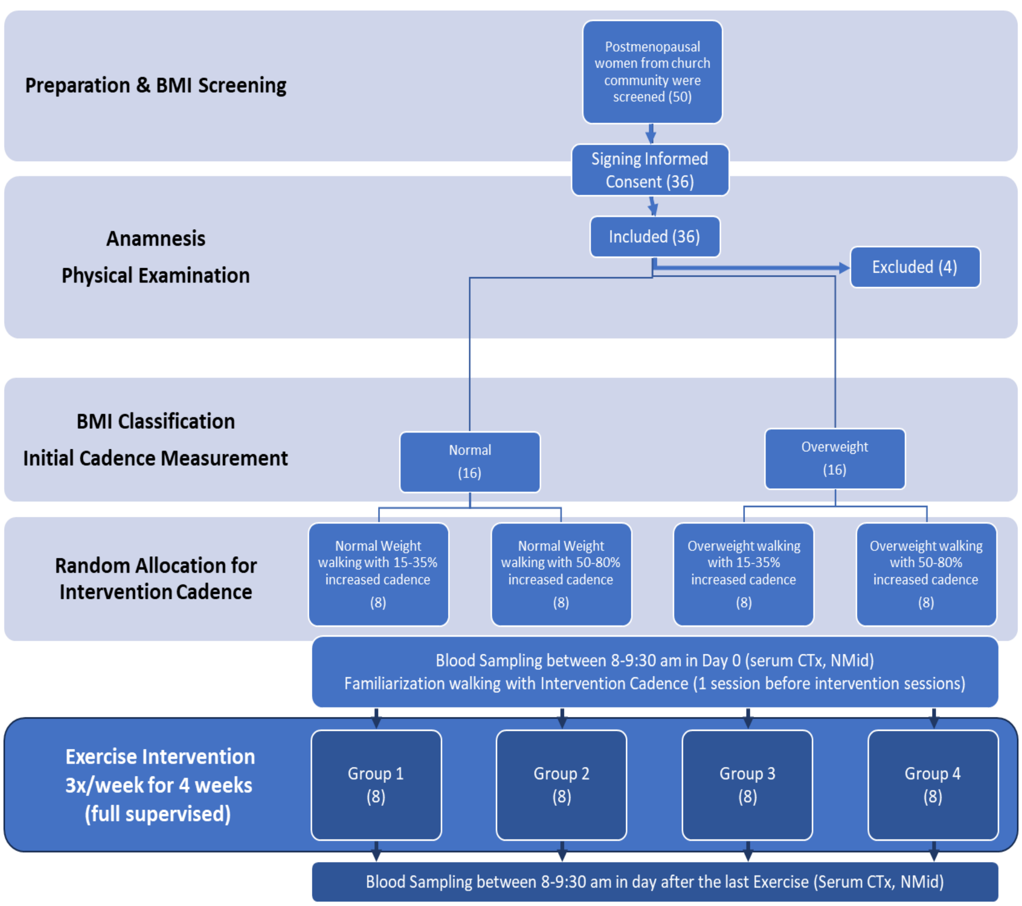

Figure 1. Research Protocols

Preparation

On preparation and BMI screening phase, 50 candidates were invited to get the information about the research. There were 36 postmenopausal women between 45-65 years old of age who signed informed consent form and were included to undergo anamnesis, physical examination (including electrocardiography measurement), and fill the International Physical Activity Questionnaire (IPAQ). The exclusion criteria were using long-term steroid, magnesium and diuretic, suffering from severe knee osteoarthritis, cardiac problems or abnormal ECG, and chronic disease with the ambulation complication. Four women were excluded because of having abnormal ECG (1 woman), long-term use medication (2 women) and knee osteoarthritis (1 woman). Thirty-two postmenopausal women subjects were included and consisted of 16 normal weight (BMI) and 16 overweight (BMI). After that, subjects in each group were randomized allocated to intervention cadence groups (increased 15-35% or 50-80% from initial cadence). The next day, after one night fasting, they underwent blood sampling around 8-9:30 am (for serum CTx and N-Mid level) and initial cadence measurement.

Exercise Intervention

Every subject received the information about the exercise program. Speed Play Walking Exercise (SPWE) method was used in this research with composition of intervention cadence (increased 15-35% or 50-80% from initial cadence) in four minutes followed by initial cadence in eight minutes, repeated two times, with warming up before (3-4 minutes) and cooling down after exercise (3-4 minutes). It was assumed that in the range 15-35% a human can walk in the medium cadence, and in the range 50-80% in the fast cadence. Frequency of exercise was three times a week for four weeks. The pulse was monitored before and after exercise, to monitor the cardiorespiratory response to exercise. Blood samplings after exercise was done in the morning on the day

after the last exercise session. Data analysis used the descriptive statistic and homogeneity tests for all variables, Paired T-test and ANOVA to analyze the changes in the bone cellular activity.

