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Energy-restricted Central-European diet stimulates liver microsomal function in obese postmenopausal women – a randomized nutritional trial with a comparison to energy-restricted Mediterranean diet

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Abstract. – OBJECTIVE: Obesity and metabolic syndrome are risk factors for liver diseases like non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. A healthy food pattern is vital for managing these health problems, therefore, this study investigated how two calorie-restricted diets, the Central European diet (CED) and Mediterranean diet (MED), altered microsomal liver function in obese postmenopausal women with a risk of metabolic syndrome.

PATIENTS AND METHODS: One-hundred-forty-four subjects were randomly assigned to the CED (n=72) or the MED (n=72) groups. A 13C-methacetin breath test was performed, before and after the intervention to assess CPDR (Cumulative Percentage Dose Recovery at 120 minutes of the test), TTP (Time to Peak - maximal momentary recovery of 13C) and Vmax (the maximum momentary 13C recovery).

RESULTS: There was a statistically significant increase in TTP and Vmax in the CED group only (*p*=0.0159 and *p*=0.0498, respectively). Changes in CPDR and TTP due to intervention were significantly higher in the CED group than in the MED group (*p*=0.0440 and *p*=0.0115, respectively).

CONCLUSIONS: This is the first study to document a stimulatory effect of the energy-restricted CED on liver microsomal function as compared to MED. The relatively short dietary intervention led to a significant difference in the CYP1A2 activity between groups. The trial was registered in the German Clinical Trials Register (DRKS-ID: DRKS00012958; URL: https://www.germanctr.de/).

Key Words:
Metabolic syndrome, Nutrition, Methacetin breath test, CYP1A2.

Introduction

Lifestyle and diet changes over the last decades, including increased calorie intake, consumption of high-processed food products, and lower energy expenditure, have led to a considerable increase in the prevalence of overweight and obesity worldwide, which has been termed an epidemic[1]. Indeed, the term "globesity" was coined to underline the scale of a problem. It is estimated that in developed countries, more than half of the adult population is overweight and obese, which makes them a significant public health concern[2]. After puberty and childbirth, menopause is the third most critical moment in a woman's life. Postmenopausal women are more prone to gain weight, and to develop overweight and obesity, and obesity-related diseases[3,4]. As

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the metabolic syndrome (MetS) is associated with obesity, the observed changes contribute to a higher prevalence of MetS in postmenopausal than in premenopausal women[5].

MetS is a complex disorder comprising risk factors for cardiovascular disease and diabetes mellitus, including high blood pressure, dyslipidaemia, high glucose levels, obesity, and insulin resistance. It is probably only slightly less prevalent than obesity. According to various sources, MetS occurs in 7 to 70% of the general population[6] and patients with MetS have a twice higher risk of death due to heart infarction or stroke than healthy peers[5,7]. Also, they may have impaired liver function as evidenced by the frequent occurrence of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)[8]. Two key components of MetS, glucose and triglycerides, are overproduced by the fatty liver. Therefore, the liver may be a key determinant of metabolic abnormalities. Thus, simple methods to evaluate liver dysfunction might be helpful predictors of the metabolic risk[9]. Among the potential options, the ^{13}C-methacetin breath test (MBT) seems to be appropriate due to its safety and non-invasiveness.

A dietary model of the Mediterranean Diet (MED), characterised by high intake of plant foods and olive oil, moderate consumption of dairy products and low consumption of meat, mainly fish and poultry[10], is linked with many beneficial effects on metabolic health and disease prevention, including cardiovascular diseases, diabetes, obesity and cancer[6,11,12]. However, it was noted that the adoption of this dietary pattern by non-Mediterranean countries is costly as typical MED products are more expensive and less available outside Southern Europe. Moreover, adherence to MED in non-Mediterranean populations is rather low[13]. Therefore, there is a need for a dietary model based on local products that could have a similarly beneficial impact and be used in the prevention of metabolic disorders. Diets based on local healthy products can have positive health outcomes, e.g., Nordic Diet (assessed in the Danish cohort study) showed lower total mortality in the observed population[14], thus, the interest in the effects of balanced traditional food patterns has increased[15]. For central Europe, the so-called Central European diet (CED) that includes native food items, like whole-grain rye and oats, cabbages, root vegetables, plums, and apples, could be applied[16].

