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Effect of metformin on cardiovascular risk factors in middle-aged Thai women with metabolic syndrome: A randomized placebo-controlled trial

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Abstract

Aim: To evaluate the effect of metformin on cardiovascular risk factors in middle-aged Thai women with metabolic syndrome that are in menopausal transition.

Methods: This study was double-blind randomized placebo-controlled trial. Metabolic syndrome was diagnosed using American Heart Association and National Heart, Lung, and Blood Institute criteria. After taking metformin 1700 mg/day for 6 months, cardiovascular risk factors were evaluated at baseline and month-6; the values of which were used to calculate delta (Δ, month-6 minus baseline values).

Results: Forty menopausal participants were equally, randomized into either the placebo or metformin group. The two groups had comparable metabolic parameters at baseline, except that the mean triglyceride level was higher in the metformin group than in the placebo group. The significant improvements found only in the metformin group were body mass index, fasting blood glucose, high-sensitivity C-reactive protein and 10-year risk of coronary heart disease (Framingham heart study) (P = 0.0004, P = 0.049, P = 0.035 and P = 0.029); whereas that only in the placebo group was high density lipoprotein cholesterol. However, there was no statistically significant difference in the improvement between the two groups.

Conclusion: Metformin can improve some parameters of metabolic syndrome in middle-aged Thai women. Metformin is not superior to placebo for the improvement of cardiovascular risk factors.

Key words: cardiovascular disease, menopause, metabolic syndrome, metformin.

Introduction

Metabolic syndrome, a condition that includes abdominal obesity, varying degrees of glucose intolerance, dyslipidemia and hypertension, is the most important modifiable risk factor for atherosclerotic cardiovascular disease (CVD),[1] which is the leading cause of death worldwide.[2,3] Incidence of CVD in Thailand has been increasing over the last decade.[4] The impact of CVD is vast, including high healthcare costs and low quality of life in the affected population. Presence of metabolic syndrome can predict approximately 25% of all new-onset CVD cases.[5] Postmenopausal women have high risk of developing metabolic syndrome as they often have enlarged waist circumference (WC), elevated blood pressure

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(BP), decreased insulin sensitivity and higher rates of dyslipidemia.[6,7] Previous study found that prevalence of metabolic syndrome increased with age and body mass index (BMI).[8–10] Our previous study showed that the prevalence of metabolic syndrome in Thai women increased from less than 5% in women younger 40 years old to nearly 20% in those older than 50 years old.[10] As the risk of developing metabolic syndrome increased considerably in middle-aged Thai women, an intervention to reduce such risk would be benefit for their future cardiovascular health and quality of life.

It is postulated that early and appropriate management of the modifiable risk factors, that is, metabolic syndrome components, would reduce the risk of CVD. Postmenopausal hormone therapy (pHT) can improve various components of metabolic syndrome,[11] and pHT users have lower risk of CVD if they start the pHT during the 'window of opportunity', that is, menopause less than 5 years or age less than 60 years.[12] Despite, pHT is not indicated for prevention of CVD.[13] Evidences support that healthy lifestyle and/or metformin can prevent metabolic syndrome development and resolve the pre-existing one by improving values of its components.[14,15] Therefore, it is interesting to prove the benefit of such interventions in middle-aged women whose cardiovascular risk is rising.

The benefit of healthy lifestyle on metabolic syndrome was clearly seen in the US Diabetic Prevention Program (DPP) lifestyle intervention. The US-DPP aimed to achieve a minimum of 7% weight loss/weight maintenance and a minimum of 150 min of physical activity; the intervention of which resulted in a 58% reduction in the incidence rate of diabetes[16,17] and the secondary analysis of the data showed the impact of the intervention on metabolic syndrome.[14] Similar benefits of various lifestyle interventions on metabolic syndrome were also evidenced in various reports.[15,18–20]

Metformin, an insulin-sensitizing drug, is currently the first-line therapy for type 2 diabetes mellitus (T2DM). The T2DM is associated with a 2–3-fold increase of CVD risk[21,22] while good glycemic control results in the reduction of microangiopathy, cardiovascular morbidity and mortality.[23,24] The benefit of metformin on metabolic syndrome components was established in subjects with insulin resistance.[14,20] Interestingly, metformin also has glucose-lowering independent beneficial effects on BP, C-reactive protein (CRP) and plasma lipids in the T2DM.[25,26] Therefore, metformin might be beneficial for women with metabolic syndrome even though they did not have insulin resistance.

