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Assessment of Differences on Inflammatory and Metabolic Indicators between Pre- and Post-Menopause Women among Hypertensive and/or Diabetic Patients

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ABSTRACT

To assess the differences on inflammatory and metabolic indicators between pre-menopause and post-menopause women among hypertensive and/or diabetic type-2 women. A total of 236 obese women included in the study have chosen from Primary Health Care Centers in Gaza City, Palestine, through a cross-sectional study. Selection depended on health status hypertensive and/or diabetic type-2 (HT, T2DM, HT+T2DM). In HT group, post-menopause women had significant higher values than pre-menopause women on TC (200±47 vs. 172.5±55 mg dL^{-1}, $p<0.01$) and TG (166±89 vs. 120.5±82 mg dL^{-1}, $p<0.01$). In T2DM group, post-menopause women had significant higher values than pre-menopause women on SBP (132±24 vs. 120±20 mm Hg, $p<0.01$), TC (213±40 vs. 185±46 mg dL^{-1}, $p<0.05$) and TG (196±118 vs. 136±64 mg dL^{-1}, $p<0.05$). Finally, in HT+T2DM group, post-menopause women had significant higher value than pre-menopause women on SBP (144±21 vs. 133±14 mmHg, $p<0.05$), TC (214±54 vs. 181±55 mg dL^{-1}, $p<0.05$), TG (231±83 vs. 158±85 mg dL^{-1}, $p<0.05$), IL-6 (2.32±1.34 vs. 1.71±1.45 pg mL^{-1}, $p<0.05$) and BMI (36.48±7.1 vs. 32.18±5.6 kg m^{-2}, $p<0.05$). Post-menopause women diseased of HT and T2DM accompanied with higher rates of BMI are at risk for developing inflammatory and metabolic morbidities.

Key words: Menopause, inflammation, hypertension, diabetes, obesity

INTRODUCTION

Menopause is defined as a cessation of menstruation for 12 month caused by termination of ovarian follicular recruitment; the average age of menopause is 51 years old and may be genetically predetermined. There are many risk factors for menopause as cigarette smoking and surgery (hysterectomy) (Norwitz and Schorge, 2013). The hypoestrogenic changes cause major symptoms as vasomotor instability that represented by hot flashes and osteoporosis, which resulted on vertebral fracture in about 50% of woman aged >75 years (Yang and Reckelhoff, 2011).

Pre-menopausal women have a lower risk and incidence of hypertension and cardiovascular disease (CVD) compared to age-matched men, this sex advantage for women gradually disappears after menopause, suggesting that sexual hormones play a cardioprotective role in women (Yang and

Reckelhoff, 2011). However, randomized prospective primary or secondary prevention trials failed to confirm that hormone replacement therapy affords cardioprotection (Yang and Reckelhoff, 2011). The changes in adipose tissue metabolism may contribute to the changes in body fat distribution seen during the menopause transition in both the abdominal and gluteal fat depots, the lower lipolysis and higher adipose tissue lipoprotein lipase activity in postmenopausal women may predispose them to gain body fat after menopause (Ferrara *et al*., 2002). In addition, the postmenopausal state was significantly associated with the presence of dysglycemia independently of normal aging, although the increased probability in postmenopausal women did not equal that in men (Heianza *et al*., 2013).

It has been well established that women generally have lower incidence rates of hypertension and diabetes than men at similar ages and these differences may vary with age. It also has been observed in many studies that after menopause, Blood Pressure (BP) increases in women to levels even higher than in men (Kim *et al*., 2014). During the menopause transition, woman experience risk of different diseases as an increase in CVDs, diabetes and bone resorption which inversely associated with Body Mass Index (BMI) (Sowers *et al*., 2013). Furthermore, menopausal symptoms in women can affect the overall quality of life, where the exercise has been assessed as an alternative treatment option for alleviating menopausal symptoms (Stojanovska *et al*., 2014).

In this study, we aimed to assess the difference of inflammatory and metabolic indicators between pre-menopausal and post-menopausal women with regard to obesity and health status involving hypertension (HT) and diabetes type-2 (T2DM). The importance of this study arose from very little evidences and data that discussed menopause with inflammatory and metabolic indicators in Palestine.

MATERIALS AND METHODS

The study was conducted at seven primary health care centers in three regions in Gaza City (Palestinian Territories) from November 2013-May 2014. It was approved ethically from Ethical Committee of University Putra Malaysia (JKEUPM), Ref No.: FPSK_Mac (13) 04 and Helsinki Committee for Ethical Approval of Gaza, Palestine (Number: PHRC/HC/11/13).