RESULT

This study enrolled 32 postmenopausal women, with mean of age 57.0 ± 4.83 (45-65) years old, menopause on 50.3 ± 3.76 (40-56) years old, menopause period 6.6 ± 4.14 (1-17) years, body height 1.52 ± 0.05 (1.41-1.63) m, body weight 58.3 ± 9.15 (41-80) kgs, body mass index (BMI) 25.14 ± 2.99 (18.7-30.0) kg/m2, baseline cadence 93.31 ± 12.59 (67-120) steps/minute, step length 46.58 ± 5.96 (34-60) cm, leg length 83.39 ± 4.61 (76-94) cm, IPAQ 4.84 ± 1.40 (3.6-7.0) METs.

Table 1. Characteristic of Four Groups of Postmenopausal Women

	Group 1 (Normal BMI, walked with 15-35% Increased cadence)	Group 2 (Normal BMI, walked with 50-80% Increased cadence)	Group 3 (Overweight BMI, walked with 15-35% Increased cadence)	Group 4 (Overweight BMI, walked with 50-80% Increased cadence)	*P*
N	8	8	8	8	
Age (years)	57.9 ± 2.99	54.3 ± 5.63	56.6 ± 6.14	59.3 ± 3.06	0.124
BMI (kg/m2)	22.4 ± 2.18	22.9 ± 1.50	27.8 ± 1.39	27.5 ± 1.49	0.306
Baseline Cadence (step/minute)	99.1 ± 6.81	88.6 ± 9.88	101.6 ± 11.64	93.9 ± 13.33	0.085
Step length (cm)	48.5 ± 3.63	45.9 ± 5.94	48.4 ± 7.76	43.0 ± 4.87	0.169
Leg length (cm)	84.0 ± 5.40	81.4 ± 3.58	85.3 ± 5.70	82.3 ± 3.20	0.233
Pre Exercise CTx (ng/ml)	0.40 ± 0.23	0.54 ± 0.30	0.45 ± 0.27	0.50 ± 0.29	0.740
Pre Exercise N-Mid (ng/ml)	23.10 ± 8.75	41.68 ± 13.63	30.41 ± 12.11	31.15 ± 12.90	0.433
Pre Exercise CTx/N-Mid Ratio	0.017 ± 0.005	0.013 ± 0.005	0.015 ± 0.005	0.015 ± 0.005	0.200

*significant on $p<0.05$ (Kolmogorov Smirnov)

Table 1. shows all basic characteristics of these four groups, and they were homogeneous. The homogeneity test for the four groups shows that the basic characteristic, anthropometric, gait parameter and serum CTx, N-Mid levels and CTx/N-Mid ratio were homogenous within groups.

