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UK Food Standards Agency *cis*-monounsaturated fatty acid workshop report

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The UK Food Standards Agency convened a group of expert scientists to review current research investigating the optimal dietary intake for *n*-9 *cis*-monounsaturated fatty acids (MUFA). The aim was to review the mechanisms underlying the reported beneficial effects of MUFA on CHD risk, and to establish priorities for future research. The issue of optimal MUFA intake is contingent upon optimal total fat intake; however, there is no consensus of opinion on what the optimal total fat intake should be. Thus, it was recommended that a large multi-centre study should look at the effects on CHD risk of MUFA replacement of saturated fatty acids in relation to varying total fat intakes; this study should be of sufficient size to take account of genetic variation, sex, physical activity and stage of life factors, as well as being of sufficient duration to account for adaptation to diets. Recommendations for studies investigating the mechanistic effects of MUFA were also made. Methods of manipulating the food chain to increase MUFA at the expense of saturated fatty acids were also discussed.

Monounsaturated fatty acids: Saturated fatty acids: Coronary heart disease

The UK Food Standards Agency (FSA) held a workshop on 12 December 2001 to review the outcomes from two FSA-funded studies designed to investigate the optimal level for *n*-9 *cis*-monounsaturated fatty acids (MUFA) dietary intake in relation to cardiovascular health. To enable the work to be presented in the wider context, speakers from non-FSA-funded studies were invited and an international chair was appointed. The day consisted of four presentations followed by a structured discussion chaired by Professor Mike Gibney. The aim of the workshop was to determine where this work has taken us and where further work should be concentrated, as well as acting as a vehicle for dissemination.

Background

A reduction in saturated fat intake lowers the risk of CHD (Clarke *et al.* 1997). This can be achieved either through a decrease in total fat intake, concomitant with a decrease in saturated fat intake, or by replacement of saturated fats with *cis*-unsaturated fats. Considerable scientific interest has been focussed on how MUFA intake affects risk for CHD, and specifically on the optimal quantity of MUFA in the diet. This issue has remained unresolved, however, because of uncertainty regarding whether MUFA or carbohydrate should be substituted for saturated fatty acids (SFA).

The seminal work of Keys *et al.* (1986) demonstrated a protective effect against CHD of a relatively high-fat diet (33–40 % total energy) rich in MUFA and low in SFA (7–8 % total energy). Since then a body of evidence has been gathered demonstrating a hypocholesterolaemic effect of the isoenergetic replacement of SFA with MUFA (Mensink & Katan, 1987, 1989; Mcdonald *et al.*

Abbreviations: FSA, Food Standards Agency; MUFA, monounsaturated fatty acids; SFA, saturated fatty acids.

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1989; Berry *et al.* 1991; Foley *et al.* 1992; Mata *et al.* 1992; Sirtori *et al.* 1992; Wahrburg *et al.* 1992; Lichtenstein *et al.* 1993; Howard *et al.* 1995; Kris-Etherton *et al.* 1999; Williams *et al.* 1999).

A reduction in total and saturated fat intake leads to decreased total and LDL-cholesterol serum levels; a similar reduction in total and LDL-cholesterol levels can also be achieved through the isoenergetic replacement of SFA with MUFA. Furthermore, the isoenergetic replacement of SFA with MUFA does not increase serum triacylglycerol concentrations or lower HDL-cholesterol concentrations as low fat diets do, both of which are associated with increased risk for CHD (Mensink & Katan, 1987, 1992; Kris-Etherton *et al.* 1999). However, factor VII coagulant activity (factor VIIc) which is also associated with increased CHD risk, is raised by increased fat intake (factor VII is a key protein in thrombosis; Miller *et al.* 1989). There has, therefore, been much debate as to which is the best approach to reduce SFA intake, and thereby risk to CHD in the general population and the relative importance of these risk factors for CHD in different subpopulations and under different conditions (Katan *et al.* 1997; Connor & Connor, 1997; Marckmann & Astrup, 2000; Kris-Etherton *et al.* 2000).

Because of the multi-factorial nature of CHD, increased understanding of the disease processes involved has led to recognition of diet-related risk factors other than circulating cholesterol concentrations; indeed, the cholesterol component of CHD may have been over-emphasised, while other components have been overlooked. The studies presented at the FSA workshop investigated the effects of isoenergetic replacement of SFA with MUFA on haemostasis, postprandial responses, endothelial function and insulin sensitivity as well as on lipoprotein metabolism.

