

The effect of low advanced glycation end product diet on bone health and cardio-metabolic parameters in overweight and obese postmenopausal women: study protocol for a randomised controlled trial (AGEs study)

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ABSTRACT

Advanced glycation end products (AGEs) have been suggested to play an important role in osteoporosis. However, no randomised controlled trial has investigated the effect of a diet with low AGEs on densitometric parameters. This study will evaluate the effect of a 12-month low AGEs diet on bone health and cardio-metabolic parameters in postmenopausal overweight and obese women. In total, 80 subjects will be included in the study and randomly divided into two groups: low AGEs diet and standard AGEs diet for 12 months. The mineral density and content will be measured at the lumbar spine, femoral neck, and total body during the pre- and post-intervention period. Selected markers of bone formation and resorption will be assessed. Anthropometric parameters and body composition will be evaluated and markers of glucose, insulin, lipid metabolism, inflammatory and endothelial parameters will be measured. Adherence to the diet will be monitored using dietary records.

Research Project Objectives

The study's primary aim will be to assess the effect of low advanced glycation end products (AGEs) diet on bone mineral density (BMD) and content (BMC), as well as markers of bone formation and resorption in overweight and obese postmenopausal women. Moreover, the study will examine the impact of a low AGEs diet on cardio-metabolic parameters, including anthropometric parameters, body composition, glucose and insulin homeostasis, lipid metabolism, endothelial dysfunction parameters and inflammatory markers. The following research null hypotheses were formulated:

1. Low AGEs diet does not affect BMD and BMC in overweight and obese postmenopausal women.
2. Low AGEs diet does not affect markers of bone formation and resorption in overweight and obese postmenopausal women.
3. Low AGEs diet does not affect anthropometric parameters and body composition in overweight and obese postmenopausal women.
4. Low AGEs diet does not affect glucose and insulin homeostasis in overweight and obese postmenopausal women.
5. Low AGEs diet does not affect lipid metabolism in overweight and obese postmenopausal women.
6. Low AGEs diet does not affect endothelial dysfunction parameters in overweight and obese postmenopausal women.
7. Low AGEs diet does not affect inflammatory parameters in overweight and obese postmenopausal women.

8. Low AGEs diet does not affect blood pressure in overweight and obese postmenopausal women.

Research Plan and Basic Concept

Basic Concept

The menopause period is often a turning point in a woman's life. Menopause is associated with an increase in fat mass, insulin resistance, dyslipidaemia and endothelial dysfunction, as well as a higher prevalence of osteoporosis [1]. Decreased ovarian oestrogen production and relative androgen excess around menopause onset are some of the most studied factors linking menopause, bone and cardiometabolic health [2]. Excessive body weight, often observed in postmenopausal women, seems to have a particularly unfavourable effect on bone metabolism and cardio-metabolic markers. Unfortunately, factors protecting against the development of perimenopausal disorders have not been identified so far [3].

AGEs include a diverse group of compounds that are the products of nonenzymatic reactions between reducing sugars and proteins, lipids or nucleic acids [4]. The majority of AGEs are obtained from the consumption of food. Foods of animal origin, particularly those rich in protein and fat, exhibit the highest levels of AGEs, whereas carbohydrate-rich foods demonstrate the lowest amounts. Additionally, cooking methods such as grilling, roasting, broiling, or frying produce higher levels of AGEs than boiling, poaching, stewing, or steaming [5].