Most of the evidences regarding the interventions on metabolic syndrome in women are derived from clinical trials in polycystic ovary syndrome or insulin resistance population. Such evidences in middle-aged women are lacking. It is unknown whether the interventions have window of opportunity for the reduction in cardiovascular risk if they are initiated during midlife; the evidence of which found in the pHT studies. The present study aimed to investigate the effect of metformin on cardiovascular risk factors in middle-aged Thai women with metabolic syndrome.

Methods

The present double-blind randomized placebo-controlled trial was conducted at the Siriraj Menopause Clinic, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University. Siriraj Hospital is the Thailand's largest university-based tertiary referral hospital. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and all of its subsequent amendments. The protocol for this study was approved by the Siriraj Institutional Review Board (COA No. *Si* 091/2011). A written informed consent was obtained from all participants prior to inclusion in the study.

Study population

Eligible participants were women 45–60 years old with metabolic syndrome who attended Siriraj Menopause Clinic during the May 2013 to August 2014 study period. We excluded women who were taking glucose-lowering medication, lipid-lowering medication or hormone therapy. We also excluded women who had coronary heart disease, cerebrovascular disease, hepatic failure, chronic hypoxic lung disease, lactic acidosis and/or abnormal laboratory result(s) at the screening visit (visit 0), that is, abnormal electrocardiogram (ECG,) fasting blood sugar (FBS) ≥200 mg/dL, glycated hemoglobin (HbA1c) >8%, creatinine >1.4 mg/dL and/or triglycerides (TG) ≥500 mg/dL.

Study procedures

This 6-month study comprised three visits including baseline, month-3 and month-6. At baseline,

sociodemographic data, medical history, physical examination data and baseline laboratory data were collected in a structured case record form. Physical examination data included height (cm), weight (kg), neck circumference (NC; cm), WC (cm) and BP (mmHg). The details of measurement for each parameter in our clinic were reported elsewhere.[10] Body mass index (kg/m^2) was then calculated. Biochemical blood tests included complete blood count, FBS (mg/dL), fasting insulin, 75-g oral glucose tolerance test, high-sensitivity C-reactive protein (hs-CRP) and lipid profile (i.e., TC, total cholesterol; TG, total triglycerides; HDL-C, high-density lipoprotein cholesterol and LDL-C, low-density lipoprotein). Biochemical assays were performed in the Department of Clinical Pathology (ISO 15189 certified laboratory), Faculty of Medicine Siriraj Hospital, Mahidol University. Homeostatic measurement assessment-insulin resistance (HOMA-IR) and fasting glucose/insulin ratio (G/I ratio) were calculated. Details relating to each assay were reported elsewhere.[27] All participants underwent a conventional 12-lead ECG testing. At month-3 and month-6, clinical data and drug accountability (using pill calendar and pill count) were recorded. Follow-up laboratory data were collected at month-6. All anthropometric parameters of women were surveyed by an independent nurse without recognized the result of the previous data.

Health education program

The Siriraj Menopause Clinic health education program is a half-day education program specifically for middle-aged women, run bi-weekly by a team of nurse specialists in women health. The program addresses about menopause issue, health promotion via healthy lifestyle, health screening and service delivered by the clinic. It is conducted in a class of 10–15 attendants undergoing the following activities: 20-min session of Thai aerobic dance workout, 1-h interactive lecture and demonstration and practice of self-breast exam. At the end of the class, a health education package and a DVD of Thai aerobic dance workout are provided to each attendant free of charge. Eligible attendants are patients in the waiting list of Siriraj Menopause Clinic who are expected to attend the program only once, but they are welcome to re-attend the program as a refresher at any time.

