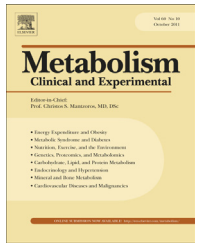
Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com



Clinical Science

Walnut-enriched diet reduces fasting non-HDL-cholesterol and apolipoprotein B in healthy Caucasian subjects: A randomized controlled cross-over clinical trial

Liya Wu[a], *Katja Piotrowski*[a], *Tiina Rau*[a], *Elisa Waldmann*[a], *Uli C. Broedl*[a], *Hans Demmelmair*[b], *Berthold Koletzko*[b], *Renee G. Stark*[c], *Jutta M. Nagel*[a], *Christos S. Mantzoros*[d], *Klaus G. Parhofer*[a,*]

[a] *Division of Endocrinology and Metabolism at Medical Department 2, University of Munich Medical Center, Munich, Germany*
[b] *Division of Metabolic and Nutritional Medicine at Dr. von Hauner Children's Hospital, University of Munich Medical Center, Munich, Germany*
[c] *Helmholtz Zentrum Muenchen, Institute for Health Economics and Healthcare Management, Neuherberg, Germany*
[d] *Division of Endocrinology, Diabetes, and Metabolism at Beth Israel Deaconess Medical Center, Boston, MA, USA*

ARTICLE INFO

Article history:
Received 26 July 2013
Accepted 8 November 2013

Keywords:
Nuts
Lipids
Glucose
Endothelial function
Peripheral artery tonometry

ABSTRACT

Background. Walnut consumption is associated with reduced risk of coronary heart disease (CHD).

Objective. We assessed the effect of walnuts on lipid and glucose metabolism, adipokines, inflammation and endothelial function in healthy Caucasian men and postmenopausal women ≥50 years old.

Design. Forty subjects (mean ± SEM: age 60 ± 1 years, BMI 24.9 ± 0.6 kg/m^2; 30 females) were included in a controlled, cross-over study and randomized to receive first a walnut-enriched (43 g/d) and then a Western-type (control) diet or vice-versa, with each lasting 8 weeks and separated by a 2-week wash-out. At the beginning and end of each diet phase, measurements of fasting values, a mixed meal test and an assessment of postprandial endothelial function (determination of microcirculation by peripheral artery tonometry) were conducted. Area under the curve (AUC), incremental AUC (iAUC) and treatment × time interaction (shape of the curve) were evaluated for postprandial triglycerides, VLDL-triglycerides, chylomicron-triglycerides, glucose and insulin.

Abbreviations: ALA, alpha-linolenic acid; apoB, apolipoprotein B; AUC, area under the curve; BMI, body mass index; CHD, coronary heart disease; CM, chylomicrons; CRP, C-reactive protein; fRHI, Framingham-reactive hyperemia index; HDL, high-density lipoprotein; iAUC, incremental area under the curve; HOMA-IR, homeostasis model assessment estimate of insulin resistance; ICAM-1, intercellular adhesion molecule-1; LDL, low-density lipoprotein; MUFA, monounsaturated fatty acids; PAT, peripheral arterial tonometry; PUFA, polyunsaturated fatty acids; QUICKI, quantitative insulin-sensitivity check index; RHI, reactive hyperemia index; SFA, saturated fatty acids; VCAM-1, vascular cell adhesion molecule-1; VLDL, very low-density lipoprotein.

* *Corresponding author at:* Medical Department 2 – Grosshadern, University of Munich, Marchioninistraße 15,81377 Munich, Germany. Tel.: +49 89 7095 3010; fax: +49 8879.
E-mail address: klaus.parhofer@med.uni-muenchen.de (K.G. Parhofer).

http://dx.doi.org/10.1016/j.metabol.2013.11.005

Results. Compared with the control diet, the walnut diet significantly reduced non-HDL-cholesterol (walnut vs. control: −10 ± 3 vs. −3 ± 2 mg/dL; p = 0.025) and apolipoprotein-B (−5.0 ± 1.3 vs. −0.2 ± 1.1 mg/dL; p = 0.009) after adjusting for age, gender, BMI and diet sequence. Total cholesterol showed a trend toward reduction (p = 0.073). Fasting VLDL-cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and glucose, insulin, HOMA-IR, and HbA1c did not change significantly. Similarly, fasting adipokines, C-reactive protein, biomarkers of endothelial dysfunction, postprandial lipid and glucose metabolism and endothelial function were unaffected.