Influence of monounsaturated fats on lipoprotein subfractions and VLDL apolipoprotein B metabolism

Kinetic studies have previously demonstrated that plasma LDL concentrations are dependent on the production rate of small VLDL lipoproteins ($VLDL_2$, S_f 20–60) (Packard *et al.* 2000). This suggests that the hypocholesterolaemic effect of MUFA may be due to an alteration of $VLDL_2$ particle production rates, but not of the larger triacylglycerol-rich $VLDL_1$ particles (S_f 60–400), as plasma triacylglycerol levels are unaffected by MUFA. Dr Jason Gill presented results from a recently completed FSA-funded project, the aim of which was to assess the effects of low- (7·8 (SE 0·2) g/100 g total fat), moderate- (10·3 (SE 0·2) g/100 g total fat) and high-MUFA (13·7 (SE 0·2) g/100 g total fat) diets on fasting and postprandial lipoprotein subfractions and on VLDL apolipoprotein B kinetics, thereby increasing understanding of the mechanisms responsible for the LDL-lowering effect.

Thirty-five subjects with moderately elevated plasma cholesterol (5·3–8·4 mmol/l) each underwent three 6-week dietary interventions, with a washout period of at least 6 weeks between each intervention period. The intervention diets were isoenergetic, with the same total fat intake (32–33 % energy). At the end of each dietary intervention period, blood samples were obtained from all subjects in the fasted state for determination of lipoprotein subfraction and insulin concentrations. The kinetics of $VLDL_1$ and $VLDL_2$ apolipoprotein B were analysed using a [^{2}H]leucine tracer after the low- and high-MUFA diets in seventeen subjects. Postprandial responses to a standard high-fat test meal were assessed in the other eighteen subjects after the low- and high-MUFA diets.

Isoenergetic replacement of SFA with MUFA in the diet reduced LDL-cholesterol and LDL concentration in a dose-dependent manner: the medium- and high-MUFA diets resulted in 5 and 12 % reductions respectively as compared with the low-MUFA diet. Increasing dietary MUFA did not alter the concentrations of $VLDL_1$, $VLDL_2$ or intermediate-density lipoproteins. The mean production rate and fractional catabolic rate of $VLDL_1$ apolipoprotein B were unaltered by changing MUFA content of the diet, in line with the lack of change in plasma triacylglycerol concentration. $VLDL_2$ production and fractional catabolic rate were also unaffected, negating the primary hypothesis that MUFA might reduce $VLDL_2$ synthesis. This suggests that the LDL-lowering effect of increasing dietary MUFA is mediated either by an upregulation of LDL clearance or by reduced conversion of intermediate-density lipoprotein into LDL. Thus, MUFA did not change triacylglycerol, but decreased LDL-cholesterol, a similar effect to phytoestrogens.

Although particle dynamics were unaffected, the cholesterol ester: triacylglycerol ratio was lower in $VLDL_2$ and intermediate-density lipoprotein (but not $VLDL_1$) on the high-MUFA diet. This may be linked to observations that high-MUFA diets and low-fat diets have been shown to decrease plasma cholesterol ester transfer protein concentrations (Jansen *et al.* 2000) and to decrease cholesterol ester transfer protein activity (Groener *et al.* 1991) relative to a high-SFA diet. This would have the effect of potentially reducing cholesterol ester and triacylglycerol exchange between lipoproteins, although it would also be expected to alter $VLDL_1$ composition. Dietary MUFA may, therefore, exert other actions on lipid metabolism that influence the core of these particles.

Acute effects of monounsaturated fats on CHD risk

Diets high in MUFA may have more favourable effects on the plasma total: HDL-cholesterol ratio, which is a better predictor of CHD risk than total cholesterol (Assmann *et al.* 2002), as compared with low-fat–high-carbohydrate diets; however, work presented by Professor Thomas Sanders suggests that they may also have adverse effects on haemostatic function which may be of greater significance for populations with established atherosclerosis. The results from acute test meal studies and 2–3 week controlled metabolic feeding studies examining both the fasting and postprandial responses to MUFA meals relative to low-fat or saturated-fat meals were presented.