In addition to the present study, the participants would obtain information about metabolic syndrome at the baseline visit. A research nurse encouraged the participants to change to healthy lifestyle in accordance with the Adult Treatment Panel III guidelines,[28,29] in brief, regular exercise and healthy diet (low fat and high fiber). The nurse would remind and encourage the participants to maintain her healthy lifestyle whenever she contacted them.

Treatment allocation and trial medications

Patients were allocated into either the placebo or the metformin group by simple randomization. A pharmacist who was not involved with the recruitment process produced randomization codes using a computer generated list of random numbers. The codes were individually enclosed and sealed in opaque envelopes that were sequentially numbered. An independent research nurse opened the envelopes and dispensed the trial medications, accordingly.

Trial medications were metformin 850 mg or placebo twice daily for 6 months. The placebo was manufactured by the Pharmacy Department, Siriraj Hospital. Trial medications were identical in physical appearance and were packed in identical opaque zip lock-style plastic bags. Each bag contained 60 tablets of trial medication. The pharmacist who generated the randomization codes was the only person that had access to the code, and that pharmacist prepared the trial medications, accordingly.

Reproductive status of study participants

According to the 2011 Stages of Reproductive Aging Workshop (STRAW+10) staging system,[30] our participants were in the stages of menopause transition (stage-1 and stage-2) and early postmenopausal (stage +1a, +1b and +1c).

Criteria for diagnosis of metabolic syndrome

Metabolic syndrome was diagnosed using American Heart Association and National Heart, Lung, and Blood Institute criteria for Asian population.[31] Metabolic syndrome was diagnosed if three of five of the following criteria were present: (i) abdominal obesity defined as Asian WC ≥80 cm; (ii) elevated BP defined as systolic BP ≥130, or diastolic ≥85 mmHg, or previously treated hypertension; (iii) elevated fasting plasma glucose ≥100 mg/dL, or previously diagnosed T2DM; (iv) reduced HDL-C (<50 mg/dL) and (v) elevated TG (≥150 mg/dL).

Cardiovascular risk assessment

The 10-year risk of developing CVD was evaluated at baseline and at month-6 of treatment using Framingham heart study score[32] and Ramathibodi-Electricity

Generating Authority of Thailand (RAMA-EGAT) score.[33]

Statistical analysis

Sample size was calculated using a formula for comparing the means of two independent populations under the following conditions: two-sided type I error of 0.05, power of 80%, a mean difference of total cholesterol between the placebo and metformin groups of 35 mg/dL with a standard deviation (SD) of 34[34] and with an assumption of equal variance. The calculated minimum sample size was 18 participants for each group.

Data were analyzed using SPSS Statistics version 18.0 (SPSS, Inc.). Data are presented as mean and SD, number (*n*) and percentage (%) or median and interquartile range [IQR], as appropriate.

Efficacy outcome analysis was based on per protocol and modified intent-to-treat (ITT) (i.e., all patients who took at least one dose of trial medication were included in the analysis). For patients that were lost to follow-up, we applied the last observation carried forward method for ITT analysis. Continuous data were tested for normality using histogram, normal Q–Q plot, and/or Kolmogorov–Smirnov test. Baseline and month-6 data within the same group were compared using paired *t*-test or Wilcoxon signed-rank test for continuous data and McNemar chi-square test for categorical data. We used one-way analysis of variance (ANOVA) for parametric variables and legacy test for non-parametric variables to compare baseline or treatment effects between groups. Delta (Δ) value was calculated by subtracting the baseline value from the month-6 value. The between groups comparison of Δ value was conducted using analysis of covariance (ANCOVA) or Mann–Whitney *U* test. All tests were two-tailed and a *P*-value <0.05 was considered statistically significant.

Results

Forty participants were enrolled and equally allocated into either the placebo group or the metformin group (Fig. 1). One participant in the metformin group did not return at month-3 and withdrew from the study. We were, however, able to contact her by telephone to inquire about any adverse effects she had experienced. This participant was excluded from the per protocol analysis.

