

Short Communication

Dietary fat modifications and blood pressure in subjects with the metabolic syndrome in the LIPGENE dietary intervention study

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Hypertension is a key feature of the metabolic syndrome. Lifestyle and dietary changes may affect blood pressure (BP), but the knowledge of the effects of dietary fat modification in subjects with the metabolic syndrome is limited. The objective of the present study was to investigate the effect of an isoenergetic change in the quantity and quality of dietary fat on BP in subjects with the metabolic syndrome. In a 12-week European multi-centre, parallel, randomised controlled dietary intervention trial (LIPGENE), 486 subjects were assigned to one of the four diets distinct in fat quantity and quality: two high-fat diets rich in saturated fat or monounsaturated fat and two low-fat, high-complex carbohydrate diets with or without 1.2 g/d of very long-chain *n*-3 PUFA supplementation. There were no overall differences in systolic BP (SBP), diastolic BP or pulse pressure (PP) between the dietary groups after the intervention. The high-fat diet rich in saturated fat had minor unfavourable effects on SBP and PP in males.

Metabolic syndrome: Diet: Fatty acids: Blood pressure: LIPGENE

Hypertension is a key feature of the metabolic syndrome⁽¹⁾. Weight loss, exercise, smoking cessation, and restriction of alcohol and sodium are lifestyle changes that are well known to lower blood pressure (BP)^(2,3). Although such modifications often promote minor alterations in BP, even small reductions may be beneficial on a population basis as hypertension is a

major public health challenge. Dietary fat modification may influence BP as shown previously^(4–6), but the knowledge of the effects in subjects with the metabolic syndrome is limited. Targeted interventions in these subjects are important as they have increased risk of hypertensive organ damage⁽⁷⁾ and elevated pulse pressure (PP) that predicts cardiovascular

Abbreviations: ANCOVA, analysis of covariance; BP, blood pressure; DBP, diastolic BP; HMUFA, high content of MUFA; HSFA, high content of SFA; LFHCC, low-fat, high-complex carbohydrate; PP, pulse pressure; SBP, systolic BP.

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events^(8,9). The objective of the present analysis was to investigate the effect of an isoenergetic change in dietary fat quality and quantity on BP in subjects with the metabolic syndrome.

Experimental methods

The LIPGENE study was a 12-week parallel, randomised controlled trial that was performed in eight European centres as part of an European Union Sixth Framework Project (<http://www.ucd.ie/lipgene/>). The study was conducted according to the Declaration of Helsinki, and all procedures involving human subjects were approved by the local ethics committees at all centres. Written informed consent was obtained from all subjects. US National Library of Medicine Clinical Trials registry number: NCT00429195.

Subjects

Study participants were of Caucasian ethnicity, aged 35–70 years (BMI 20–40 kg/m²), and had the metabolic syndrome defined by three or more of the following slightly modified National Cholesterol Education Program Adult Treatment Panel III criteria⁽¹⁾: levels of fasting plasma glucose >5.5 mmol/l, TAG ≥1.5 mmol/l, HDL-cholesterol <1.0 mmol/l (males) or <1.3 mmol/l (females), systolic BP (SBP) ≥130 mmHg or diastolic BP (DBP) ≥85 mmHg or on BP-lowering medication, and waist circumference >102 cm (males) or >88 cm (females). Antihypertensive medication, hormone replacement therapy, multivitamin supplements and non-fatty acid-based nutritional supplements were allowed if the subjects adhered to the same diet regimen throughout the study. Exclusion criteria included pre-diagnosed diabetes, inflammatory diseases, use of statins and anti-inflammatory drugs, fatty acid supplements, alcohol abuse and a recent weight change ≥3 kg.

Diets

Subjects were randomly assigned to one of the four isoenergetic diets differing in fat quantity and quality as

described extensively⁽¹⁰⁾. In short, two diets provided 38 % energy from fat: one with high content (16 % energy) of SFA (HSFA diet) and another with high content (20 % energy) of MUFA (HMUFA diet). Two low-fat, high-complex carbohydrate (LFHCC) diets contained 28 % energy from fat, with diet LFHCC *n*-3 including 1.2 g/d supplement of very long-chain marine *n*-3 PUFA and diet LFHCC control including a control high-oleic acid sunflower-seed oil capsule (Lipid Nutrition, Lodders Croklaan, Wormerveer, The Netherlands). A food exchange model was developed, and fat-modified food products (margarines, cooking and baking fats, oils, dressings and biscuits) were supplied by Unilever (Vlaardingen, The Netherlands). All participants completed a 3 d weighed food record and a FFQ to estimate dietary intake. Food records were also completed mid- and post-intervention to assess compliance. Nutrient composition was calculated using centre-specific dietary analysis programmes, including the nutrient composition of the LIPGENE intervention foods. Dietary targets were achieved with aimed differences in fat quantity and quality⁽¹⁰⁾.