AGEs have a significant impact on human health. Previous studies showed an association between AGEs levels and a variety of conditions such as diabetes mellitus [6], cardiovascular diseases [7], metabolic syndrome [8], Alzheimer's disease [9], some cancer [10] or polycystic ovary syndrome [11]. Elevated AGEs levels were also associated with a higher risk of all-cause mortality [12]. Several studies also investigated the effects of AGEs on bone health [13–17]. It has been suggested that AGEs might affect bone through their accumulation in collagen fibres [13]. Moreover, AGEs have been found to significantly inhibit osteoblast proliferation, differentiation and mineralisation and induce osteoblast apoptosis [14]. Circulating AGEs also lead to decreased bone strength by damage to structural bone [15]. Higher AGEs levels were observed in subjects with osteoporosis and osteopenia compared to healthy participants. Moreover, a negative correlation was found between AGEs levels and BMD. Yang et al. [16] demonstrated that women with elevated AGEs concentrations had a 5.34 times higher risk of developing osteopenia in terms of the lumbar spine T-score and a 3.31 times higher risk of osteopenia in relation to the hip T-score. In another study, pentosidine, a type of AGEs, was negatively correlated with BMC in adolescents, suggesting that the accumulation of AGEs may affect peak bone mass in young people [17]. While numerous studies have shown the negative impact of a high AGEs diet on bone properties in animal models [18–19], research is scarce regarding the role of dietary AGEs in human bone health. Only one human study investigated the relationship between AGEs intake and bone health. It demonstrated a positive association with the prevalence of prevalent vertebral, a non-significant trend for major osteoporotic fractures, and no association with BMD and trabecular bone score [20].

Several studies demonstrated a relationship between dietary AGEs intake and cardio-metabolic parameters [21–25]. A recent meta-analysis reported a reduction in insulin resistance, fasting insulin, total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in the low AGEs group compared with the high AGEs group [21]. Moreover, another meta-analysis has shown a significant decrease in body mass index (BMI), weight and leptin and an increase in adiponec-

tin levels after consumption of the low AGEs diet compared to the high AGEs diet [22]. On the other hand, other studies showed that consumption of low AGEs diet did not improve the inflammatory and endothelial markers [23–25]. Nevertheless, it has been reported that the reduction in dietary AGEs with a low-fat plant-based diet was associated with a significant reduction in the frequency of severe and moderate-to-severe postmenopausal hot flashes, independent of changes in energy intake and weight loss [26]. However, most trials investigating the effect of a low AGEs diet are limited by a short duration period and a small sample size. Therefore, further randomised controlled trials with a correct methodology and increased quality assessing the effect of low AGEs diet on cardio-metabolic markers are needed.

Research Plan

The study followed a parallel-group, prospective, randomised controlled trial design. The protocol was registered in the Deutsches Register Klinischer Studien (registration number: DRKS00034643, registration date: 16 July 2024) and was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [27–28]. Ethical approval for the study was obtained from the Bioethical Committee of Poznań University of Medical Sciences (ref. 112/24, dated 8 February 2024), and the research will be conducted in compliance with the principles of the Declaration of Helsinki [29]. Funding for the study was provided by the Nutricia Foundation (Bobrowiecka 8 Str., Warsaw, Poland). However, the sponsor had no involvement in the study design and will have no role in data collection, management, analysis, interpretation, manuscript writing, or the decision to submit the paper for publication.

Research team members will obtain informed consent from all study participants. Participants will be informed that they can withdraw from the study at any time without facing any consequences. The informational materials provided to potential volunteers include detailed information about the study's objectives and nature. All biological samples (e.g., blood samples) obtained from participants will be anonymised and identified using unique patient codes. Study participants will be assured that their personal data will

not be shared with others and that they retain the right to access, correct, or delete their data. Additionally, participants may submit a complaint to the Personal Data Protection Office in Warsaw (Stawki 2 Str., Warsaw, Poland) if they believe their data has been processed in violation of data protection regulations. The study will utilise the RedCap (Vanderbilt University, Nashville, Tennessee, USA) tool for data collection, anonymisation, validation, quality control, and export. Data storage procedures will comply with the regulations of the Poznan University of Medical Sciences, Poznań, Poland. All electronic data will be encrypted and protected against unauthorised access. Anonymised data stored in electronic files will follow strict security measures. For any data stored in paper format, documents will be organised according to participant codes and kept in binders. These binders will be stored in locked cabinets within secure rooms to prevent unauthorised access. Before statistical analysis, all collected data will undergo careful review to identify and correct any errors or anomalies. The final trial dataset will be retained by the Principal Investigator and made available upon reasonable request.