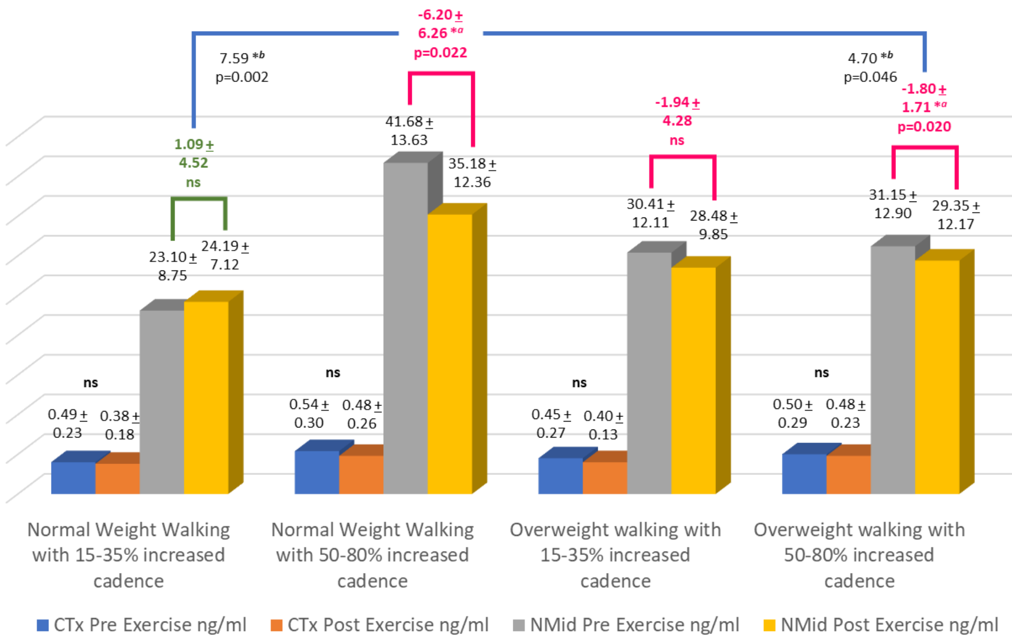

Figure 2. Comparison of Pre-Post Exercise Biochemical Bone Markers Between Groups.
Note : [a]Paired T-test, [b]ANOVA, *significant *(p<0.05)*, red font & line: decrease, green font & line: increase, blue line significant comparison in multiple comparison

Normal and Overweight BMI, walked with 50-80% increased cadence (Group 2 and 4) showed significant decrease on serum N-Mid, with mean difference were -6.20 ± 6.26 ng/ml and -1.8 ± 1.71 ng/ml, respectively. There were significant differences in serum N-Mid level between the four groups (p=0.019), which were significant differences occurred on serum N-Mid level between Normal BMI, walked with 15-35% vs 50-80% increased cadence (Group 1 vs Group 2, mean difference=7.59 ng/ml, p=0.002), and between Normal BMI vs Overweight BMI groups walked with 50-80% increased cadence

(Group 2 vs Group 4, mean difference=4.70 ng/ml, p=0.046). Normal BMI, walked with 50-80% increased cadence group showed most reduced bone formation marker compared to other groups (**Figure 2**).

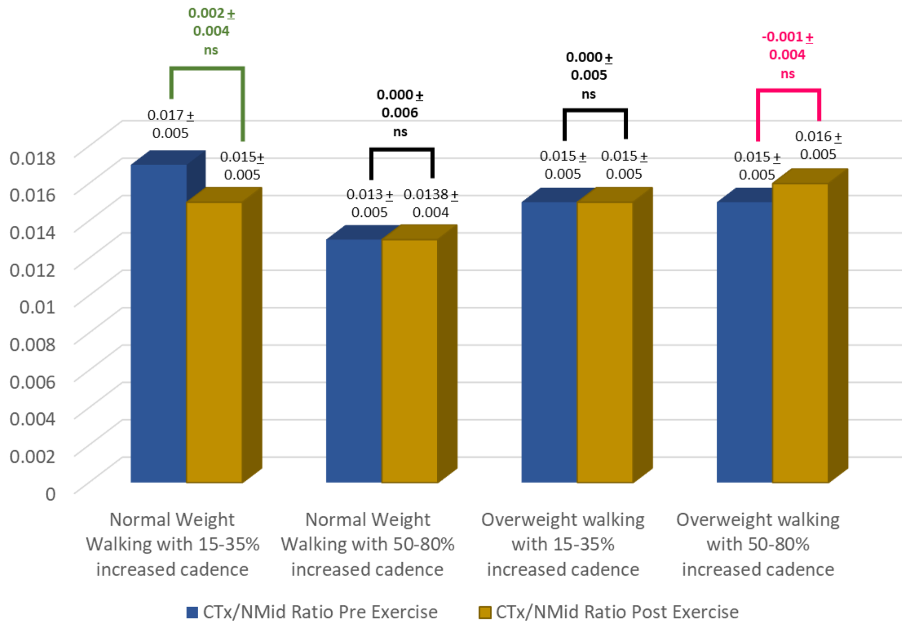

Figure 3. Comparison of Pre-Post Exercise CTx/N-Mid Ratio Between Groups.
Note : Using Paired T-test and ANOVA, *significant *(p<0.05)*, red font & line: increase, green font & line: decrease, black font & line: no change

Ratio of CTx/NMid reflected the bone resorption activity trends. Group 1 (Normal BMI, walked with 15-35% increased cadence) showed reduce trend of bone resorption activity, Group 2 (Normal BMI, walked with 50-80% increased cadence) and Group 3 (Overweight BMI, walked with 15-35% increased cadence) showed no change on bone resorption activity and Group 4 (Overweight BMI, walked with 50-80% increased cadence) showed increase trend of bone resorption activity (**Figure 3**).

