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A 1,3-diacylglycerol-rich oil induces less atherosclerosis and lowers plasma cholesterol in diabetic apoE-deficient mice

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Abstract

Objective: Recent studies have demonstrated that 1,3-diacylglycerol (1,3-DAG) has several metabolic advantages over triacylglycerol (TAG) in humans and in animal models despite both oils having a similar fatty acid composition. In our current study, we have examined the effects of long-term feeding of a 1,3-DAG-rich oil on the dyslipidemia and atherosclerosis in the experimental model of the diabetic apolipoprotein E (apoE)-deficient mouse that develops accelerated atherosclerosis.

Methods and results: Diets containing 1,3-DAG-rich oil or TAG oil were administered to control non-diabetic apoE-dificient and diabetic apoE-deficient mice for 20 weeks. In diabetic apoE-deficient mice, 1,3-DAG reduced the extent of atherosclerotic lesions in the aortic arch and thoracic aorta by 37 and 44%, respectively, compared to TAG. Further, in diabetic apoE-deficient mice, plasma total cholesterol and triglyceride levels were significantly lower in the 1,3-DAG-fed group than in the TAG-fed group. This occurred partially through an apparent reduction in the size of triglyceride-rich lipoproteins but not apparently by reducing the number of lipoprotein particles. By contrast the control non-diabetic apoE-deficient mice showed no differential responses to the type of oil at least over 20 weeks.

Conclusions: We have demonstrated that dietary 1,3-DAG-rich oil reduced atherosclerosis in diabetic apoE-deficient mice, and was associated with reduction in plasma cholesterol especially within larger triglyceride-rich lipoproteins.

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Keywords: Diacylglycerol; Diabetic apoE-deficient mice; Dyslipidemia; Atherosclerosis; Triglyceride-rich lipoprotein

1. Introduction

Dietary diacylglycerol (DAG), which comprised mainly the 1,3-isoform, occurs naturally in various edible oils as a minor component [1,2]. Consequently, 1,3-DAG is widely consumed. Most ingested triacylglycerol is however hydrolysed by 1,3-specific lipase to 1,2 or 2,3-DAG and fatty acids in the intestinal lumen [3]. These DAG are then hydrolysed to 2-monoacylglycerol (MAG) and fatty acid [3]. Subsequently, these substances are absorbed into the intestinal epithelium and rapidly resynthesised into triacylglycerol by the 2-MAG pathway in the intestinal mucosal cells [3]. In contrast, 1,3-DAG is hydrolysed to 1(3)-MAG and fatty acid in the intestinal lumen [4]. 1(3)-MAG is assumed to be absorbed into the intestinal epithelium or further hydrolysed to release the remaining fatty acid and glycerol [4]. Consequently, 1,3-DAG does not appear to be resynthesized to triacylglycerol to the same extent as 2-MAG. Thus, 1,3-DAG probably has a different metabolic pathway compared to that of DAGs derived from triacylglycerol.

Recent studies have demonstrated that dietary 1,3-DAG-rich oil has several advantages over dietary triacylglycerol (TAG oil)[1] in humans and in animal models despite both oils having a similar fatty acid composition. Rats consuming dietary 1,3-DAG oil showed significantly lower serum triacylglycerol levels than after being fed TAG oil [5]. Clinical studies have shown that long-term dietary 1,3-DAG oil reduced serum triacylglycerol levels in type II diabetic

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[1] Although 1,3-DAG oil contains other lipids (see Table 1), it will be referred to in this term. The triacylglycerol oil will be referred to as TAG.

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patients with hypertriacylglyceridemia and in one patient with lipoprotein lipase deficiency [6,7]. Moreover, the long-term ingestion of 1,3-DAG oil decreased body weight and body fat in humans and in high fat-fed C57Bl/6J mice [8,9]. Thus, although there are several studies showing that 1,3-DAG ameliorates obesity and hypertriacylglyceridemia, the effect of this novel DAG on atherosclerosis has not yet been demonstrated.

Patients with type 2 diabetes generally develop a more extensive and inflammatory form of atherosclerosis than non-diabetic individuals [10–12]. Atherosclerosis leading to myocardial infarction and stroke is the major serious complication in diabetics [12] although the precise molecular mechanisms underlying the development of a more severe form of atherosclerosis remain uncertain. Postprandial hypertriacylglyceridemia is a recognized risk factor for cardiovascular disease in diabetics in whom the degree of lipemia is greater than in non-diabetic subjects [13–15]. It is likely that reducing hypertriacylglyceridemia may be an important strategy important in combating atherothrombotic vascular disease as suggested by at least one secondary prevention trial [16].