A total of 236 women out of 310 screened for eligibility were chosen based on inclusion and exclusion criteria of cross-sectional study. The inclusion criterion was: (1) obese [BMI$\geq$30 kg m^{-2}], (2) HT and/or T2DM patients and (3) aged less than 60 years. The exclusion criterion was: (1) non-obese [BMI$\leq$30 kg m^{-2}], (2) pregnant, (3) patients with regular intake of NSAID's or cholesterol lowering agent statin or Insulin dependent patients and (4) suffer from other systemic diseases that may change physical or laboratory tests like cerebrovascular or heart conditions, renal, thyroid, hepatic, respiratory, chronic inflammatory diseases as arthritis, malignancies or infectious diseases.

Interview questionnaire: Interview questionnaire was used to conduct the information of personal characteristics, lifestyle factors, health history and type of treatments. Personal characteristics factors included the age and menopause status (pre- or post-menopause). Lifestyle habits have discussed two factors; smoking habits and physical activity pattern based on lifestyle explanation of Ellulu *et al*. (2014). The smoking habits assessed according to modified form of the Behavioral Risk Factor Surveillance System (BRFSS) approved by CDC's Survey Data (Department of Health and Human Services, 2011). Physical Activity (PA) pattern evaluated according to modified form of Global Physical Activity Questionnaire (GPAQ) Version-2 that takes into account the Palestinian conditions (WHO., 2002). Health history depended on self-recognition of participants, which included HT patients, T2DM patients and HT+T2DM.

Anthropometric measurements: Anthropometric measurements were assessed as physical measurements. Seca Stadiometer was used to assess BMI according to classification of World Health Organization (WHO., 2000) [obese: ≥30 kg m^{-2}] and Seca 201 non-elastic tape was used to assess Waist Circumference (WC).

Clinical data: Serum biochemical measures included inflammatory indicators: high sensitivity C Reactive Protein (hs-CRP), interleukin 6 (IL-6) and adiponectin and metabolic markers: Fasting Blood Sugar (FBS), Total Cholesterol (TC), Triglyceride (TG), Systolic BP (SBP) and Diastolic BP (DBP). Quantitative method used to assess FBS, TC, TriG and hs-CRP. The CRP turbidimetric latex 1:5 kit was used to measure hs-CRP. Enzymatic colorimetric method with sugar oxidase was used to estimate FBS. Commercial kits used to assess TC and TG, all of quantitative data evaluated by Mindray BS-120 Chemistry Analyzer. The IL-6 and adiponectin assessed via ELISA kits (Sigma-Aldrich®). Finally, validated and standard mercury sphygmomanometer was used to assess systolic and diastolic blood pressure (SBP and DBP).

Data collection and handling: Blood collected by physicians or trained nurse at the health center, 7 mL of blood sample -into two tubes- have drawn into vacutainer tubes. One of tubes used to evaluate quantitative biochemical measures (hs-CRP, FBS, TC and TG), while the second one stored at -80°C after separation of serum to be analyzed through One-Run of ELISA reader in order to assess the IL-6 and adiponectin.

All women completed the informed consent form before attending the interview questionnaire and collecting blood sample. All women were assured of confidentiality and any required information was provided. Every attempt has been made to minimize biases and to conduct the study of the most ethical manner possible.

Statistical analysis: Data was analyzed using the Statistical Package for Social Sciences (SPSS) version 21.0 software (SPSS Inc., Chicago, IL, USA). Chi-square test (χ^2) compared the categorical variables of subjects' characteristics menopause status (pre and post-menopause). Central tendency of continuous variables presented as (median±interquartile range). A non-parametric method of Mann-Whitney U test was used due to skewed variables. The p value of ≤0.05 was considered statistically significant at level of confidence equaled 95%.

RESULTS

This study aimed to evaluate the differences of biomedical data including inflammatory indicators (hs-CRP, IL-6 and adiponectin) and metabolic markers (FBS, TC, TG and BP) between pre-menopause and post-menopause women. All of women participated in the study were obese and diseased by HT and/or T2DM. The involvement of women in the study started in January 2014 and continued to May 2014. The study included 60 women diseased by HT (36 pre-menopause and 24 post-menopause), 58 women diseased by T2DM (25 pre-menopause and 33 post-menopause) and 118 women diseased by HT+T2DM (29 pre-menopause and 89 post-menopause). All of participated women were obese (BMI≥30 kg m^{-2}). The differences between pre-and post-menopause women have presented in Table 1. The included HT women used oral treatment of a beta-blocker (Atenolol) or a calcium channel blocker (Amlodipine) with or without the angiotensin converting enzyme inhibitor (Enalapril). In addition, the included T2DM women used oral treatment of a sulfonylurea (Glibenclamide) with or without the biguanide (Metformin); none of T2DM used insulin in the treatment of hyperglycemia.

