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# Left ventricular remodelling changes without concomitant loss of myocardial fat after long-term dietary intervention☆,☆☆

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ABSTRACT

*Background:* Accumulation of myocardial triglycerides (MTG) is associated with impaired left ventricular (LV) remodelling and function in obese and diabetic subjects. The role of MTG accumulation in development of heart failure in this group of patients is unknown. Short-term studies suggest that diets that lead to weight loss could mobilize MTG, with a favourable effect on cardiac remodelling. In a 24-month, randomized, investigator-blinded study, we assessed the effect of two different diets and subsequent weight loss on cardiac function and MTG in postmenopausal women.

*Methods:* Sixty-eight healthy postmenopausal women with body mass index [BMI] ≥27 kg/m$^2$ were randomized to an ad libitum Palaeolithic diet (PD) or a Nordic Nutrition Recommendation (NNR) diet for 24 months. Morphology, cardiac function, and MTG levels were measured using magnetic resonance (MR) scanning, including proton spectroscopy at baseline and 6 and 24 months.

*Results:* Despite mean weight losses of 4.9 (1.0) kg (NNR) and 7.8 (1.1) kg (PD), the MTG content did not change over time ($p = 0.98$ in the NNR and $p = 0.11$ in the PD group at 24 months). Reduced left ventricular mass was observed in both diet groups over 24 months. Blood pressure was reduced at 6 months, but returned to baseline levels at 24 months. End diastolic volume, stroke volume, and cardiac output decreased over time. No differences between diet groups were observed.

*Conclusions:* Diet intervention and moderate weight loss over 24 months improved LV remodelling but did not alter MTG levels in overweight/obese postmenopausal women.



## 1. Introduction

Obesity is associated with structural and functional myocardial changes [1,2]. This includes volume overload, increased blood pressure, higher heart rate and cardiac output, left ventricular hypertrophy, insulin resistance, neurohormonal activation (sympathetic nervous system and angiotensin II), and disturbances in myocardial metabolism. These alterations are potential targets for different interventions [3].

A suggested mediator of cardiac dysfunction in obesity is increased myocardial triglycerides (MTG). MTG levels positively correlate with both body mass index (BMI) and left ventricular mass (LVM) in subjects with impaired glucose tolerance or obesity, and inversely correlate with systolic function [3]. Interestingly, Gavock and colleagues showed that cardiac steatosis precedes the onset of diabetes mellitus and left ventricular systolic dysfunction [4]. Exactly how MTG accumulation may lead to cardiac dysfunction and if MTG has independent cardiac effects is unknown. Experimental studies suggest that lipid over-storage cause lipotoxic injury to cardiomyocytes, thereby promoting fibrosis, apoptosis,

*Abbreviations:* BP, blood pressure; CO, cardiac output; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LVM, left ventricle mass; MR, magnetic resonance; MTG, myocardial triglyceride; NNR, Nordic Nutrition Recommendations; PD, Palaeolithic diet.

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☆☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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and contractile dysfunction [3,5,6]. It has, however, been pointed out in recent literature that intervention studies are urgently needed in humans to analyse whether there is a causal link between myocardial dysfunction and MTG.

In healthy subjects, MTG levels vary depending on energy balance. For instance, short-term caloric restriction dose-dependently increases MTG content [7], whereas a single high-fat meal does not affect MTG stores [8]. In addition, a weight-loss diet significantly reduces MTG content in humans in studies of up to 6 months [9,10]. Whether dietary interventions can successfully lower MTG content with a favourable effect on LV remodelling beyond 6 months is as yet unknown. In earlier studies, we and others have shown that a Palaeolithic diet (PD), virtually devoid of high glycaemic index carbohydrates and with an increased content of mono- and polyunsaturated fatty acids, can have powerful short-term effects on obesity-related metabolic dysfunctions [11,12].

Our hypothesis was that a 2-year dietary intervention in postmenopausal overweight women, a high risk group of metabolic disturbances, may decrease fat mass with a concomitant decrease in MTG, which would be associated with improved LV remodelling and function.

## 2. Methods

### 2.1. Subjects

All subjects were recruited in 2007 through advertisements in local newspapers. Initially, 210 women were interested in participating in the study of which 70 postmenopausal women with BMI ≥ 27 kg/m$^2$ fulfilled the inclusion criteria. The enrolment criteria have been described in a previous publication [13]. Sixty-eight subjects had magnetic resonance imaging (MRI) measurements at baseline, constituting the final study population. For technical reasons, the spectroscopy data analysis was limited to 58 subjects at baseline (n = 28 in the PD and n = 30 in the NNR group). Exclusion criteria included smoking, diabetes, history of heart disease, kidney disease, hypo- or hyperthyreosis, osteoporosis, consumption of a restricted or vegetarian diet or allergy to components in the intervention diets. Other exclusion criteria were fasting plasma glucose level ≥ 7 mmol/L, blood pressure ≥ 150/90 mm Hg, hormone replacement therapy, beta blockers, statins, and medication for psychiatric disorders.