Among metabolic syndrome women, 27 women (67.5%) had natural menopause and 36 women (90%) had overweight and obese. The mean age of all participants was 53.1 ± 4.4 years and mean BMI was 26.9 ± 3.1 kg/m^2. Menopause women presented with hypertension, central obesity, impaired fasting glucose, hypertriglyceridemia and low HDL-cholesterol were 77.5%, 97.5%, 50%, 57.5% and 60% respectively (Table 1). None of women had a history of smoking and hormonal using.

The placebo and the metformin groups were comparable in age (53.0 ± 4.2 vs 53.3 ± 4.9 years), duration since menopause (5.2 ± 5.0 vs 5.7 ± 4.3 years) and metabolic parameters at baseline (Table 2, *P* values were not shown) except for triglyceride level that was higher in the metformin group than in the placebo group (191.2 ± 73.5 vs 148.3 ± 55.6 mg/dL; $P = 0.044$).

Analysis using the ITT and per protocol data revealed similar results (data not shown). At month-6, both groups had statistically significant improvement from baseline (Δ values) in BP, WC and NC. The significant improvements found only in the metformin group were BMI, FBS, hs-CRP and 10-year risk of coronary heart disease using Framingham heart study score; whereas that only in the placebo group was HDL-C. However, there was no statistically significant difference in the improvement (Δ values) between the two groups (Fig. 2).

Adverse events were presented in Table 3. The most common complaints were diarrhea, abdominal or stomach discomfort, nausea and vomiting. There was no statistically significant difference between the two groups for any adverse effects. None of the reported adverse effects were regarded as being serious and no participants withdrew from the study due to the adverse events.

Discussion

The common metabolic abnormalities in middle-aged Thai women are overweight or central obesity, elevated BP and low HDL cholesterol.[10] These abnormalities increase the risk of CVD – the incidence of which increases markedly after menopause.[5,24] In addition, women affected by metabolic syndrome commonly have insulin resistance, followed by compensatory hyperinsulinemia and dyslipidemia, which results in intensifying cardiovascular risk.[24,27]

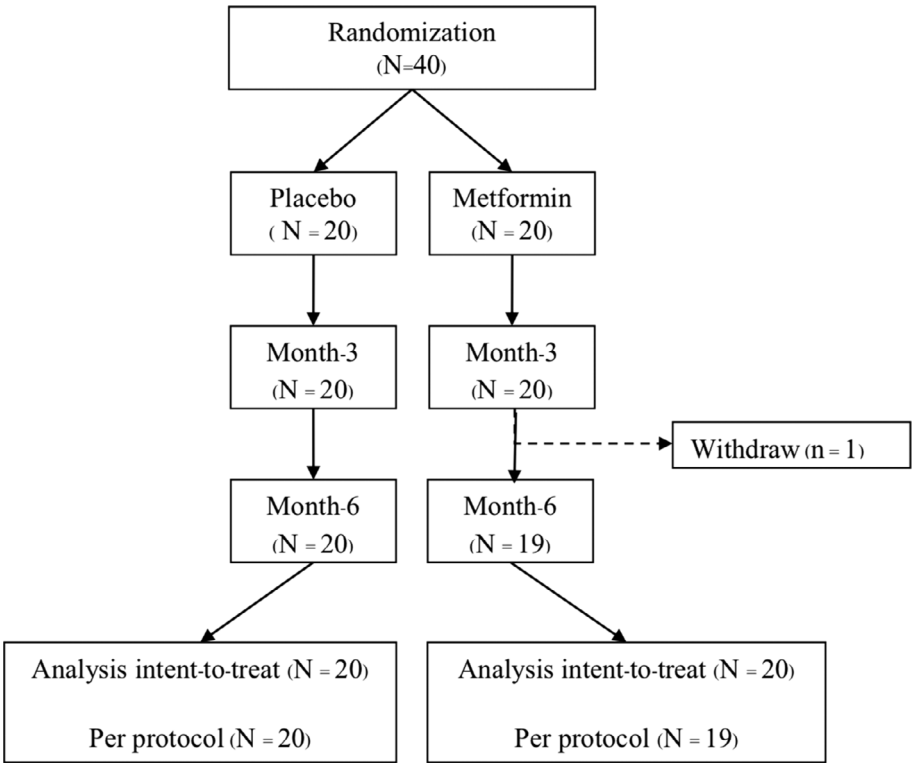

Figure 1 Flow of study participant.