Conclusion. Daily consumption of 43 g of walnuts for 8 weeks significantly reduced non-HDL-cholesterol and apolipoprotein-B, which may explain in part the epidemiological observation that regular walnut consumption decreases CHD risk.

1. Introduction

Ample evidence suggests that regular nut consumption reduces the risk of coronary heart disease (CHD). A pooled analysis of 4 prospective cohort studies showed that for each weekly serving of nuts (approximately 30 g), death from CHD decreased by 8.3% [1]. In light of accumulating evidence, the U.S. Food and Drug Administration issued a qualified health claim for nuts in 2003 and a separate health claim for walnuts in 2004, stating that daily walnut consumption of 1.5 oz (approximately 42.5 g) in the context of a low saturated fat and low cholesterol diet reduces the risk of heart disease [2].

Nuts are nutrient-dense foods with a high content of fat. While most nuts are high in monounsaturated fatty acids (MUFA), walnuts are predominantly composed of polyunsaturated fatty acids (PUFA) (47% of total weight), mainly linoleic acid and alpha-linolenic acid (ALA) [3]. Walnuts are also the only nuts with a significant amount of ALA (9%) [4], a plant-based essential omega-3 fatty acid that has been shown to elicit anti-inflammatory [5] and anti-atherogenic effects [6]. An inverse relationship between ALA and death from CHD was reported in a meta-analysis by Pan et al., who concluded that each increment of 1 g/d intake of ALA was associated with a 10% risk reduction for CHD death [7]. ALA is also the precursor of endogenous synthesis of eicosapentaenoic and docosahexaenoic acids, which are long chain n-3 PUFA typically found in oily fish and have been associated with a decrease in triglycerides [8]. In addition to a favorable lipid profile, walnuts also contain other potentially cardioprotective compounds such as fiber, phytosterols, L-arginine, polyphenols, minerals and tocopherols [9].

Numerous human feeding trials have demonstrated beneficial effects of walnuts on blood lipid profile [10]. Several studies also showed that walnuts improved endothelial function in hypercholesterolemic [11,12] and type 2 diabetic subjects [13]. While epidemiological evidence suggested an inverse relationship between walnut consumption and type 2 diabetes [14], intervention studies have not consistently shown an improvement in glycemic control [15–19]. Previous studies focused primarily on examining the effect of walnuts on fasting lipid and glucose metabolism in subjects at increased risk of developing CHD (risk factors such as metabolic syndrome, type 2 diabetes, and hypercholesterolemia) [10]. The majority of the subjects in the few studies involving healthy individuals were selected from a younger age group (< 50 years) [20–23]. Therefore, we aimed to study whether the favorable changes in fasting lipid and glucose metabolism as well as endothelial function observed in previous studies would also apply to healthy Caucasian men and women of a higher age group (≥ 50 years). Since postprandial lipid [24] and glucose parameters [25] are also linked to atherosclerosis, we additionally analyzed these parameters together with circulating levels of adipokines and C-reactive protein (CRP).

2. Subjects and methods

The study was registered at ClinicalTrials.gov (NCT01188902) and performed between January 2011 and April 2012 at Medical Department 2 at the University of Munich Medical Center. The Study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures were approved by the ethics committee of the Faculty of Medicine of the University of Munich.

2.1. Subjects

All subjects were recruited through posters on hospital bulletin boards and in pharmacies or via an article in a local newspaper and in the University of Munich hospital magazine. The screening evaluation involved obtaining subject's medical history, a physical examination and a fasting blood test. Individuals with obesity (BMI ≥ 35 kg/m^2), LDL cholesterol ≥ 190 mg/dL, triglycerides ≥ 350 mg/dL, acute or chronic inflammation, acute malignancy, uncontrolled thyroid disease or other endocrine diseases, any systemic disease (e.g. hypertension, diabetes mellitus, liver or kidney disease), known nut allergy or lactose intolerance were excluded. Individuals with tobacco, drug or alcohol abuse (women: > 70 g/week, men: > 140 g/week) or treatment with antidiabetic, hypolipidemic, antihypertensive or anti-inflammatory drugs, vitamin E or hormonal replacement therapy in the previous 3 months were also excluded. A total of 96 Caucasian men and postmenopausal women aged 50 and above were interviewed and examined. Of 72 eligible subjects, 15 declined participation. Fifty-seven subjects were randomized. Eleven subjects dropped out before study