Recruitment for the study will be carried out in clinics, primary healthcare facilities, and other medical centres in Poznań (Poland) and the surrounding areas. Additionally, information about the recruitment will be sent by post to offices, companies, universities, and other educational institutions within the Poznań district, as well as to senior clubs and local media outlets. The recruitment campaign will also be promoted through social media platforms.

Potential participants will be screened by a physician at the Department of Pediatric Gastroenterology and Metabolic Diseases, Poznań University of Medical Sciences, Poland, to ensure compliance with the protocol requirements. The following inclusion criteria will be used:

- › Sex: women,
- › BMI ≥ 25.0 kg/m²,
- › Age: 50–70 years,
- › Menopause: at least 12 months prior to study enrolment.

Exclusion criteria will include:

- › Menopause before the age of 40 years,
- › Previously diagnosed osteoporosis or other serious bone diseases,

- › Taking medications that affect bone metabolism,
- › Taking hormone replacement therapy,
- › Taking calcium or vitamin K supplements in the last 3 months,
- › Diagnosed acute or chronic autoimmune diseases, inflammatory diseases, infectious diseases, viral, bacterial or parasitic infections,
- › Malignant neoplastic disease treated with chemo- or radiotherapy within the last 5 years,
- › Acute and chronic kidney and liver diseases,
- › Underactive or overactive parathyroid glands.

The study population (n = 80) will be randomised (allocation ratio 1:1) into two groups: low AGEs (n = 40) and standard AGEs (n = 40). During the one-year intervention period, participants in the low AGEs group will receive guidance from dietitians on reducing AGE intake. Dietitians will monitor compliance through dietary records and monthly phone calls with the study participants. Based on results from previous studies [22,23], it is estimated that the average AGEs intake in the study population before the intervention will exceed 15,000 kU AGEs/day. During the intervention, the AGEs intake in the low AGEs group is expected to be three times lower than in the standard AGEs group. All participants will be instructed to follow an isocaloric diet and supplement with vitamin D throughout the intervention. They will also be advised to maintain their usual level of physical activity. Additionally, participants will be required to report any adverse effects to the research team.

The minimum sample size was calculated using G*Power software (University of Kiel, Kiel, Germany). To obtain a power of 90% ($\alpha = 0.05$, $\beta = 0.1$), at least 33 subjects per group should be included in the study. Assuming a maximum 20% drop-out rate, at least 40 subjects per group will be recruited.

Randomisation will be performed by Python using numpy library by an independent researcher. Blocked randomisation (with stratification according to age, 25(OH)D levels and whether participants have previously taken vitamin D supplementation) will be performed. A randomisation list will be generated, and the allocation sequence list will be concealed until the interventions are assigned. Neither the study participants nor the research staff will know the allocation

sequences. Due to the nature of the intervention, only outcome assessors and data analysts will be blinded.

Research Methodology

The anthropometric parameters, including body weight, body height, waist and hip circumferences, will be measured, and BMI and waist-to-hip ratio (WHR) will be calculated pre- and post-intervention. Self-measured body weight will also be monitored monthly during the intervention. Body composition (the percentage of fat (%FM) and free-fat mass (%FFM) for the total body and individual body regions (arms, trunk, legs, head), male-specific (android) and female-specific (gynoid) area, visceral adipose tissue (VAT), appendicular lean mass index (ALMI) and lean mass index (LMI) and densitometric parameters (BMD and BMC at the lumbar spine (L1-L4), femoral neck and total body) will be assessed before and after the intervention using dual-energy X-ray absorptiometry methods utilising the DEXA Hologic QDR Discovery (Bedford, Massachusetts, USA) analyser. Pre- and post-intervention systolic (SBP) and diastolic blood pressure (DBP) will be measured using an electronic blood pressure monitor (Omron M2, Kyoto, Japan). Prior to and following the intervention the following biochemical parameters will be assessed: osteocalcin, bone-specific alkaline phosphatase (BSAP), cross-linked C-terminal telopeptide of type I collagen (CTX-I), fasting glucose and insulin, TC, low-density LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), asymmetric dimethylarginine (ADMA), soluble vascular cell adhesion molecule-1 (sVCAM-1), high-sensitivity C-reactive protein (hs-CRP), 25-hydroxyvitamin D (25(OH)D) and AGEs levels. Moreover, follicle-stimulating, luteinising, oestradiol, progesterone and parathyroid hormones levels will be measured during the enrolment phase to confirm participants' menopausal status and to exclude underactive or overactive parathyroid glands. Glucose, insulin, lipid profile, hsCRP, osteocalcin, BSAP, 25(OH)D and hormones will be measured in the commercial laboratory (Diagnostyka sp. z o.o., Życzkowskiego 16 Str., Cracow, Poland) using standard laboratory procedures and other parameters will be evaluated in the Laboratory of