The Framingham Study was developed from US population. Age, sex, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, diabetes status and smoking status were used for the estimation of absolute cardiovascular risk. Previous studies suggested that the Framingham risk score may overestimate the risk in Asia.[4,35] RAMA-EGAT score[4] used similar components and additional waist circumference in determining cardiovascular risk. Furthermore, it was developed by using Thai participants' data. Therefore, RAMA-EGAT score is more appropriate for predicting coronary artery disease risk in the Thai population.

Metformin can be used as an alternative treatment in improving the cardiovascular risk factors related to the metabolic syndrome. For example, metformin administration resulted in a variable response in BP control, lipid profile regulation and a dose-dependent anti-hyperglycemic action. As a result, metformin treatment was suggested to be associated with decreased cardiovascular risk.[21,36] However, in this study, metformin was not proved to be superior to placebo in improving such parameters. This may be resulted from the relatively low dose of metformin (1700 mg/day) in overweight and obese woman and it was possible that the improvement might be attributable to the effect of lifestyle change while the women were participating in the trial, as we encouraged all women to engage in healthy lifestyle.

The benefit of intensive lifestyle intervention and metformin 850 mg twice daily on metabolic syndrome was demonstrated in the US-DPP, although the impact of intensive lifestyle intervention was much more marked than that of metformin.[14] In the present study we found the statistical improvement after 6 months of treatment in many parameters of metabolic syndrome and cardiovascular risk factors including BP, WC, NC, BMI, FBS, hs-CRP and 10-year risk of coronary heart disease (Framingham heart study). Our results were in line with those of previous studies.[21,25,26,37]

Unfortunately, our study was not designed to evaluate the impact of lifestyle modification in the study population. An intensive lifestyle intervention program in the US-DPP was effective, although it might not be applicable in general practice, as the program needed resources, for example, individual case managers and frequent contact to assure participants' adherence to the program.[16] Noteworthy, the value of lifestyle modification to improve health markers still

Table 1 Baseline characteristics of middle-aged Thai women with metabolic syndrome

Baseline characteristics	Mean ± SD or *n* (%) or median [interquartile range, IQR]
Clinical	
Age (year)	53.1 ± 4.4
Natural menopause	27 (67.5)
Duration since menopause (year)	5.4 ± 4.6
Body mass index (kg/m^2)	26.9 ± 3.1
≥23	36 (90)
Neck circumference (cm)	35.0 ± 2.2
Waist circumference (cm)	88.8 ± 6.6
≥80 cm	39 (97.5)
Systolic blood pressure (mmHg)	134.4 ± 16.7
≥130	31 (77.5)
Diastolic blood pressure (mmHg)	75.6 ± 10.1
≥85	7 (17.5)
Carbohydrate metabolic profiles	
Fasting blood glucose (mg/dL)	98.5 ± 14.0
≥100	20 (50)
2-h blood glucose (mg/dL)	153.9 ± 57.7
≥140	19 (47.5)
Fasting insulin (μU/mL)	10.6 ± 5.1
2-h insulin (μU/mL)	104.2 ± 54.8
≥100	7 (35)
Fasting glucose/insulin ratio	9.3 [4.6–11.5]
<4.5	0
HOMA-IR	2.3 [0.1–6.7]
≥2	30 (75.5)
Hemoglobin A1c (%)	6.1 ± 0.6
≥6	27 (67.5)
Lipid profiles	
Triglyceride (mg/dL)	169.7 ± 67.9
≥150	23 (57.5)
HDL-cholesterol (mg/dL)	50.4 ± 12.7
<50	24 (60)
LDL-cholesterol (mg/dL)	143.9 ± 29.2
Cardiovascular risk	
hs-CRP(mg/L)	2.7 [0.2–24.1]
RAMA-EGAT score	9 [3–16]
Framingham heart study score	8 [5–10]