Table 1: Difference between pre-menopause and post-menopause women

	HT		T2DM		HT+T2DM	
Menopause status	Pre-(n = 36)	Post-(n = 24)	Pre-(n = 25)	Post-(n = 33)	Pre-(n = 29)	Post-(n = 89)
Age (Years)	40.5±9	56.5±6**	39±10	56±7**	46±7	57±6**
BMI (kg m^{-2})	34.6±5.4	37.5±9.5	33.03±7.7	32.33±6.7	32.18±5.6	36.48±7.1*
WC (cm)	110±16	115±15	102±28	112±12	118±14	120±16
Smoking [PS, NS]	[14,22]	[15,9]	[9,16]	[13,20]	[11,18]	[47,42]
PA [M, L]	[15,21]	[3,21]*	[14,11]	[8,25]*	[6,23]	[8,81]
SBP (mm Hg)	138±18	140±33	120±20	132±24**	133±14	144±21*
DBP (mm Hg)	87.5±10	84.5±13	76±15	80±12	88±14	85±10
FBS (mg dL^{-1})	95.5±35	93±31	184±99	183±55	166±84	171±98
TC (mg dL^{-1})	172.5±55	200±47**	185±46	213±40*	181±55	214±54*
TG (mg dL^{-1})	120.5±82	166±89**	136±64	196±118*	158±85	231±83*
HS-CRP (mg L^{-1})	4.14±6.48	3.10±3.94	5±5.34	4.29±5.69	6.16±5.93	7.92±8.2
IL-6 (pg mL^{-1})	2.25±1.1	2.10±1.23	1.66±0.87	1.9±0.59	1.71±1.45	2.32±1.34*
Adiponectin (mg L^{-1})	11.8±10.1	12.8±4	10.3±3.38	11.2±5.8	11.15±6.8	8.5±5.4

PS: Passive smoker; NS: Non-smoker, PA: Physical activity, M: Moderate, L: Low, *Significant at the level ≤0.05, **Significant at the level ≤0.01, BMI: Body mass index, WC: Waist circumference, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, FBS: Fasting blood sugar, TC: Total cholesterol, TG: Triglyceride, IL-6: Interlink 6, hc-CRP: High sensitivity C reactive protein, HT: Hypertension, T_2DM: Type 2 diabetes mellitus

In HT women: Post-menopause women had significant higher age, TC and TG than pre-menopause women (56.5±9 vs. 40.5±9 years, p<0.01, 200±47 vs. 172.5±55 mg dL^{-1}, p<0.01, 166±89 vs. 120.5±82 mg dL^{-1}, p<0.01, respectively) and significant lower physical activity status (p<0.05) while the significant differences have disappeared on all other comparisons. In T2DM women: post-menopause women had significant higher age, SBP, TC and TG than pre-menopause women (56±7 vs. 39±10 years, p<0.01, 132±24 vs. 120±20 mmHg, p<0.01, 213±40 vs. 185±46 mg dL^{-1}, p<0.05, 196±118 vs. 136±64 mg dL^{-1}, p<0.05, respectively) and significant lower physical activity status (p<0.05), while the significant differences between of them disappeared on all other comparisons. Finally, in HT+T2DM women: Post-menopause women were higher than pre-menopause women on age, BMI, SBP, TC, TG and IL-6 (57±6 vs. 46±7 years, p<0.01, 36.48±7.1 vs. 32.18±5.6 kg m^{-2}, p<0.05, 144±21 vs. 133±14, p<0.05, 214±54 vs. 181±55 mg dL^{-1}, p<0.05, 231±83 vs. 158±85 mg dL^{-1}, p<0.05, 2.32±1.34 vs. 1.71±1.45 pg mL^{-1}, respectively), at time no significant differences detected on the other parameters.

DISCUSSION

The study aimed to assess the differences between pre-menopause and post-menopause women on inflammatory and metabolic indicators based on health status. Women were chosen if HT and/or T2DM and the comparisons involved personal characteristics (anthropometric measurements and lifestyle habits), inflammatory indicators (hs-CRP, IL-6 and adiponectin) and metabolic markers (SBP, DBP, FBS, TC and TG). The personal characteristics of post-menopause women revealed significant higher age in all groups and lower physical activities in HT and T2DM group. Furthermore, BMI difference was significant only in the group of HT+T2DM. The post-menopause women in all groups were significantly higher in lipid profile markers (TC and TG). In addition, SBP was significant higher in post-menopause women among T2DM and HT+T2DM groups, while IL-6 observed significantly lower among pre-menopause women in the group of HT+T2DM. On the other hand, similarities on WC and smoking habits were presented in comparing pre-menopause and post-menopause women in all groups. By evaluating the differences on FBS, hs-CRP and adiponectin for all groups, there were no differences appeared between pre- and post-menopause women.