There is evidence for the impact of various dietary agents on the modulation of liver microsomal activity measured by MBT[17]. Several studies[11,12] have investigated how dietary interventions can affect metabolic parameters in patients with MetS, however, there is a lack of information regarding the impact on microsomal liver function. Therefore, this work investigated how two calorie-restricted diets, Mediterranean diet and Central European diet, alter microsomal liver function in obese postmenopausal women with a risk of metabolic syndrome.

Patients and Methods

Characteristics of the Study Group

One-hundred-forty-four Caucasian, non-smoking, centrally obese postmenopausal women were recruited. The postmenopausal status of the study participants was defined as the absence of menses for at least 12 months. Except for central obesity (waist circumference ≥80 cm in European women), the participants met at least one of the following criteria[18]: decreased HDL cholesterol level (<50 mg/dL), increased triglycerides level (at least 150 mg/dL), elevated fasting plasma glucose (at least 100 mg/dL), increased blood pressure (systolic BP >130 or diastolic BP >85 mm Hg). All participants declared the wish to lose weight. Details of all inclusion and exclusion criteria have been reported elsewhere[16]. Moreover, exclusion criteria also included contraindications for performing the MBT test. Volunteers were recruited through advertisements in local newspapers. Figure 1 illustrates how the participants proceeded through the trial. Two-hundred-sixty-nine women expressed an interest in participation, of which, one hundred twenty-five were excluded. The remaining 144 were invited for a screening visit, during which the study protocol and potential benefits and risks were explained. Written consent was collected from each participant. All screened women underwent the randomisation process to form two groups, CED and MED, with 72 subjects in each group. Age (median <IQR>: 61.0< 57.8–64.0 > *vs.* 60.0< 56.8–64.0 > years) and BMI (32.9<30.28–36.58> *vs.* 32.8<30.38–35.75> kg/m^2, for the CED and MED group respectively) did not differ between the studied groups.

One hundred twenty-eight women completed the study, 65 and 63 participants from MED and CED group, respectively. Sixteen (11.0%) subjects dropped out (7 from the MED group and

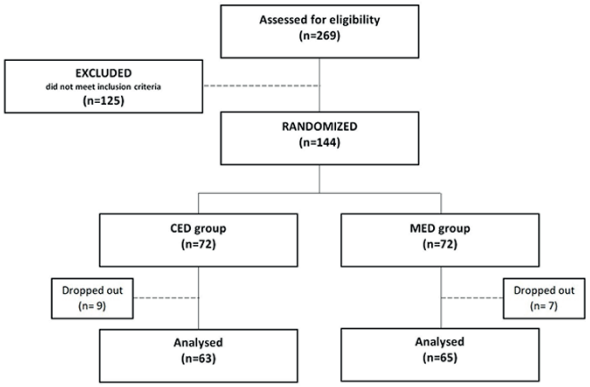

Figure 1. Flowchart illustrating participants progress through the trial.

9 from CED group), among which, 9 could not follow the dietary recommendation (6 from CED and 3 from MED), 7 resigned due to reasons not related to the study.

Dietary Intervention

The study was designed as a randomized, single-blind nutritional trial. Participants were randomly assigned to one of the study groups, CED or MED, by a computer program and stratified according to body mass index. The participants' allocation to CED or MED was unknown to investigators until the end of the trial except for dietitians, who were responsible only for diet planning and analysis.

The diets were energy-restricted with a deficit of ~2.93 MJ per day compared to estimated individual energy requirements. Details of the composition of the study diets have been reported previously[16]. The MED was specifically designed to provide approximately 37% of energy from total fat, with 20% coming from MUFAs (monounsaturated fatty acids), 9% from PUFAs (polyunsaturated fatty acids), 8% from SFAs (saturated fatty acids), 45% of energy from carbohydrates and 18% from proteins. The MED diet included food items typical for the Mediterranean area, such as olive oil and nuts, that were served to participants every day. The CED was designed to provide 27% of energy from total fat, with 10% coming from MUFAs, 9% from PUFAs, 8% from SFAs, 55% of energy from carbohydrates and 18% from proteins. This diet was based on products typical for central Europe like cereals (barley, oatmeal, buckwheat, and millet), root vegetables, cruciferous vegetables, pulses and fruits. Food items with refined sugar, refined fats, and salt were excluded from both diets. The nutritional intervention lasted 16 weeks and has been described in detail by Bajerska et al[16].