### 2.2. Anthropometric data and blood samples

Anthropometric measurements were made at baseline and after 6, 12, 18, and 24 months. Body weight was measured using a calibrated electronic digital scale (Tanita BWB-800 MA, Umedico AB, Rosersberg, Sweden) while the subject wore light indoor clothing and no shoes. Systolic and diastolic brachial artery blood pressure was measured twice at 2-min intervals while subjects were in a sitting position after five minutes rest using an automatic blood pressure metre (Bosomedicus, Bosch, Jungingen, Germany). Waist circumference was measured with a tape measure between the lower rib margin and the iliac crest. Fasting blood samples were drawn from the antecubital vein after a resting period. Aliquots were immediately frozen at −20 °C and stored until analysed.

### 2.3. Dietary interventions

After baseline measurements, all participants were randomized to a PD or a Nordic Nutrition recommendation (NNR) diet for 24 months. All study personnel (except the dieticians) were blinded to the dietary allocation of the subjects. The PD was based on lean meat, fish, eggs, vegetables, fruits, berries, and nuts, and was to provide 30% of the energy intake (E%) from protein, 40 E% from fat, and 30 E% from carbohydrates. Added salt, refined salt, cereals, and dairy products were excluded. The NNR diet was based on low-fat dairy products and high fibre products, and was to provide 15 E% protein, 25–30 E% fat and 55–60 E% carbohydrates. Both diets were consumed ad libitum. The subjects were given recipes and written instructions, and participated in cooking classes and follow-up sessions. The group sessions were held by a trained study dietician (one dietician per diet) throughout the 24-month study period. Dietary intake was assessed using 4-day estimated self-reported food records conducted at baseline; monthly for 6 months; and at 9, 12, 18 and 24 months thereafter as previously described [13].

### 2.4. Blood chemistry

Insulin was analysed using an Elecsys Insulin kit (Roche Diagnostics Scandinavia AB, Bromma, Sweden) on a Modular E 170 immunoanalyzer (Roche Diagnostics, Indianapolis, IN, USA). Glucose and lipids were analysed using Vitros slides (Ortho-Clinical Diagnostics, Johnson & Johnson, NJ, USA) on an automated chemistry analyser (Vitros 5.1FS, Johnson & Johnson, Plaza New Brunswick, NJ, USA). NT-proBNP was analysed on a Cobas® immunoanalyzer (proBNP II STAT, Roche Diagnostics GmbH, Mannheim, Germany). Non-esterified fatty acids (NEFA) were analysed using an in vitro enzymatic colorimetric method (HR Series NEFA-HR [2], Wako Diagnostics, CA, USA).

### 2.5. Cardiovascular magnetic resonance

All MRI, including the morphology and function of the heart, were assessed with a 1.5 T ACS NT MR scanner (Philips, Best, the Netherlands). The subjects lay head first in a supine position in the bore of the magnet. A balanced steady-state free precession (b-SSFP) sequence was used with electrocardiogram (ECG)-gating and expiratory breath holding for cardiac function and morphology. The heart was imaged in the short-axis orientation in slices from the apex to the base. Left ventricular structure and ejection fraction were quantified by manually drawing endocardial and epicardial contours. The papillary musculature was included as part of the left ventricular mass in end-diastole and end-systole in the short-axis orientation from apex to base. Dedicated software (Segment) was used to assess left ventricular end-diastolic volume, end-systolic volume, stroke volume, cardiac output, ejection fraction, and left ventricular mass [14]. One operator analysed all cardiac MR scans and was blinded to diet assignment.

### 2.6. Spectroscopy

High-resolution cardiac images aligned to three orthogonal planes of the heart were acquired in order to locate the interventricular septum. Images at end-systole were used to position a spectroscopic sample volume of 10 × 20 × 30 mm$^3$ within the ventricular septum. During spectroscopic data acquisition, simultaneous ECG triggering at end-systole (delay from the R-wave was calculated in cine images) and respiratory triggering at end-exhalation, using a navigator sequence, were accomplished using the physiological gating capabilities of the scanner's spectroscopy package. MR spectra were recorded using the PRESS sequence (point-resolved spectroscopy) with a repetition time (TR) typically set to 6 heart beats, giving a TR of at least 4 s and an echo time (TE) of 28.7 msec, which was the shortest achievable echo time. Sixty-four signal averages were acquired from the spectroscopic volume over 1024 data points covering a 1000-Hz spectral width. Two spectra were acquired from each volume; one with water suppression and one without water suppression.

Spectra were analysed using Stephen Provencher's LCModel (GyrTools Ltd., Zürich, Switzerland) version 6.3–1 J using the built-in model for lipid spectra and employing an analysis window between 3.6 ppm and −1.0 ppm. Signal intensities were extrapolated to zero echo time on the assumption that the $T_2$ relaxation time of water is 40 msec and the $T_2$ relaxation time for triglycerides is 78 music at 1.5 T, while the signal was acquired at 28.7 music echo time. The results are reported as percent fat signal, a ratio between the metabolite