



# Late age at menopause positively associated with obesity-mediated hypertension

Satoshi Morimoto<sup>1</sup> · Atsuhiko Ichihara<sup>1</sup>

**Keywords** Estrogen · Body mass index · Adipocyte · Menarche

Received: 27 January 2023 / Accepted: 10 February 2023 / Published online: 28 February 2023  
© The Author(s), under exclusive licence to The Japanese Society of Hypertension 2023

Menopause is an important process in women's lives. It is characterized by the loss of ovarian activity and permanent cessation of menses and diagnosed after 12 consecutive months of amenorrhea [1]. Estrogen is known to promote vasodilation and lower blood pressure (BP) [2], and thus, loss of estrogen during menopause is considered to drive the development of hypertension in postmenopausal women. Scuteri et al. have reported that postmenopausal women who received hormone replacement therapy had a lower systolic BP increase than non-users over a 10-year follow-up period [3]. Estrogen therapy is recommended in patients with hypertension. Moreover, among postmenopausal women, age at menopause has been reported to be inversely associated with BP and the risk of hypertension [4, 5].

However, several studies have demonstrated a positive association between age at menopause and hypertension [6–8]. Additionally, a positive association between age at menopause and obesity has been reported [9, 10]. In the Japanese Nurse's Health Study, a positive association between age at menopause and hypertension was described; however, the association disappeared after adjusting for body mass index (BMI) [7]. Shen et al. have also reported that the age at menopause was positively associated with hypertension mediated by BMI [6]. Thus, late age at menopause may be associated with higher BP mediated by obesity; however, this presumption remains to be elucidated.

In this issue of *Hypertension Research*, Wu et al. [11] reported data investigating the mediation effects of obesity indicators, including BMI, waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio

(WHtR), on the association between age at menopause and BP in 5,429 natural postmenopausal women in a Chinese cohort study. In this study, a non-linear (U-shape-like) association was observed between age at menopause and hypertension with a nadir of 50 years. No significant association between age at menopause and BP was observed in 1,722 women aged < 50 years. By contrast, among 3,707 women with a menopausal age of ≥50 years, significant and positive associations were observed between age at menopause and systolic or diastolic BP, which were mediated by BMI, WC, WHR, and WHtR.

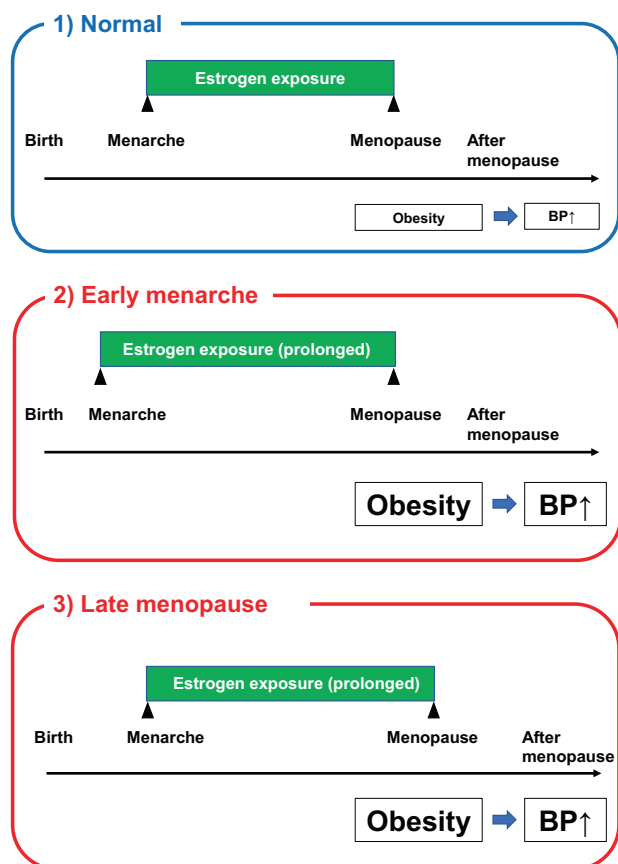
These data are interesting because they were generally consistent with those of previous studies indicating that late age at menopause was associated with higher risks of obesity and elevated BP and have added to the literature by estimating the proportion of mediation through obesity indicators.

The mechanism by which late age at menopause is associated with higher BP mediated by obesity remains unclear. However, prolonged estrogen exposure may play a key role in this phenomenon (Fig. 1). Estrogen reportedly causes accumulation of adipose tissues [12]. Additionally, adiposity has been considered a mediator in the association between earlier age at menarche and a higher prevalence of hypertension [13, 14]. Therefore, prolonged estrogen exposure may induce obesity and hypertension. However, neither obesity indicators nor BP data at the time of menopause were included in this study. The loss of estrogen with menopause shifts adipose tissue accumulation away from the lower body towards central/abdominal deposition [15]. Furthermore, the association between estrogen and adiposity may be bidirectional [16]. Therefore, causal relationships cannot be estimated in a cross-sectional study, as in this study. Longitudinal studies on obesity indicators and BP before and after the onset of menopause should be conducted in the future.