Methacetin Breath Test

MBT is a non-invasive isotopic breath test used for the assessment of microsomal liver function. Methacetin (N-(4-methoxy-13C-phenyl)acetamide) is an exogenous substance that is well absorbed and undergoes the first-pass effect. It is metabolised by cytochrome P450, mainly isoenzyme CYP 1A2, to acetaminophen and $^{13}CO_2$, which is subsequently eliminated with exhaled air. The $^{13}CO_2/^{12}CO_2$ ratio is measured using mass spectrometry in samples of expiratory air collected in set intervals and compared with the basal sample. The obtained measurements were used to derive the following parameters: CPDR (Cumulative Percentage Dose Recovery at 120 minutes of the test), TTP (Time to Peak, time of maximal momentary recovery of ^{13}C) and Vmax (the maximum momentary ^{13}C recovery).

MBT was performed at the baseline (week 0) and the endpoint (week 16) of the trial. None of the subjects studied had contraindications for MBT, such as transjugular portosystemic shunt (TIPS), hepatocellular carcinoma, congestive heart failure (LEV<20%), pulmonary hypertension (pulmonary artery systolic pressure >45 mmHg assessed in echocardiography), uncontrolled diabetes (glycated haemoglobin A1c>9.5%), therapy with immunosuppressants, bariatric surgery or extensive resection of the intestine in the past, parenteral nutrition, allergy to acetaminophen in the past, chronic obstructive pulmonary disease (COPD) and taking medications that can affect the test result (e.g., fluvoxamine, ciprofloxacin, amiodarone, cimetidine, famotidine, rifampicin or carbamazepine).

Patients were instructed to avoid consumption of dietary products with a naturally high content of isotope ^{13}C, like sugar cane, maize, pineapple, kiwi fruit and products with a high amount of CO_2, like sparkling beverages for 48 hours before the examination. The test was conducted after overnight rest and fasting (at least 12 hours). All subjects rested for 30 minutes before collection of the basal exhaled air sample (designated as "0"). Expiratory air samples were collected into plastic bags and stored for further analysis. Subsequently, 75 mg of ^{13}C-methacetin dissolved in 200 mL of unsweetened tea was administered to each patient. Samples of breath air were collected in plastic bags every 10 minutes during the first

hour of test and every 20 minutes in the second hour (0 - basal, 10, 20, 30, 40, 50, 60, 80, 100, 120 minutes proceeding substrate administration). Then, collected samples were analysed with isotope-selective nondispersive infrared spectrometry (IRIS, Wagner Analysen Technik GmbH, Bremen, Germany).

Statistical Analysis

The outcomes are presented as medians with interquartile ranges (IQRs) and means with standard deviations (SDs). For statistical analysis, STATISTICA 12 software (StatSoft Inc., Tulsa, OK, USA) was used. The U Mann-Whitney test was performed to analyse changes in CPDR, TTP and Vmax values (ΔCPDR, ΔTTP, ΔVmax) between the CED and MED groups. The Wilcoxon-rank test was used to compare baseline and final results of CPDR, TTP and Vmax inside groups. The significance level was set at $p<0.05$.

The Bioethical Committee of Poznan University of Medical Sciences, Poland, approved the study protocol (603/14). All the performed procedures complied with the Declaration of Helsinki guidelines. The project was financed by a National Science Centre based on decision number DEC-2013/09/B/NZ9/02365 (JB) and Poznan University of Medical Sciences (JW502-0101103115-07588), Poland. The design, analysis of results, and writing of this publication were conducted independently of any commercial entities.

Results

Table I presents the baseline characteristics of the ^{13}C-methacethin breath test in study groups, showing that there were no significant differences between the CED and MED groups.

The intervention did not result in significant changes in CPDR either in the CED group or the MED group, whereas there was a statistically significant increase in TTP and Vmax in the CED group ($p=0.0159$ and $p=0.0498$, respectively) (Table II). The ΔCPDR and ΔTTP were significantly higher in the CED group than in the MED group ($p=0.0440$ and $p=0.0115$, respectively) (Table III).