In both healthy subjects and men at increased risk of CHD, meals high in MUFA increased postprandial lipaemia and resulted in a marked increase in factor VIIc 3–7 h following a test meal compared with low-fat meals (which resulted in a fall in factor VIIc). This transient postprandial change was shown to be a consequence of an

increase in factor VII activation (factor VIIa) rather than of the zymogen, which tends to fall postprandially (Sanders *et al.* 1997, 1999, 2001; Oakley *et al.* 1998). The absolute increase was greatest in subjects homozygous for the R allele with the R353Q factor VII polymorphism. This polymorphism is associated with elevated factor VIIc concentrations and an increased risk of CHD (Iacoviello *et al.* 1998).

The acute effects of oleic acid-rich meals were similar or greater than long-chain saturated fatty acids (Sanders *et al.* 1999, 2000). Stearic acid, when present as a randomized triacylglycerol, resulted in a smaller increase in factor VIIa compared with being present in an unrandomized symmetrical triacylglycerol such as cocoa butter, which elicits an increase in factor VIIa almost identical to high-oleate oils (Sanders *et al.* 2001). A high-oleate test meal impaired endothelial function postprandially in healthy subjects compared with a low-fat test meal (Ong *et al.* 1999).

Prospective cohort studies have suggested that the risk of sudden cardiac death is related to total fat intake (Ascherio *et al.* 1996). It is possible that this reflects an increased risk of thrombosis. Although the relationship between factor VIIc and CHD risk is complex, there is evidence from intervention trials that lowering factor VIIc, using low-dose warfarin, results in a decreased incidence of CHD (Medical Research Council's General Practice Research Framework, 1998). The transient increase in factor VIIc observed following a high-fat meal may acutely increase the risk of thrombosis following plaque rupture. Lower-fat diets (25–30 % energy from fat) may, therefore, be more appropriate for those groups most at risk of fatal ischaemic heart disease than diets containing large amounts of fat.

Diets high in monounsaturated fats promote beneficial postprandial chylomicron and factor VII metabolism

Professor Christine Williams reported the findings from a four-centre collaborative FSA-funded study in which the response of subjects to a reference SFA-rich diet (similar to the current UK diet) was compared with the response to a MUFA-rich diet (15–17 % total energy). Particular features of the study were: (1) the MUFA-rich diets were followed for a period of 16 weeks to determine whether responses that have been reported for short-term studies are also maintained in the long-term; (2) young healthy volunteers were studied to determine whether effects reported in middle-aged subjects are also seen in subjects with low blood lipid levels; (3) a comprehensive range of atherogenic and thrombogenic risk factors, including postprandial triacylglycerol and blood coagulation factors were measured; (4) a sub-study incorporating the use of stable-isotope labelled fatty acids enabled the impact of the background diet on the disposition of meal fats to be evaluated.

The study was conducted in a student hall of residence at the University of Reading, with dietary fat modification achieved through changes in cooking fats used in the kitchens and by provision of experimental spreads, baked products (biscuits, cakes) and snacks to volunteers. Some of the experimental foods were provided via collaboration with Van den Bergh Oils (Purfleet, UK) and United Biscuits Ltd (High Wycombe, UK).

The MUFA-rich diets had beneficial effects on total and LDL-cholesterol (reduced by 6 %) and on tendency to blood clotting (reduced platelet aggregatory response to ADP and postprandial activation of factor VII (Kelly *et al.* 2001; Smith *et al.* 2001). Fasting and postprandial apolipoprotein B-48 levels were reduced, suggesting lower circulating levels of atherogenic remnant particles (Silva *et al.* 2001*b*). However, fasting triacylglycerol levels and fasting concentrations of fibrinogen, factor VIIc, factor VIIag, tissue-type plasminogen activator and body weight were unaffected by the dietary intervention.

Novel findings were observed with respect to the effects of MUFA-rich diets on chylomicron metabolism. Although the diets did not alter the postprandial triacylglycerol and retinyl ester responses to a standard test meal, the fasting and postprandial concentrations of apolipoprotein B-48 were markedly reduced on both diets. Use of exogenous markers of dietary triacylglycerol (^{13}C-labelled fatty acids and ^{13}C-labelled retinyl esters), allowed estimation of chylomicron particle size which was increased by 50 % on the MUFA-rich diet. These results suggested that the MUFA-rich diet resulted in the generation of reduced numbers of chylomicrons but with particles of larger size. Since triacylglycerol in larger chylomicrons appears to be cleared more rapidly and since intestinal cholesterol is packaged within chylomicron particles, the investigators speculated that the net effect would be a reduced delivery of chylomicron remnants and thereby remnant cholesterol to the liver. Since remnant particles have also been implicated in the activation of factor VII, the investigators also proposed that the reduced postprandial activation of factor VII (but not fasting factor VII) observed in this study may occur via reduction in chylomicron particle number in the postprandial period (Silva *et al.* 2001*a*).