Note: Data are mean ± SD, median [interquartile range, IQR], or number (%). HDL-cholesterol, high-density lipoprotein cholesterol; HOMA-IR, homeostatic measurement assessment-insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LDL-cholesterol, low-density lipoprotein cholesterol; RAMA-EGAT score, Ramathibodi-Electricity Generating Authority of Thailand.

existed in various lifestyle intervention programs modified from the original version of US-DPP and applied to various settings.[38] A formal education program for Ecuadorian postmenopausal women with metabolic syndrome was able to increase awareness of the women on their health issues; the program was deemed a cost-effective measure to reduce cardiovascular-related morbidity and mortality among high-risk postmenopausal women.[28] Interestingly, our Siriraj Menopause Clinic health education program, a simple 1-session program provided by a research nurse through teaching, talking and encouraging, seemed to have benefit for health parameters of our participants.

The decrease in BMI and WC reflects a reduction in visceral fat that is normally followed by an improvement in insulin resistance[21,25,37] and levels of CRP.[39,40] Although our participants had reduction in BMI, WC and CRP level, we did not find statistically significant change on carbohydrate metabolic parameters, except for FBS. It was possible that our study did not have enough power to detect the improvement in carbohydrate metabolism as we calculated the sample size to detect the improvement in cholesterol level.

Table 2 Baseline parameters and outcomes of the intention to treat (ITT) population

Parameters	Placebo (n = 20)			Metformin (n = 20)			P^1	P^2	P^3
	Baseline	Month-6	Delta	Baseline	Month-6	Delta			
Clinical									
BMI (kg/m^2)	29.0 ± 2.6	26.6 ± 2.4	−0.4 ± 0.8	26.9 ± 3.5	25.9 ± 3.4	−0.7 ± 1.0	0.059	0.004*	0.219
NC (cm)	35.5 ± 2.5	34.4 ± 1.7	−1.1 ± 1.5	34.5 ± 1.7	33.6 ± 2.0	−0.7 ± 1.3	0.006*	0.025*	0.413
WC (cm)	88.1 ± 5.8	86.5 ± 4.7	−1.6 ± 2.9	89.6 ± 7.5	87.1 ± 8.4	−2.1 ± 3.9	0.024*	0.028*	0.679