In conclusion, this study reveals a significant finding that maintaining a healthy body weight may be beneficial in preventing BP elevation after menopause, especially in

✉ Satoshi Morimoto  
morimoto.satoshi@twmu.ac.jp

<sup>1</sup> Department of Endocrinology and Hypertension, Tokyo Women's Medical University, Tokyo, Japan



**Fig. 1** Proposed mechanism of blood pressure elevation in women with early menarche and those with late menopause. In women with early menarche and those with late menopause, prolonged exposure to estrogen may induce obesity, causing elevated blood pressure after menopause. BP blood pressure

women experiencing menopause at a late age. Further studies focusing on the associations between age at menopause and metabolic factors such as obesity, glycolipid metabolism, and BP are warranted.

### Compliance with ethical standards

**Conflict of interest** The authors declare no competing interests.

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

### References

1. Goodman NF, Cobin RH, Ginzburg SB, Katz IA, Woode DE, American Association of Clinical E. American Association of

Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of menopause. *Endocr Pract.* 2011;17 Suppl 6:1–25.

2. Caulin-Glaser T, Garcia-Cardena G, Sarrel P, Sessa WC, Bender JR. 17 beta-estradiol regulation of human endothelial cell basal nitric oxide release, independent of cytosolic Ca<sup>2+</sup> mobilization. *Circ Res.* 1997;81:885–92.
3. Scuteri A, Bos AJ, Brant LJ, Talbot L, Lakatta EG, Fleg JL. Hormone replacement therapy and longitudinal changes in blood pressure in postmenopausal women. *Ann Intern Med.* 2001;135:229–38.
4. Song L, Shen L, Li H, Liu B, Zheng X, Zhang L, et al. Age at natural menopause and hypertension among middle-aged and older Chinese women. *J Hypertens.* 2018;36:594–600.
5. Izumi Y, Matsumoto K, Ozawa Y, Kasamaki Y, Shinno A, Ohta M, et al. Effect of age at menopause on blood pressure in postmenopausal women. *Am J Hypertens.* 2007;20:1045–50.
6. Shen L, Wang L, Hu Y, Liu T, Guo J, Shen Y, et al. Associations of the ages at menarche and menopause with blood pressure and hypertension among middle-aged and older Chinese women: a cross-sectional analysis of the baseline data of the China Health and Retirement Longitudinal Study. *Hypertens Res.* 2019;42:730–8.
7. Lee JS, Hayashi K, Mishra G, Yasui T, Kubota T, Mizunuma H. Independent association between age at natural menopause and hypercholesterolemia, hypertension, and diabetes mellitus: Japan nurses' health study. *J Atheroscler Thromb.* 2013;20:161–9.
8. Roa-Diaz ZM, Asllanaj E, Amin HA, Rojas LZ, Nano J, Ikram MA, et al. Age at natural menopause and blood pressure traits: mendelian randomization study. *J Clin Med.* 2021;10:4299.
9. Yang L, Li L, Millwood IY, Lewington S, Guo Y, Sherliker P, et al. Adiposity in relation to age at menarche and other reproductive factors among 300 000 Chinese women: findings from China Kadoorie Biobank study. *Int J Epidemiol.* 2017;46:502–12.
10. Park CY, Lim JY, Park HY. Age at natural menopause in Koreans: secular trends and influences thereon. *Menopause.* 2018;25:423–9.
11. Wu YJ, Jiang CQ, Zhu T, Jin YL, Zhu F, Zhou BJ, et al. Obesity indicators as mediators on the association between age at menopause and blood pressure. *Hypertens Res.* 2023. <https://doi.org/10.1038/s41440-023-01184-3>.
12. Krotkiewski M, Bjorntorp P, Sjostrom L, Smith U. Impact of obesity on metabolism in men and women. Importance of regional adipose tissue distribution. *J Clin Invest.* 1983;72:1150–62.
13. Liu D, Qin P, Liu Y, Sun X, Li H, Wu X, et al. Association of age at menarche with hypertension in rural Chinese women. *J Hypertens.* 2021;39:476–83.
14. Zhang L, Li Y, Zhou W, Wang C, Dong X, Mao Z, et al. Mediation effect of BMI on the relationship between age at menarche and hypertension: The Henan Rural Cohort Study. *J Hum Hypertens.* 2020;34:448–56.
15. Lee CG, Carr MC, Murdoch SJ, Mitchell E, Woods NF, Wener MH, et al. Adipokines, inflammation, and visceral adiposity across the menopausal transition: a prospective study. *J Clin Endocrinol Metab.* 2009;94:1104–10.
16. Kutzer K, Hill JL, McIver KB, Foster MT. Lipedema and the potential role of estrogen in excessive adipose tissue accumulation. *Int J Mol Sci.* 2021;22:11720.