Methods

BP was measured at screening, baseline and at the end of the study using an automatic BP measuring device. According to the European Society of Hypertension Guidelines⁽⁶⁾, BP measurement was obtained with an appropriate sized cuff positioned at the heart level, after the subjects had rested for at least 5 min. The same arm was used for each measurement and at least two measurements were performed at each visit, and the average was used for data processing. PP was calculated as the difference between SBP and DBP.

Statistical methods

Baseline data are presented as group means and standard deviations, and BP changes are given as mean per group and 95 % CI. General linear models (two-way analysis of covariance (ANCOVA)) were used to assess differences

Table 1. Baseline clinical characteristics
(Mean values and standard deviations)

	Males (<i>n</i> 196)			Females (<i>n</i> 232)		
	Mean	SD	<i>n</i>	Mean	SD	<i>n</i>
Age (years)	53.4	10.1		55.9	7.9	
SBP (mmHg)	139.4	13.9		137.9	15.1	
DBP (mmHg)	87.5	8.4		84.6	8.8	
PP (mmHg)	51.9	10.8		53.3	13.2	
Body weight (kg)	99.5	13.9		85.6	11.1	
BMI (kg/m ²)	32.1	3.9		32.8	4.3	
Waist circumference (cm)	111.2	10.1		102.8	10.1	
Body fat (%)	30.0	5.7	185	42.4	6.4	228
Fasting glucose (mmol/l)	6.1	0.9	195	5.9	0.8	231
Total cholesterol (mmol/l)	5.1	0.9	195	5.5	0.9	
LDL-cholesterol (mmol/l)	3.1	1.0	194	3.3	1.1	230
HDL-cholesterol (mmol/l)	1.0	0.2	195	1.2	0.3	
TAG (mmol/l)	1.9	1.0	195	1.7	0.8	
Physical activity level (AU)	7.7	1.3	137	7.7	1.2	178
Smoke (yes/no)	36/154			34/196		

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; AU, arbitrary units.

in BP between groups, adjusted for baseline BP, centre, age and body weight. The ANCOVA model in which weight change was included yielded the same point estimates and *P* values of the dietary effects on BP that were the same as those yielded by the model in which weight change was not included. Moreover, weight change was not a significant factor in the adjusted model. A two-sided *P* value <0.05 was regarded significant. Analyses were performed using SPSS for Windows 16.0 (SPSS, Inc., Chicago, IL, USA) and R 2.8.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Pre-investigation was completed in a total of 486 subjects across the eight centres, and 428 subjects had baseline BP measurements available (196 males and 232 females, HSFA *n* 102, HMUFA *n* 115, LFHCC control *n* 109 and LFHCC *n*-3 *n* 115). Clinical characteristics are described in Table 1; there were no differences between dietary groups at baseline. Baseline BP did not differ between completers and non-completers, and the non-completers were evenly distributed between dietary groups.

In the overall ANCOVA, there were no differences in the changes observed in SBP, DBP or PP between the four dietary groups (*P*=0.52, 0.24 and 0.78, respectively). We investigated whether hypertensive and normotensive individuals responded differently to the intervention, but no differences were observed. Body weight remained unchanged in the two high-fat dietary groups, but it was slightly reduced in the two low-fat dietary groups (LFHCC control: -0.9 (95 % CI -1.3, -0.6) kg and LFHCC *n*-3: -0.7 (95 % CI -1.0, -0.3) kg).

In a secondary analysis, we compared the HSFA and the HMUFA diets, and a significant diet × sex interaction for PP (*P*=0.01) was seen. In a sex-specific subanalysis, the effect in males differed between the two diets. The PP increased in the HSFA group by 2.8 (95 % CI 0.0, 5.7) mmHg, and it did not change in the HMUFA group. There was also a significant diet × sex interaction for SBP (*P*=0.03) and PP (*P*=0.01) between the HSFA diet and the low-fat diets. In a sex-specific subanalysis, SBP and PP differed between these diets only in males. The HSFA diet was associated with an increase in PP and no change in SBP, whereas the low-fat diets were followed by a decrease in SBP (-3.7 (95 % CI -6.0, -1.4) mmHg) and a NS change in PP (-1.8 (95 % CI -3.9, 0.3) mmHg) (Table 2).