Discussion

This is the first study to document the difference in the effect of the CED and MED diets on microsomal liver function in postmenopausal women. We aimed to investigate using MBT how two calorie-restricted, balanced diets (MED and CED) affect liver function. There is information regarding the impact of particular food items on the activity of CYP1A2-isoenzyme, for example, cruciferous vegetables (broccoli, cauliflower, cabbage, Brussels sprouts, etc.) are known for their stimulatory effect on CYP1A2. Kall et al[19] reported the introduction of 500 g/day of broccoli to a diet leads to a 25% increase in the elimination of CYP1A2-derived caffeine metabolites[17]. In contrast, apiaceous vegetables (celery, carrots, parsley, parsnips, etc.) have an inhibitory effect on CYP1A2 activity[20,21]. However, the current approach was to investigate the influence on the metabolism of a dietary pattern (CED diet), rather than a single food product[22,23].

The study group comprised postmenopausal women with central obesity with a high risk of MetS[4,5]. There are many different dietary patterns like MED, low-fat diet, or low-carbohydrate diets, that are recommended for patients with a risk of cardiovascular diseases, including patients with MetS[24]. Their influence on body weight, glucose and lipid metabolism has been widely documented[25-27]. However, it seems essential to investigate other aspects of their impact on metabolism, e.g., microsomal liver function, especially since obesity and MetS have become a global health issue.

The results of this study indicate a stimulatory

Table I. Baseline characteristics of the ^{13}C-methacethin breath test in study groups.

Parameter	CED (n = 63)		MED (n = 65)		p-value
	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	
CPDR [% ^{13}C]	33.9 (31.3-37.9)	34.4 ± 6.0	35.8 (31.8-39.5)	35.2 ± 6.6	0.2678
TTP [min]	20 (10-20)	15.6 ± 6.0	20 (10-20)	17.6 ± 6.3	0.1182
Vmax [dose/h]	34.5 (30.8-38.2)	35.6 ± 9.4	36.9 (28.0-42.2)	36.0 ± 9.1	0.2616

CED – Central European diet, MED – Mediterranean diet. IQR – interquartile range, SD – standard deviation. CPDR – cumulative percentage dose recovery, TTP – time to peak.

Table II. Changes in the ^{13}C-methacethin breath values during the intervention.

		CED (n = 63)		MED (n = 65)	
		Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD
CPDR [% ^{13}C]	Pre	33.9 (31.3-37.9)	34.4 ± 6.0	36.5 (32.5-40.4)	36.0 ± 6.5
	Post	36.4 (31.8-39.1)	35.3 ± 4.8	35.4 (31.1-38.7)	34.9 ± 5.9
	p-value	0.2019		0.1366	
TTP [min]	Pre	20 (10-20)	15.6 ± 6.0	20 (10-20)	18.7 ± 7.4
	Post	20 (10-20)	18.1 ± 6.2	20 (10-20)	16.8 ± 6.1
	p-value	**0.0159**		0.1392	
Vmax [dose/h]	Pre	34.5 (30.8-38.2)	35.6 ± 9.4	37.4 (29.8-43.1)	36.8 ± 9.2
	Post	36.9 (31.7-42.2)	37.6 ± 9.2	36.6 (30.6-42.0)	36.3 ± 8.8
	p-value	**0.0498**		0.7616	

CED – Central European diet, MED – Mediterranean diet. IQR – interquartile range, SD – standard deviation. CPDR – cumulative percentage dose recovery, TTP – time to peak.

effect of CED on CYP1A2 activity in contrast to MED. The CED-related ^{13}C-MBT changes concerned TTP and Vmax, with statistically significant differences between CED and MED for TTP and CPDR, the latter being considered the most important parameter of the MBT results. TTP values reflect the prolonged time of activity and the consequent shift of the pick caused by stimulation, rather than virtual delay of maximal momentary recovery of ^{13}C (Vmax). With high probability, the inducing effect of CED may result from its high content of cruciferous vegetables like cabbage.

