Dietary Patterns, Metabolomic Profiles, and Metabolic Outcomes by Menopausal Status

Barbieri Giulia[1,2,3], *Naixin Zhang*[2,3], *Marta Trius-Soler*[2,3], *Cristian Pattaro*[1], *Marta Guasch-Ferré*[2,3], *Hantikainen Essi Marjatta*[1]

(1) *Eurac Research, Institute for Biomedicine, Bolzano, Italy*
(2) *Department of Public Health, Section of Epidemiology, University of Copenhagen*
(3) *Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen*

CORRESPONDING AUTHOR: *Barbieri Giulia, giulia.barbieri@eurac.edu*

INTRODUCTION

Menopause is a critical period marked by significant metabolic and hormonal changes that impact cardiometabolic disease risk.[1] Diet plays a crucial role in lipid metabolism and visceral adiposity, key components of cardiometabolic health.[2] Metabolomics, the analysis of small molecules in biological samples, offers a tool for capturing both dietary metabolites and systemic adaptations to habitual diet.[3] In addition to provide a more objective assessment of dietary intake it can reveal different profiles between subgroups of individuals, such as women at different reproductive stages.[4] However, the underlying mechanisms by which diet affects metabolism after menopause are not yet well understood, limiting the development of targeted dietary strategies to mitigate health risks in female populations.[5]

OBJECTIVE

This investigation aimed to examine the role of menopausal status in the association between dietary patterns, metabolomic profiles associated with the dietary patterns, and lipid profile. To achieve this objective, two specific aims were pursued:

1. To determine the metabolomic profile associated with different dietary patterns according to menopausal status
2. To explore how diet influences the lipid profile and visceral fat by menopausal status, considering potential differences in the metabolome.

METHODS

We conducted a cross-sectional analysis on 1,179 women participating in the Cooperative Health Research In South Tyrol (CHRIS) study,[6] stratifying by menopausal status, defined based on an algorithm incorporating self-reported information and age. We excluded women who were pregnant, non-fasting, or in the menopause transition phase at the study visit.

To evaluate the dietary patterns, we derived three well-established healthy dietary indexes: Planetary Health Diet Index (PHDI), Plant-based Diet Index (PDI), and Alternative Healthy Eating Index (AHEI). Additionally, we included the Dietary Inflammatory Index (DII) to specifically investigate the role of inflammation. The outcomes were visceral fat (%), total cholesterol (mg/dL), HDL cholesterol (mg/dL), LDL cholesterol (mg/dL), and log-transformed triglycerides (log-mmol/L) concentrations.

We used elastic net regression to identify metabolites associated with each dietary index. The dataset was divided into training (70%) and testing (30%) sets. In the training set, we performed multiple iterations of 10-fold cross-validation with 100 different seeds. Optimal lambda values were selected based on the consensus mode of the number of selected features across iterations. For each dietary index, we estimated a metabolite score, calculated as the weighted sum of selected metabolite concentrations. The trained models were subsequently applied and validated in the testing set to compute final dietary metabolite scores. Associations between dietary indexes, metabolite scores, and outcomes were assessed using linear regression models. All models were adjusted for age, physical activity, smoking, self-reported diabetes and hypertension, education, following a special diet, total energy intake, and self-reported medications for lipid control. Addi-

DOI: 10.54103/2282-0930/29189

tionally for pre-menopausal women, we adjusted for contraception use, while for post-menopausal women we adjusted for the usage of hormone replacement therapy.

Results:

In this sample of women, the pre-menopause group (n=762) had a median age of 35 years (interquartile range, IQR: 25-44 years) and a median BMI of 23 kg/m2 (IQR: 21-27 kg/m2). The post-menopause group (n=417) had a median age of 62 years (IQR: 56-69 years) and a median BMI of 26 kg/m2 (IQR: 23-30 kg/m2).

The selection of metabolites revealed group-specific profiles, with a modest overlap between the pre-menopause and post-menopause groups, except for the DII, which showed distinct metabolomic profiles in the two groups. Glycerophospholipids were consistently selected across almost all dietary patterns and in both groups.(Figure)

When examining associations between dietary indexes and outcomes,(Figure) the PDI and the AHEI were associated with lower visceral fat and LDL cholesterol among pre-menopausal women. In the post-menopausal group, the PHDI was positively associated with LDL cholesterol, while AHEI remained negatively associated with visceral fat.

When examining associations between metabolite scores and outcomes,(Figure) in the pre-menopausal group, all metabolite scores were associated with lower visceral fat. The PDI-metabolite score was additionally associated with lower total cholesterol. The PHDI-metabolite score was associated with lower HDL cholesterol and higher triglyceride levels. The DII-metabolic score was associated with higher levels of total, LDL, and HDL cholesterol, and with lower triglycerides. The AHEI-metabolite score was also associated with higher triglyceride levels. In post-menopausal women, the DII-metabolite score was negatively associated with total, LDL, and HDL cholesterol. The PHDI-metabolite score was associated with lower total and HDL cholesterol. The AHEI-metabolite score was positively associated with HDL cholesterol.

CONCLUSION

The metabolomic profiles associated with dietary patterns varied by menopausal status. We observed a general consistency when investigating associations between dietary indexes, their corresponding metabolomic profiles, and lipid marker concentrations. However, the associations with metabolite scores were notably stronger than those with dietary index, suggesting that while dietary patterns do influence metabolic outcomes, the specific metabolomic profiles might provide a more precise and robust measure of these associations.

REFERENCES

1. El Khoudary SR, Aggarwal B, Beckie TM et al., Menopause Transition and Cardiovascular Disease Risk: Implications for Timing of Early Prevention: A Scientific Statement From the American Heart Association. Circulation. 2020 Dec 22;142(25):e506-e532.
2. Guasch-Ferré M, Bhupathiraju SN, Hu FB. Use of Metabolomics in Improving Assessment of Dietary Intake. Clin Chem. 2018 Jan;64(1):82-98.
3. Amiri M, Karabegović I, van Westing AC et al., Whole-diet interventions and cardiovascular risk factors in postmenopausal women: A systematic review of controlled clinical trials. Maturitas. 2022 Jan;155:40-53.
4. Erdélyi A, Pálfi E, Tűű L et al., The Importance of Nutrition in Menopause and Perimenopause-A Review. Nutrients. 2023 Dec 21;16(1):27.
5. Picó C, Serra F, Rodríguez AM et al., Biomarkers of Nutrition and Health: New Tools for New Approaches. Nutrients. 2019 May 16;11(5):1092.
6. Pattaro C, Gögele M, Mascalzoni D, et al., The Cooperative Health Research in South Tyrol (CHRIS) study: rationale, objectives, and preliminary results. J Transl Med. 2015 Nov 5;13:348.

DOI: 10.54103/2282-0930/29189