This intervention study was carried out over a longer period than many previous studies and the findings support the possibility that the attenuated apolipoprotein B-48 response reflects a long-term adaptation to high-MUFA diets, since these and other investigators have observed greater apolipoprotein B-48 in response to single MUFA-rich meals compared with SFA- or PUFA-rich meals. The fact that an opposite effect is observed on a long-term diet suggests there is an adaptational response occurring at the level of the enterocyte that may involve the action of gut hormones. The possibility that MUFA have differing effects on triacylglycerol-rich lipoproteins acutely, as compared with chronically, is supported by the impact of the diet on postprandial factor VII activation. When given as single meals to subjects with a typical UK background diet, MUFA have been reported to enhance postprandial factor VII activation compared with other dietary oils (Oakley *et al.* 1998). However, the present study agrees with previous work that suggests that a background diet rich in MUFA attenuates the acute procoagulant effects of fatty meals (Roche *et al.* 1998; Larsen *et al.* 1999).

Influence of monounsaturated fats on insulin sensitivity

Insulin sensitivity, or the relative inability of insulin to facilitate the disposal of glucose, is considered to be a risk factor for both diabetes and CHD. Professor Bengt Vessby presented findings from the KANWU study (Vessby *et al.* 2001) showing better insulin sensitivity and lower blood pressure when comparing the effects of a diet rich in MUFA and SFA respectively, in healthy subjects.

The KANWU study was a multi-centre study performed simultaneously in Kuopio, Aarhus, Naples, Wollongong and Uppsala. The study included 162 healthy subjects chosen at random to receive a controlled, isoenergetic diet for 3 months containing a high proportion of either SFA or MUFA. Insulin sensitivity was significantly impaired on the SFA-rich diet (−10 %, $P=0{\cdot}03$), but did not change on the MUFA-rich diet (+2 %, NS) ($P=0{\cdot}05$ for difference between diets). Insulin secretion was not affected. The favourable effects of substituting a MUFA-rich diet for an SFA-rich diet on insulin sensitivity was only seen at a total fat intake below median (37 % energy). In analysis of this subgroup, insulin sensitivity was 12·5 % lower and 8·8 % higher on the SFA- and MUFA-rich diet respectively. The LDL-cholesterol concentration and the diastolic blood pressure were significantly lower on the MUFA-rich diet while the level of lipoprotein(a) was increased compared with the SFA-rich diet.

This study suggests a significant impairment of a saturated-fat diet on insulin sensitivity and that the improved insulin sensitivity on the MUFA-rich diet is due to the reduced SFA intake, rather than to a specific effect of the MUFA. Recently, a study in young healthy adults demonstrated that isoenergetic substitution of carbohydrates for MUFA for SFA improved insulin sensitivity, suggesting that both diets were adequate alternatives for improving glucose metabolism (Pérez-Jiménez *et al.* 2001). The effects of the carbohydrate-rich diets on lipids, blood glucose, insulin etc. is highly dependent on the type of carbohydrate rich foods chosen in the subjects diet: a diet high in carbohydrate-rich foods and with a high-fibre content and containing foods with a low glycaemic index does not seem to impair insulin sensitivity as compared with a diet rich in MUFA (see recommendations by the Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes, 2000).

Discussion

What is the optimal level of momounsaturated fatty acids in the diet and does this vary for subgroups of the population?

The issue of optimal MUFA intake is contingent upon optimal total fat intake; however, there is no consensus of opinion on what the optimal total fat intake should be. Thus, the issue of the optimal level of total fat in the diet and whether this varies for subgroups of the population needs to be addressed.

The current UK dietary recommendations (Department of Health, 1994) are for the average contribution of SFA to dietary energy to be reduced to no more than about 10 % energy and a reduction in the average contribution of total fat to dietary energy in the population to about 35 % energy. The latest figures for the UK, however, (Department of the Environment, Food and Rural Affairs, 2001) show average intakes of total fat are just over 38 % energy and total SFA are 15 % energy. It may be, therefore, that a more effective public health approach would be to use a combined strategy involving both reduction in total fat and replacement of SFA with *cis*-unsaturated fats. Such a strategy may be more efficacious in achieving the target of <10 % energy as SFA, which is fundamental to reducing population cholesterol levels and CHD risk.