The growing interest in different food patterns and their impact on metabolic health explains the need for investigating the influence of dietary changes on liver microsomal activity. It seems essential, especially in patients with multimorbidity or diseases causing polypharmacy like MetS[28], as changes in cytochrome P450 activity can affect drug metabolism. Isoenzyme CYP1A2 that is assessed by MBT makes up almost 13% of cytochrome P450 expressed in the liver and metabolises about 5% of all currently used drugs. Exogenous substrates for CYP1A2 include acetaminophen, theophylline, propranolol, lidocaine, tacrine, and triamterene[29] and diets inducing this isoenzyme activity can eliminate such drugs faster. Furthermore, patients with MetS are at risk of developing NASH and NAFLD, diseases that could lead to liver fibrosis[8]. The gold standard for diagnosing liver fibrosis is still liver biopsy, nonetheless, the importance of non-invasive breath tests like MBT is growing[30]. Therefore, it is important to understand how specific food patterns affect liver microsomal activity, as diets which stimulate CYP1A2, like CED, can reduce the sensitivity of MBT and delay the diagnosis of liver fibrosis. Due to induced CYP1A2 activity, MBT results can be within reference ranges, while the fibrosis has already occurred.

The present research involved a uniform female study group, (eliminating potential gender-related differences), randomisation, and single-blind character, thereby reducing the risk of bias. Furthermore, a catering company provided the participants with all their main meals, resulting in high adherence. However, the effect of repetitive MBT on the study results should be considered, as Kasicka-Jonderko et al[31] reported that repeating the MBT test in 2-3 week intervals leads to

Table III. Comparison of ^{13}C-methacethin breath changes during the intervention.

Parameter	CED (n = 63)		MED (n = 65)		*p*-value
	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	
ΔCPDR [% C^{13}]	1.1 (-2.5-4.0)	0.9 ± 5.9	-1.6 (-5.1-2.4)	-1.1 ± 7.9	0.0440
ΔTTP [min]	0 (0-10)	2.5 ± 7.2	0.0 (-10-0)	-1.9 ± 9.1	0.0116
ΔVmax [dose/h]	3.0 (-4.4-9.1)	2.0 ± 10.7	-1.1 (-7.7-7.6)	-0.6 ± 11.6	0.1353

CED – Central European diet, MED – Mediterranean diet. IQR – interquartile range, SD – standard deviation. CPDR – cumulative percentage dose recovery, TTP – time to peak.

stimulation of CYP1A2. However, there is no evidence in the literature that this phenomenon can be observed for a longer time. In the present study, MBT was repeated after 16 weeks, which possibly eliminated the impact of the first breath test on cytochrome P450 activity. The comparison of CED and MED, not CED and habitual diet, could be regarded as both a strength and limitation of the study. Furthermore, energy restriction could also have its impact, so differences in the influence on microsomal liver function between energy-restricted and *ad libitum* diet should be investigated. However, differences between the effects of CED and MED were observed. Finally, the novelty of the study should be highlighted, as this is the first report of the stimulatory effect of the energy-restricted Central European diet on liver microsomal function in obese postmenopausal women, as compared to energy-restricted Mediterranean diet.

Conclusions

This study showed the stimulatory effect of the energy-restricted Central European diet on liver microsomal function in obese postmenopausal women, as compared to the energy-restricted Mediterranean diet. Relatively short 16-week dietary intervention led to a significant difference in the CYP1A2 activity between dietary groups. To our best knowledge, this is the first study documenting the impact of the Central European diet on microsomal liver function. The novel results of the present study could contribute to changes in pharmacotherapy depending on patient dietary patterns, as changes in cytochrome P450 activity affect drug metabolism. However, further investigations are warranted.

Conflict of Interest

Authors declare no conflict of interest associated with this publication. There has been no financial support for this work that could have influenced its outcome.

Statement of Interests

Declaration of funding interests: this study was funded in part by a National Science Centre grant number DEC-2013/09/B/NZ9/02365 (JB) and in part by Poznan University of Medical Sciences, Poland grant number (JW502-0101103115-07588). The design, analysis of results, and writing of this publication were carried out independently of any commercial entities. SB (WKMOMU) and JW (PUMS) were supported by the Social Health Insurance Project, Republic of Kazakhstan (Contract No. SHIP-2.3/CS-02).

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