Discussion

We found no major BP effects of isoenergetic dietary fat modification in subjects with the metabolic syndrome. However, the HSFA diet had a minor unfavourable effect on BP in males. The potential of dietary changes to lower BP was clearly demonstrated in the Dietary Approaches to Stop Hypertension (DASH) study⁽⁵⁾. A low-fat diet with increased consumption of fruit and vegetables, low-fat dairy and whole-grain products substantially decreased SBP and DBP compared with a control diet. The fat content and composition of the DASH diet and control diet in this trial were similar to those of the LIPGENE LFHCC and HSFA diets. We observed

Table 2. Blood pressure (BP) and pulse pressure (PP) at baseline and change during intervention (Mean values, standard deviations and 95 % confidence intervals)

	HSFA			HMUFA			LFHCC control			LFHCC <i>n</i> -3															
	Baseline		Change	Baseline		Change	Baseline		Change	Baseline		Change													
	<i>n</i>	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	95 % CI											
SBP																									
All	93	137.9	14.8	-2.7	-5.3	0.0	105	139.4	15.1	-3.2	-5.7	-0.7	100	139.5	15.0	-4.3	-6.5	-2.2	93	137.5	13.4	-4.3	-6.8	-1.8	
Males	41	138.3	16.8	1.4	-2.6	5.3	44	139.2	12.5	-2.3	-6.2	1.7	43	140.3	12.7	-3.5	-6.7	-0.3	44	138.9	13.2	-3.8	-7.3	-0.3	
Females	52	137.6	13.3	-5.8	-9.3	-2.4	61	139.6	16.8	-3.9	-7.2	-0.6	57	139.0	16.6	-5.0	-8.0	-2.0	49	136.3	13.7	-4.7	-8.4	-1.0	
DBP																									
All	93	85.9	8.3	-1.8	-3.2	-0.4	105	86.7	9.0	-1.4	-2.7	-0.1	100	85.5	9.2	-1.9	-3.3	-0.5	93	85.4	8.2	-2.7	-4.5	-0.9	
Males	41	87.3	8.2	-1.5	-3.7	0.8	44	88.7	8.4	-0.7	-3.1	1.7	43	86.8	8.4	-1.1	-3.3	1.1	44	87.2	8.0	-2.6	-5.1	-0.2	
Females	52	84.8	8.2	-2.1	-3.8	-0.4	61	85.3	9.3	-1.9	-3.5	-0.3	57	84.5	9.7	-2.4	-4.3	-0.6	49	83.8	8.2	-2.7	-5.4	0.0	
PP																									
All	93	52.0	12.1	-0.9	-3.0	1.2	105	52.7	12.6	-1.8	-3.7	0.1	100	54.0	13.4	-2.5	-4.5	-0.4	93	52.1	11.2	-1.6	-3.8	0.5	
Males	41	51.0	12.9	2.8	0.0	5.7	44	50.4	8.8	-1.6	-4.3	1.2	43	53.5	11.5	-2.4	-5.4	0.5	44	51.7	10.2	-1.2	-4.2	1.8	
Females	52	52.8	11.4	-3.8	-6.6	-0.9	61	54.3	14.6	-2.0	-4.6	0.7	57	54.4	14.8	-2.5	-5.4	0.4	49	52.5	12.1	-2.0	-5.3	1.2	

HSFA, high-fat diet rich in saturated fat; HMUFA, high-fat diet rich in monounsaturated fat; LFHCC control, low-fat, high-complex carbohydrate diet with control supplement; LFHCC *n*-3, LFHCC with very long-chain *n*-3 PUFA supplement; SBP, systolic BP; DBP, diastolic BP.

a similar tendency in SBP in males only, and no effect in the total LIPGENE cohort. However, the LIPGENE cohort was more overweight, and the whole diet approach taken in the DASH study was different from the LIPGENE modification of macronutrient composition. In line with the present findings, no difference in BP was observed between a high saturated fat diet and a low-fat diet in a small crossover study in normotensive subjects with type 2 diabetes⁽¹¹⁾.