DISCUSSION

Basic Characteristics

This study enrolled 32 postmenopausal women, with mean of age of subjects 57.0 ± 4.83 (45-65) years old, these subjects are classified as late middle-aged adults to old adults.[10] The menopause age occurred between 40-56 years old, with the mean on 50.3 ± 3.76 years old, similar to the mean age of menopause reported by Diyu.[11] We did not explore about the socioeconomic level of the subjects specifically, but most of them were housewives and from middle socioeconomic level. Most of them already passed the postmenopausal window period (5 years since menopausal onset), which means their hormonal dynamic is in new stable condition already. Pre0exercise/baseline cadence is a preferred cadence usually used by subjects in daily living. In our subjects, the mean cadence is 93.31 ± 12.59 (67-120) steps/minute, classified as slow to moderate speed according to Schmitz classification in Hispanic population.[12] A systematic review by Slaght et al. concluded that 100 steps/minute for adults related to moderate intensity, but older adults may require a higher cadence.[13] The anthropometric differences between population used in our study compared to Schmitz's study are on body height (body height in our study was 1.52 ± 0.05 (1.41-1.63) m compared to Schmitz's study which was 1.66 ± 0.06 m). Body weight 58.3 ± 9.15 (41-80) kgs, body mass index (BMI) 25.14 ± 2.99 (18.7-30.0) kg/m2. step length 46.58 ± 5.96 (34-60) cm, leg length 83.39 ± 4.61 (76-94) cm, IPAQ mean was 4.84 ± 1.40 (3.6-7.0) METs. They were classified into four groups according to increase cadence class (15-35% vs 50-80% increased from initial cadence) and BMI (normal vs overweight) as shown in **Table 1**. Pre-exercise levels of serum CTx and N-Mid reflected the baseline bone cellular activities.

Post-Exercise CTx and N-Mid

Bone turnover consists of two processes: bone resorption and bone formation.[14] There was reduced osteoclast activity as shown by the reduced serum CTx level in all groups, with the most in the Group 2 (Normal BMI, walked with increased cadence of 50-80%). But osteoblast activity tended to reduce as a response of reduced osteoclast activity in all groups, except in Group 1 (Normal BMI, walked with increased cadence of 15-35%), which showed the increased serum N-Mid osteocalcin. An elevation in serum N-Mid osteocalcin concentration indicates an acceleration of bone formation.[15] The effect size between these two walking speed groups in Normal BMI was 1.33 (high size effect). CTx/N-Mid ratio is associated with a bone resorption activity trend. The higher the CTx/N-Mid ratio means more bone loss, and vice versa. This ratio is usually used to assess various diseases caused by bone metabolism.[16] In our study, the group of Normal BMI, walked with 15-35% increased cadence and showed reduce trend of bone resorption activity, even though it was not significant.

This study is in line with previous study conducted by Kitareewan et al. on women at the age of 30-70 (menstruating vs menopausal women), with moderate intensity treadmill walking exercise for 30 minutes, with frequency three times a week over a 3-month period. Bone markers used in that research were CTx, PINP, and N-Mid osteocalcin. The results were reduces bone resorption and bone turnover markers in both groups. All of the bone markers were highly corelated.[17]

A cross-sectional study on 80 healthy middle aged (41-60 year old adults) by Tuddor-Locked et al. concluded that cadence thresholds of 100 and 130 steps/min emerged as heuristic values associated with three and six METs, respectively.[18] Our study shows that Normal BMI had beneficial effects associated with moderate intensity of walking exercise. Normal BMI groups show regular bone adaptation process according to force amplitude and frequency, and increased cadence of 15-35% meet the proper dose for this groups, but the increased cadence of 50-80% shows excessive exercise response that may stimulate inflammatory mediators release and reduce the osteoblast's bone formation capacity because of more osteoblast apoptosis, leading to a decrease in bone formation, mineralization, and density.[19,20]

Historically, it was believed that overweight or obesity has a protective effect on the bone health. BMI is part of the fracture risk assessment tool (FRAX), and higher BMI leads to reduce risk of fractures. However, in recent years, epidemiological and clinical investigations have questioned this theory. Some studies suggest that there is an association between abdominal adiposity and osteoporosis, whereas other studies suggest that this association is probably more complex and site-dependent. Typically, there exists a double association between high BMI and bone, encompassing both mechanical and metabolic aspects.[21] From the metabolic aspect, the Overweight BMI groups are hypothesized to have more leptin (which is associated with higher amounts of adipose tissue) with its estrogen-like effect, which is important in the energy homeostasis and interacting with the reproduction axis sites, which in turn stimulates the GH-IGF axis. Estrogen deficiency stimulates osteoclastogenesis, which is shown by elevated levels of receptor activator of nuclear factor kappa-B ligand (RANKL), as well as with leptin. Increased leptin levels have been shown to increase BMD by influencing the RANKL/OPG pathway.[22,23] Osteoprotogerin (OPG) is an inhibitor of RANKL and RANK binding, thereby inhibiting osteoclastogenesis.[21] From the mechanical aspect, an overweight or obese person has a greater mechanical loading on bone. Mechanical loading induces bone formation by reducing apoptosis and enhancing the proliferation and differentiation of osteoblasts and osteocytes. However, it is well-stated that the dynamic loads generated by muscular contractions are more anabolic to bone than static loads that are induced by excess body fat. Therefore, overweight or obesity alone may not provide any mechanical benefits to the bone unless it is accompanied by a higher amount of lean mass and a non-sedentary lifestyle.[24]