sBP (mmHg)	138.3 ± 18.2	131.2 ± 11.5	−7.1 ± 12.9	130.5 ± 14.5	127.2 ± 19.2	−3.7 ± 19.5	0.023*	0.414	0.514
dBP (mmHg)	76.3 ± 11.2	74.7 ± 8.9	−1.6 ± 8.8	75.0 ± 9.2	71.3 ± 12.8	−3.3 ± 10.8	0.426	0.025*	0.598
Carbohydrate									
FBG (mg/dL)	102.7 ± 14.9	98.9 ± 11.1	−3.8 ± 10.6	94.3 ± 12.1	89.8 ± 8.9	−4.6 ± 9.8	0.130	0.049*	0.793
2-h BG (mg/dL)	158.2 ± 61.9	157.8 ± 54.4	−2.4 ± 40.3	149.6 ± 54.4	148.9 ± 51.2	−2.3 ± 51.8	0.795	0.845	0.994
Fasting insulin (μU/mL)	11.2 ± 5.1	12.0 ± 5.8	0.8 ± 5.8	10.0 ± 5.3	10.7 ± 6.8	0.2 ± 5.8	0.557	0.889	0.610
2-h insulin (μU/mL)	97.2 ± 40.9	89.9 ± 54.5	−2.6 ± 57.4	110.8 ± 60.7	106.6 ± 58.3	−5.4 ± 63.6	0.850	0.711	0.890
G/I ratio	9.7 [4.7–15.9]	9.1 [6.4–11.9]	−1.0 [−2.4–1.3]	8.3 [4.7–16.2]	9.0 [7.0–16.1]	0.8 [−1.8–7.1]	0.263	0.266	0.176
HOMA-IR	2.5 [0.1–6.7]	2.4 [2.1–3.6]	−0.1 [−0.6–0.6]	2.2 [0.9–4.5]	2.2 [1.1–2.5]	−0.2 [−1.0–0.4]	0.695	0.492	0.331
HbA1c (%)	6.2 ± 0.8	6.2 ± 0.4	−0.1 ± 0.6	6.1 ± 0.3	5.9 ± 0.3	−0.1 ± 0.3	0.637	0.244	0.262
Lipid									
TC (mg/dL)	227.3 ± 23.8	236.7 ± 32.5	9.4 ± 28.1	230.0 ± 25.7	223.5 ± 33.8	−6.5 ± 26.4	0.151	0.285	0.730
TG (mg/dL)	148.3 ± 55.6	141.6 ± 50.3	−6.7 ± 54.1	191.2 ± 73.5	169.9 ± 75.3	−21.3 ± 68.9	0.586	0.184	0.760
HDL-C (mg/dL)	48.9 ± 10.6	52.5 ± 9.8	3.6 ± 7.5	51.9 ± 14.7	54.0 ± 11.8	2.1 ± 8.2	0.048*	0.279	0.547
LDL-C (mg/dL)	147.5 ± 26.7	156.6 ± 35.3	9.0 ± 28.5	140.3 ± 31.8	138.1 ± 34.8	−2.2 ± 30.4	0.172	0.749	0.234
Cardiovascular									
hs-CRP (mg/L)	2.4 [1.8–4.1]	3.0 [1.7–5.3]	0.3 [−0.8–1.6]	2.7 [1.3–4.5]	2.3 [1.0–5.4]	−0.4 [−1.6–0]	0.887	0.035*	0.102
RAMA-EGAT score	8 [7–9.8]	9 [7.0–10.0]	0 [0–0]	9 [7–9]	8.5 [6.0–9.5]	−0 [−0.8–0]	0.157	0.408	0.206
10-year CHD risk (%)	2 [2–2.8]	2 [2–3]	0 [0–0]	2 [2–2]	2 [1–2]	−0 [−0.3–0]	0.163	0.302	0.331
Framingham heart study score	8 [6.3–11.5]	8 [6.0–10.0]	−0.5 [−2.0–1.8]	7 [4–9]	5.5 [4.0–8.3]	−2.0 [−3.3–1.3]	0.221	0.058	0.443
10-year CHD risk (%)	2 [1–3]	2 [1.0–2.0]	−0 [−1.0–0]	2 [1–2]	1 [1.0–2.0]	−1.0 [−1.0–0]	0.218	0.029*	0.553