Although the beneficial impact of MUFA on the plasma lipid profile is possibly less than that of *n*-6 *cis*-PUFA (Clarke *et al.* 1997), intakes of PUFA greater than 10 % energy may have adverse effects on HDL-cholesterol levels (Department of Health, 1994). There are also issues of the greater oxidisability of PUFA, both in foods during processing and cooking, and in the body, where oxidised lipids are implicated in protein and DNA damage. Replacement of SFA with MUFA, therefore, could offer a suitable approach.

Compliance with dietary recommendations remains a major problem and it has been suggested that directly altering the food supply may be the most effective way to ensure compliance (Schaefer, 2002). As 40 % fat in the diet is from manufactured produce, public health nutritionists need to work with industry to encourage the replacement of 'invisible' saturated fats with MUFA. The methods used in the study presented by Christine Williams and previous work (Roche *et al.* 1998; Williams *et al.* 1999) could be employed at the population level: modified oils in catering, in food and spreads manufacture, and in the production of 'healthy' snacks. There is also the possibility of enabling modification in the fatty acid composition of animal fats and dairy products, an opportunity that has not been fully realised despite considerable research evidence for feasibility, efficacy and safety, especially for enrichment with MUFA. Issues such as the higher costs of MUFA relative to SFA and subsequent effects on shelf life would need to be addressed as well as effects on palatability. There would be need to provide industry with an incentive and clear scientific advice.

Workshop recommendations

To provide the scientific basis for such an approach it was recommended that a large multi-centre study, of sufficient size to take account of genetic variation, sex, physical activity and stage-of-life factors should be undertaken. It should also be of sufficient duration to account for adaptation. Because the relative importance of the different risk factors for CHD in different populations and under different conditions is much debated, it is important that any study should assess a comprehensive set of risk factors including endothelial function, insulin sensitivity, lipoprotein metabolism, factor VII and haemostasis, and immune function. The study should look at MUFA replacement of SFA in relation to total lipid intake, e.g. 30, 35 and 40 %

energy with variations in MUFA intake while SFA and PUFA intake remain constant. Industry should be involved in the provision of study diets.

It was also recommended that mechanistic studies should be undertaken to look at the effect of MUFA on: (1) gut control (do MUFA inhibit and/or reduce cholesterol uptake from the gut and is this an effect on chylomicron assembly?, the role of MUFA in stimulating gut hormone release and their physiological consequences); (2) reverse cholesterol transport; (3) adipose tissue cytokine release and sensitive C-reactive protein release as well as other anti-inflammatory effects via monocytes; (4)LDL turnover.

The fatty acid composition of the UK diet should be assessed more frequently. The National Food Survey (Department of the Environment, Food and Rural Affairs, 2001) does not carry this level of detail (only classes of lipids in the diet) so fatty acid analyses of the total diet study should be carried out at least every 2 years.

The FSA has addressed the issue raised in the third recommendation and intends to commission the latest in a series of analyses of the individual fatty acid composition of the total diet survey during 2002. For future analyses; however, the total diet survey is not necessarily the most appropriate way of providing information on a more frequent basis, and other options are currently being considered.

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Appendix

Participants in the workshop were: Professor Mike Gibney, Trinity College, Dublin; Professor Christine Williams, University of Reading; Professor Chris Packard, University of Glasgow; Professor Thomas Sanders, King's College, London; Professor Bengt Vessby, Uppsala University, Sweden; Dr Helen Roche, Trinity College, Dublin; Dr Yvonne Finnegan, University of Reading; Dr Parveen Yaqoob, University of Reading; Dr Bruce Griffin, University of Surrey; Dr Philip Calder, University of Southampton; Dr Jason Gill, University of Glasgow; Dr Sheela Reddy, Department of Health; Dr Judy Buttriss, British Nutrition Foundation; Dr Clare Chapman, Unilever/FDF; Dr Anne Heughan, Unilever/FDF; Dr Mike Rudrum, Unilever Research; Dr Eugene Hammond, Industry Consultant; Dr Juliet Howarth, Margarine & Spreads Association, FDF; Dr Stephen French, Mars Research; Dr Alison Tedstone, FSA; Dr Lisa Jackson, FSA; Ms Alette Weaver, FSA; Dr Peter Sanderson, FSA.