Besides the positive relationship between overweight and bone health, there is also a negative relationship. From a mechanical aspect, being overweight also leads to an increase in mechanical stress due to excessive and abnormal loading patterns. Mechanoreceptors on bone are activated by the mechanical stimulation of overloading stimulation, resulting in degradation of bone matrix.[25] In addition, from metabolic aspects, overweight is believed to be associated with low-grade chronic inflammation, marked by increase in proinflammatory cytokines, such as TNF -α and IL-6, which act synergistically promoting the RANKL/RANK pathway, which activate osteoclasts and induce bone resorption (marked by increased CTx).[21,26,27]

From the biomechanic point of view, increasing walking speed at a certain level will change moment forces of lower extremities and as consequence the leg muscles will work more to achieve walk stability by increased isometric and eccentric contractions. These activities produce tensile and compression stress alternately (reflected in tissue deformation), which in turn increases force amplitude during walking exercise. This stress triggers the fluid flow within intercanalicular spaces, then increases fluid shear stress between osteocyte, preosteoblast, preosteoclast and marrow cells.[28] It also changes pressure gradient, inhibits caspase-3 enzyme and increases activity of inositol triphosphate (PI3) that in turn inhibits TNF-α activity, inhibits osteoblast apoptosis and reduces osteoclast activity. Reduced osteoblast apoptosis will increase bone formation,[29] leading to improved structural bone adaptation. Bone adapts to mechanical factors, i.e. muscle contraction or force of gravity. There are potential therapeutic effects from specific roles of muscle loads and forces of gravity in bone adaptation.[30]

The muscles accounted for more than 70% of the forces created in the thigh bone during a normal cycle of walking, while less than 30% of the forces were due to the reaction of gravity on the patient's body weight.[30] The high increase cadence leads to excessive isometric and eccentric contraction combined with excessive axial load impact, which leads to excessive force in lower extremities. It would be more severe in Overweight BMI groups because the body weight itself adds more ground reaction force (GRF).[26] It could be that high increase loading force during weight bearing activities (including walking exercise) gives more excessive force in the Overweight BMI groups, combined with existing sub-clinical systemic inflammation in the Overweight group will lead to more bone loss. In this study, the Overweight BMI groups that walked with 15-35% and 50-80% showed no significant difference after exercise (effect size 0.043), which reflects response of NMid osteocalcin to increase walking speed was blunted in those groups.

From this finding, we can give some exercise program recommendations for postmenopausal women to maintain the bone health. Postmenopausal woman can do this SPWE routinely for three times a week. The exercise consists of: warming up (3-4 minutes), walking with 15-35% increased from initial cadence (4 minutes), walking with initial cadence (8 minutes), followed with walking with 15-35% increased from initial cadence (4 minutes), walking again with initial cadence (8 minutes), and cooling down (3-4 minutes).

CONCLUSION

From this result, it can be concluded:

1. In Normal BMI groups of postmenopausal women, increasing walking speed will increase serum NMid osteocalcin in the group that walked with 15-35% increased cadence; but in the group that walked with 50-80% increased cadence, the serum NMid osteocalcin tends to decrease.
2. In Overweight BMI groups of postmenopausal women, increasing walking speed in both the 15-35% and 50-80% groups tends to slightly decrease the serum NMid osteocalcin, even though the effect is lighter than the effect in Normal BMI groups who walked with 50-80% increased cadence.

3. Increasing walking speed tends to reduce CTx/NMid ratio on Normal BMI group of the postmenopausal women that walked with 15-35% increased cadence, even though it is not significant.

Study Limitation

The absence of a body composition evaluation in this study limits the calculation of the proportion of body fat mass.

To achieve a clearer effect, we recommend to increase the sample size for further study.

DISCLOSURES

Conflict of Interest

We declare that there were no conflicts of interest in this study

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Author Contribution

All of the authors equally contributed to the study.

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