the Department of Pediatric Gastroenterology and Metabolic Diseases using enzyme-linked immunosorbent assay method. Homeostasis model assessment of insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) will be calculated. The intake of different food groups will be evaluated using the Dietary Habits and Nutrition Beliefs Questionnaire [30] before, during and after the intervention. Dietary habits will also be assessed using 3-day dietary records before and during the intervention to check protocol requirements using the Aliant software (Anmarsoft, Gdańsk, Poland). AGEs contents in diet will be estimated using Uribarri et al. [5] database. Physical activity will be determined before, during and after the intervention using the International Physical Activity Questionnaire [31]. Study participants will also be asked to complete medical history and socio-economic questionnaires before and after the intervention. The study design is illustrated in Figure 1.

The study's primary outcomes will include changes (post- minus pre-intervention values) in BMD, BMC, osteocalcin, BSAP and CTX-I levels. The secondary outcomes will be changes in fasting glucose and insulin, HOMA-IR, QUICKI, TC, LDL-C, HDL-C, TG, ADMA, sVCAM-1, hs-CRP, SBP, DBP, body weight, waist, hip circumference, BMI, %FM, %FFM, VAT, ALMI, LMI, AGEs, 25(OH)D.

Python (pandas, scipy and numpy libraries) will be used for all data analysis. A two-sided p-value < 0.05 will be considered statistically significant. The overall characteristics of subjects will be expressed as means and standard deviations with a 95% confidence interval if the data is normally distributed; otherwise, data will be expressed as medians and interquartile ranges. The normality of the distribution of the variable will be verified using the Shapiro-Wilk test of normality. Comparisons between two unpaired groups will be determined using t-tests or Mann-Whitney U tests. The paired t-test or Wilcoxon test will be used to analyse the statistical significance of the pre- and post-intervention variables. Moreover, a generalised linear model will be used to analyse the influence of the intervention on analysed parameters. Contingency tables will be used to assess relationships between categorical variables. Depending on data distribution, parametric (Pearsons) or nonparametric tests (Spearman rank) will be applied to assess correlations. Uni-

and multivariate logistic and linear regression analyses will be performed.

Measurable Effects and Expected Results

It has been shown that subjects with osteoporosis have higher serum AGEs levels than healthy individuals and serum AGEs concentrations are negatively correlated with BMD [16]. AGEs have also significantly inhibited osteoblast proliferation, differentiation and mineralisation and induced osteoblast apoptosis [14]. These observations suggest that AGEs may play an important role in bone health. Moreover, several studies reported that a low AGE diet might improve anthropometric parameters, body composition, and lipid and inflammatory profiles [21–25].

This is the first randomised controlled trial to assess the effect of low AGEs diet on BMD and BMC, selected markers of bone formation and resorption in postmenopausal overweight and obese women. The study also fills gaps in the knowledge of the effect of a low AGEs diet on cardio-metabolic parameters. The results of this study should give a better insight into the effect of a low AGEs diet on bone health and cardio-metabolic parameters in overweight and obese postmenopausal women.

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Conflict of interest statement

The authors declare no conflict of interest.

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