According to Emanuela *et al*. (2012), the increased BMI progresses to metabolic disorders including dyslipidemia, glucose intolerance and abnormal BP via inflammatory process. Adipocytes in response to obesity increase the synthesis and secretion of pro-inflammatory mediators like IL-6 and Tumor Necrosis Factor-α (TNF-α) and reduce the production of anti-inflammatory marker (adiponectin), which in turn mediate metabolic disorders as shown in Fig. 1. Moreover, the IL-6 triggers the liver to synthesize and secrete the C reactive protein on the circulation which represents the feature of systemic inflammation (Zhang *et al*., 2009). In the HT+T2DM group of the present study, the increased BMI was observed among post-menopause women, which in turn associated with significant higher IL-6 and slight lower Adiponectin associated with higher hs-CRP.

Lee *et al*. (2009) assessed the inflammatory indicators through menopausal transition for healthy women were followed up longitudinally from pre-menopausal to post-menopausal status; significant lower of Adiponectin and higher significant levels of IL-6 and hs-CRP observed in the post-menopause stage compared to pre-menopause. In contrast, Sites *et al*. (2002) did not find significant differences between pre- and post-menopause women on hs-CRP and IL-6 but they mentioned that menopausal condition could increase the incidence of inflammation due significant higher value of TNF-α.

Stefanska *et al*. (2005) investigated the relationship between hormonal changes and cardiovascular risk factors in healthy polish women; pre-menopausal had lower values than postmenopausal women in all parameters; hs-CRP, IL-6, FBS, TC and TG. Likewise, Shende *et al*. (2014) found the levels of TC and TG were higher in post-menopausal women than premenopausal women in India. In addition, Pranita *et al*. (2012) studied the difference of FBS among pre- and post- menopause women; they resulted in significant higher level for the group of post-menopause women.

Kim *et al*. (2014) designed a mini-review study on the postmenopausal effect of hypertension; they stated that the increase of age resulted in high incidence of BP among menopause women due to many factors related to decline of sex hormones "estrogen" and increased BMI as well as other factors like renal functions. In other review study, Maranon and Reckelhoff (2013) collected information related to menopausal women and blood pressure; they stated that the BP was higher

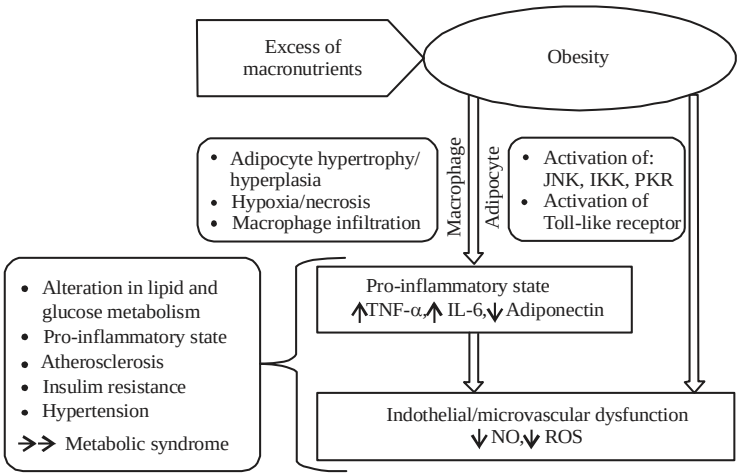

Fig. 1: Link between obesity and metabolic disorder via inflammatory process (Emanuela *et al*., 2012)

in post-menopausal than pre-menopausal women and higher than male in the same age, which indicated increase incidences of cardiovascular diseases. Moreover, Zanchetti *et al*. (2005) concluded that menopause status was associated with a slightly but significantly higher BP, even after adjustment for age and BMI.

CONCLUSION

In summary, as presented by previous studies, post-menopause women are at risk for developing metabolic disorders more than pre-menopause women. Accompanied with higher age and lower physical activity, the status of increased obesity is the main risk factor that induces metabolic disorders via inflammatory process represented by higher IL-6 and lower adiponectin as observed in HT+T2DM. In HT group, the differences observed on TC and TG. In T2DM group, the differences observed on SBP, TC and TG. Finally, in HT+T2DM, much difference differences observed on SBP, TC, TG and IL-6 accompanied with significant difference on BMI. Therefore, the increased BMI associated with poor lifestyle habits in post-menopause women increases the risk for developing metabolic and inflammatory abnormalities in HT and/or T2DM.

LIMITATIONS OF THE STUDY

The data is from a cross-sectional study and therefore, we cannot assess causality, because the data collection of the study run in a short time, or gathered on at only one point in time. Second, the behavioral data, smoking habits and physical activity, are self-reported and subject to recall and social desirability biases.

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