In our current study, we have examined the effects of long-term feeding of 1,3-DAG oil on the dyslipidemia and atherosclerosis in an experimental model of the diabetic apolipoprotein E (apoE)-deficient mouse. ApoE-deficient mice typify a well-established murine model of hypercholesterolemia [17,18] and such mice fed a Western-type diet are highly susceptible to develop atherosclerotic lesions. Additionally, streptozotocin-induced diabetic apoE-deficient mice are highly vulnerable to dyslipidemia and atherosclerosis even without supplemental fat and cholesterol [19,20]. We have compared in such mice the effects of feeding identical amounts of oil of similar fatty acid composition from either TAG or 1,3-DAG.

2. Methods

2.1. Experimental design

Six-week-old homozygous ApoE-deficient male mice (back-crossed 20 times from C57BL/6 strain; Animal Resource Centre, Canning Vale, WA, Australia) were housed at the Precinct Animal Centre, Baker Heart Research Institute. All procedures were done according to National Health and Medical Research Council guidelines after written approval was obtained from the Institute's Animal Ethics Committee. Mice were rendered diabetic by intraperitoneal injection of streptozotocin (MP Biomedicals, Eschwege, Germany) at a dose of 55 mg/kg in citrate buffer for 5 consecutive days. Control mice received citrate buffer alone. Mice that did not become diabetic were discarded. When the streptozotocin-treated mice were confirmed to be diabetic, each group diabetic and non-diabetic was divided into two groups, one receiving the TAG and the other the 1,3-DAG oil incorporated into the feed to provide an additional 15% fat by weight. Thus, four groups were studied. The non-diabetic mice were in effect a control group for the diabetic mice since the former were not expected to develop significant atherosclerosis within 20 weeks. Diabetic and non-diabetic (control) animals had unrestricted access to the synthetic diets described in Table 1 for 20 weeks using Roden Caffe (Oriental Yeast Co., Tokyo, Japan) to minimize dispersion of diets. TAG and DAG-rich oils include following fatty acids, respectively, 16:0, 5.3 and 3.1%; 18:0, 2.2 and 1.2%; 18:1, 37.6 and 38.8%; 18:2, 46.0 and 47.8%; 18:3, 7.4 and 8.0%; 20:0, 0.5 and 0.2%; 20:1, 0.7 and 0.5%; 22:0, 0.3 and 0.2%; 22:1, 0.1 and 0.1%. The diets containing oils were prepared by Specialty Feeds (WA, Australia), stored at 4 °C before use and changed three times per week.

Table 1
Composition of the diets (percentage by weight)

Ingredients	TAG diet	DAG diet
Triacylglycerol (TAG) oil	15.0	
1,3-Diacylglycerol (DAG)-rich oil[a]		15.0
Casein	20.0	20.0
Cellulose	4.0	4.0
Starch	43.4	43.4
Dextrinised starch	13.2	13.2
DL-Methionine	0.3	0.3
AIN-93-G-trace minerals	0.1	0.1
Lime (fine calcium carbonate)	1.3	1.3
Salt (fine sodium chloride)	0.3	0.3
Potassium dihydrogen phosphate	0.7	0.7
Potassium sulphate	0.2	0.2
Potassium citrate	0.2	0.2
AIN-93-G-vitamins	1.0	1.0
Choline chloride 60% (w/w)	0.3	0.3

[a] The DAG-rich oil contains approximately 90% DAG and 10% TAG. The DAG is comprised of 1,3-DAG and 1,2 (or 2,3) in a ratio of 7:3.

Growth rates, consumption of feed and blood glucose concentration were monitored at regular intervals. Food intake was monitored on a per-cage basis three times per week. At 19 weeks of the study, food intake for 24 h per mouse was measured using a metabolic cage. Body weight was measured weekly. Blood to monitor glucose concentration was collected from saphenous vein monthly. Systolic blood pressure was assessed by a computerized, non-invasive tail cuff system in conscious mice at week of 20 of the study. Mice were habituated to the device before measuring the blood pressure to ensure accurate measurements. At 20 weeks of the study, mice were anesthetized by an intraperitoneal injection of Euthal (10 mg/kg body weight, Delvet Limited, Seven Hills, Australia) and aortas were excised.

2.2. Atherosclerotic lesions

The extent of atherosclerosis was determined using an *en-face* method. Aortas were rapidly removed and fixed in phosphate-buffered 10% formalin after staining with Sudan IV–Herxheimer's solution. Aortas were then opened longitudinally, divided into arch, thoracic and abdominal segments and pinned out flat on wax blocks. Images of each segment were captured with an Axiocam Camera (Zeiss, Heidelberg,

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