Note: Data are mean ± SD or median [interquartile range, IQR]. Within group comparison were analyzed using paired t-test or Wilcoxon signed-rank test, and between groups comparison were analyzed using analysis of covariance (ANCOVA) or unpaired t-test or Mann–Whitney U test. P^1, baseline vs month-6 values within placebo group; P^2, baseline vs month-6 values within metformin group; P^3, delta values of placebo vs metformin. *P value. (F)BG, (fasting) blood glucose; BMI, body mass index; dBP, diastolic blood pressure; dBP, diastolic blood pressure; delta (Δ), month-6 value minus baseline value; G/I ratio, fasting glucose to insulin ratio; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic measurement assessment-insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; NC, neck circumference; RAMA-EGAT score, Ramathibodi-Electricity Generating Authority of Thailand; sBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

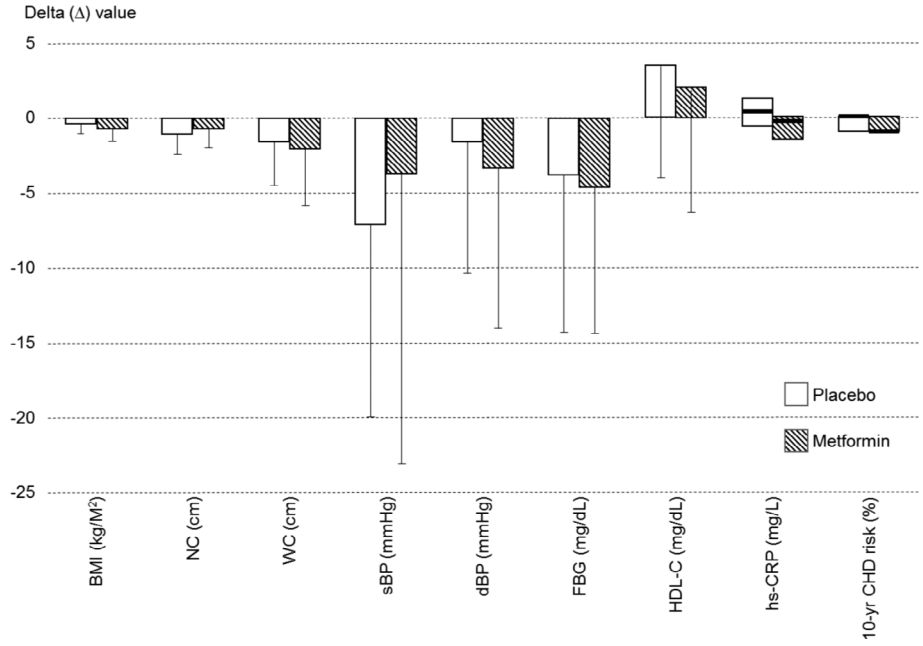

Figure 2 No statistically significant difference in delta value between placebo and metformin groups. Graph shows only the parameters that have the within-group statistically significant change from baseline. Box and whisker show mean and standard deviation. Box and thick horizontal line show interquartile range (IQR) and median. Data were analyzed using analysis of covariance (ANCOVA) or Mann–Whitney *U* test. 10-yr CHD risk, 10-year risk of coronary heart disease using Framingham heart study score; BMI, body mass index; dBP, diastolic blood pressure; delta value, month-6 value minus baseline value; FBG, fasting blood sugar; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; NC, neck circumference; sBP, systolic blood pressure; WC, waist circumference.

Table 3 Adverse events of the per protocol population

Adverse events	Placebo (n = 20)	Metformin (n = 19)	*P*
Overall	3 (15.0)	5 (26.4)	0.212
Nausea	0 (0)	1 (5.3)	
Vomiting	0 (0)	1 (5.3)	
Anorexia	0 (0)	1 (5.3)	
Abdominal or stomach discomfort	1 (5.0)	3 (15.8)	
Diarrhea	2 (10.0)	4 (21.1)	

Note: Data are number (%) and were analyzed using Fisher's exact test. Some patients had more than one adverse event.

Moreover, the decrease in BMI in our population was slightly less than 3% in 6 months which was markedly less than the decrease in BW of ≥7% in the US-DPP, the program that demonstrated reduction of diabetes risk in the population with high risk for DM received interventions for almost 3 years.[17]

The adverse event of gastrointestinal disturbance was very common. Although the incidence had no statistically significantly difference between the placebo (15.0%) and the metformin (26.4%) groups, it surely had clinical significance which might attenuate the blinding property of the study. The 'no statistical significance' could be explained by the 'not enough power' of the study to detect the difference in adverse event. However, such adverse event deemed tolerable, as none of the participants withdrew because of adverse event.

The strength of the present study was its double-blind randomized placebo-controlled trial design. This design reduced the effect of confounders, as both the treatment and the placebo groups were comparable in almost all baseline parameters. Mean baseline triglyceride level was poorer in the treatment group, which effectuated a bias against the treatment and might attenuate the beneficial effect of treatment for this parameter. Limitation of the present study was that we did not plan to evaluate the effect of co-intervention (engagement of health education and lifestyle modification) the effect of which was probably strong enough to mask the effect of metformin on cardiovascular parameters.[14]

In conclusion, metformin 1700 mg/day for 6 months is tolerable for middle-aged Thai women with metabolic syndrome. Metformin is not superior to placebo for the improvement of cardiovascular risk factors. The improvement found in both groups might be the effect of healthy lifestyle engagement which is reinforced during the study period. Further studies are needed to evaluate long-term benefit of lifestyle intervention initiated during middle-aged women.

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Disclosure

None declared.

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