DBP was reduced on a high monounsaturated fat diet compared with an isoenergetic high saturated fat diet in healthy subjects in the KANWU study⁽¹²⁾. Dietary targets and study design were comparable to the HSFA and HMUFA diets in the LIPGENE study. We did not confirm these findings in our cohort; however, we found a disadvantageous effect of saturated fat in males. This has also been reported by others; in a crossover dietary intervention study in normotensive subjects, both SBP and DBP were significantly higher during the high saturated fat period compared with isoenergetic high monounsaturated, *n*-6 or *n*-3 fatty acid periods⁽¹³⁾.

We observed no statistical differences between the LFHCC *n*-3 and the LFHCC control diets.

The lack of BP-lowering effects of the very long-chain marine *n*-3 PUFA supplementation may be due to the relatively low dose (1.2 g/d) used in the present study, as only supplements of high doses (> 3 g/d) of very long-chain marine *n*-3 PUFA are found to lower BP in hypertensive patients⁽⁹⁾.

The LIPGENE study is one of the largest dietary intervention studies carried out in subjects with the metabolic syndrome. With subjects from all over Europe, the dietary interventions were implemented on a heterogeneous dietary background. The dietary intakes, as assessed by weighed food records, were achieved with significant differences in fat quantity and quality between diets⁽¹⁰⁾. The study was designed to be isoenergetic, and the subjects were not to lose weight. Body weight did not change in the high-fat groups, but there was a minimal, although statistically significant, weight loss < 1 kg in the low-fat groups. The change in body weight, however, was not significantly correlated with changes in BP, and it did not influence the results in the ANCOVA modelling. The primary endpoint of the LIPGENE study was insulin sensitivity; therefore, the original power calculations did not include BP estimates, which limit the impact of the present analysis. However, *post hoc* analysis indicated a power of 80% to detect a 4 mmHg difference in DBP between groups. All our BP measurements were performed according to guidelines, yet both the regression to the mean effect and the habituation effect, the phenomenon that BP decreases with repetitive measurements, are well-known problems in BP research. These effects might partly explain the reduction in BP in all the four dietary groups, and could be responsible for masking differences between the diets.

In conclusion, altered quantity and quality of dietary fat had no major effects on BP in subjects with the metabolic syndrome participating in the LIPGENE dietary intervention study. The HSFA diet had minor adverse effects on SBP and PP in males.

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References

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001) Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* **285**, 2486–2497.
2. Dickinson HO, Mason JM, Nicolson DJ, *et al.* (2006) Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. *J Hypertens* **24**, 215–233.
3. Chobanian AV, Bakris GL, Black HR, *et al.* (2003) The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA* **289**, 2560–2572.
4. Shah M, Adams-Huet B & Garg A (2007) Effect of high-carbohydrate or high-*cis*-monounsaturated fat diets on blood pressure: a meta-analysis of intervention trials. *Am J Clin Nutr* **85**, 1251–1256.
5. Appel LJ, Moore TJ, Obarzanek E, *et al.* (1997) A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* **336**, 1117–1124.
6. Geleijnse JM, Giltay EJ, Grobbee DE, *et al.* (2002) Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. *J Hypertens* **20**, 1493–1499.
7. Cuspidi C, Meani S, Fusi V, *et al.* (2004) Metabolic syndrome and target organ damage in untreated essential hypertensives. *J Hypertens* **22**, 1991–1998.
8. Franklin SS, Khan SA, Wong ND, *et al.* (1999) Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. *Circulation* **100**, 354–360.
9. Mansia G, De Backer G, Dominiczak A, *et al.* (2007) 2007 Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* **25**, 1105–1187.
10. Shaw DI, Tierney AC, McCarthy S, *et al.* (2008) LIPGENE food-exchange model for alteration of dietary fat quantity and quality in free-living participants from eight European countries. *Br J Nutr* **101**, 750–759.
11. Storm H, Thomsen C, Pedersen E, *et al.* (1997) Comparison of a carbohydrate-rich diet and diets rich in stearic or palmitic acid in NIDDM patients. Effects on lipids, glycemic control, and diurnal blood pressure. *Diabetes Care* **20**, 1807–1813.
12. Rasmussen BM, Vessby B, Uusitupa M, *et al.* (2006) Effects of dietary saturated, monounsaturated, and *n*-3 fatty acids on blood pressure in healthy subjects. *Am J Clin Nutr* **83**, 221–226.
13. Lahoz C, Alonso R, Ordovas JM, *et al.* (1997) Effects of dietary fat saturation on eicosanoid production, platelet aggregation and blood pressure. *Eur J Clin Invest* **27**, 780–787.