Review Article

Metabolism of diacylglycerol in humans

Hideto Takase PhD

Health Care Products Research Labs. No.1, Kao Corporation, Tokyo, Japan

Obesity resides upstream of the constituents of metabolic syndromes such as diabetes, hypertension, hyperlipidemia, and arteriosclerosis. Postprandial hyperlipidemia is also implicated in atherogenesis. Therefore, factors that influence the body adiposity and the magnitude of postprandial hyperlipidemia have been intensively investigated. Diacylglycerol (DAG) oil, which is defined to contain DAG 80% (w/w) or greater in the present presentation, is an edible oil with similar taste and usability compared with conventional edible oil rich in TAG. Safety of DAG has been widely evaluated and listed as a GRAS (Generally Recognized as Safe) substance by US FDA. The aim of this review was to summarize the metabolism and nutritional functions of DAG based on the data from scientific journals and conference publications. Effect of DAG ingestion on postprandial elevations of serum lipids was investigated in several dosages, food formula, and in subjects in various conditions. Postprandial triglyceride in serum and the chylomicron fraction are significantly smaller after DAG consumption compared with TAG with a similar fatty acid composition in healthy subjects, and was remarkably reduced in subjects with insulin resistance. Long-term DAG ingestion in controlled diet or free-living condition significantly decreased body adiposity and improved type II diabetic complications. A single dose DAG consumption significantly increased fat oxidation as compared to eucaloric TAG ingestion. DAG oil consumption might be beneficial in reducing the risk factors for lifestyle-related diseases such as obesity, visceral obesity, postprandial hyperlipidemia, insulin resistance, and atherosclerosis.

Key Words: diacylglycerol, obesity, postprandial hyperlipidemia, type II diabetes, fat oxidation

Introduction

Increasing obesity and related disease, e.g., diabetes mellitus, hypertension, hyperlipidemia[1] and increased risk of heart disease[2] are worldwide problems in human health. Excess fat intake is thought to be one of the major causes of obesity.[3] Numerous dietary programs and utilization of fat-substitutes with regard to restricted fat intake, but obese participants rarely lose weight permanently or maintain their body mass index (BMI) in the normal range because the weight loss is often regained.[4-5] A possible reason for this weight regain may be lack of discipline in following a diet program due to the often poor palatability of low fat diets. Since fat is not only an essential energy source but contributes to the palatability in foods, a person is less likely to tolerate a low fat diet for an extended period of time. For the reasons mentioned above, development of edible oil which can be utilized equally as conventional cooking oil in daily life and be beneficial for weight management has been expected.

Diacylglycerol is a natural minor component of edible oils.[6-7] An oil rich in diacylglycerol (> 80 wt% diacylglycerol) (DAG) was reported to have physicochemical characteristics relating to taste, appearance, physical properties, and functionality similar to those of conventional cooking oil, which is mainly composed of triacylglycerol (TAG).[8] DAG was approved as GRAS (Generally Recognized as Safe) in 2000 and 2002 in US. Nutritional effects on human obesity and hyperlipidemia has been widely investigated and recognized as a FOSHU (Food for Special Health Use) and launched in 1998 in Japan.

The objective of this review is to clarify a role of DAG on obesity prevention and related risk factor by summarizing previously reported scientific literature in human studies.

Structure of DAG and its occurrence in natural oils and fats

Edible oil generally contains up to about 10 % (w/w) DAG, with the relative content depending on the origin of the oil. DAG and other acylglycerol content in the edible oils are shown in Table 1. These values may, of course, vary depending on a number of conditions such as the variety of the oil plant, storage conditions, etc. For example, olive oil contains 5.5 wt% and 8-20 mol% depending on the sample origin.

DAG can exist in two isoforms, 1,2 (or 2,3)-diacyl-sn-glycerol (1,2-DAG) and 1,3-diacyl-sn-glycerol (1,3-DAG). A metabolic intermediate after the ingestion of TAG is 1,2-DAG isoform in digestive tract. On the other hand, the majority of the DAG in edible oils has been converted to 1,3-DAG via acyl group migration during the manufacturing process under elevated temperatures[10] and/or during the storage.

Corresponding Author: Dr Hideto Takase, Health Care Products Research Labs. No.1, Kao Corporation, 2-1-3, Bunka Sumida-ku Tokyo 131-8501, Japan
Tel: 81-3-5630-7266; Fax: 81-3-55630-9436
Email: takase.hideto@kao.co.jp

Table 1. Content of acylglycerol in the edible oils of various origins[a]

	Soybean	Cottonseed	Palm	Corn	Safflower	Olive		Rapseed
Monoacylglycerol	-	0.2	-	-	-	0.2		0.1
Diacylglycerol	1.0	9.5	5.8	2.8	2.1	5.5	8-20[b]	0.8
Triacylglycerol	97.9	87.0	93.1	95.8	96.0	93.3	18-41[b]	96.8
Others	1.1	3.0	1.1	1.4	1.9	2.3		2.3

[a] Data from Ref. 6,7 expressed in weight % except for the right column of olive oil. [b] Data from Ref. 9 expressed in mol %.

Table 2. Studies of the effects of diacylglycerol ingestion on the postprandial response in humans

Study	Subjects		Ingested dosage	Test formula	Duration	Main outcomes	Ref.
Taguchi et al.	Healthy male	n=13 n=10 n=17	10g /60kg body weight 20g /60kg body weight 44g /60kg body weight	emulsion	6 hours	serum TG ↓ magnitude of postprandial lipemia ↓ chylomicron TG↓	21
Tada et al.	Healthy male	n=6	30 g /m^2 of body surface area	emulsion	8 hour	serum TG ↓ serum RLP-Cholesterol ↓	22
Takei et al.	Healthy male	n=17	10g /60kg body weight	mayonnaise	4 hour	serum TG ↓ chylomicron TG↓	23
Tomonobu et al.	Healthy male / female	n=36 (male) n=7 (female)	10g	test meal	6 hours	serum TG ↓ chylomicron TG↓ serum RLP-Cholesterol ↓	24
Takase et al.	Healthy or insulin resistance	n=8 (healthy) n=10 (insulin resistance)	10g /60kg body weight	mayonnaise	4 hour	serum TG ↓ chylomicron TG↓ maximum in serum TG ↓ maximum in chylomicron TG↓ (in subject with insulin resistance)	25
Tada et al.	Type II Diabetic male	n=6	30 g /m^2 of body surface area	emulsion	6 hours	serum TG ↓ serum RLP-Cholesterol ↓	26

Acyl-migration is an equilibrium reaction. The amount of 1,3-isoform present at equilibrium is dependent on the fatty acids in the DAG molecule. For example, at equilibrium, the amount of 1,3-dipalmitoyl-sn-glycerol is 56 % (w/w).[11] In edible oils, which are comprised of common fatty acids, approximately 70 % (w/w) of the DAG exists as 1,3-DAG.

An oil rich in 1,3-DAG can be prepared by esterifying glycerol with fatty acids from natural vegetable oils as described by Watanabe *et al.*[12] using the reverse reaction of an immobilized lipase. Most of the TAG oil used as control oil in the study was prepared by blending rapeseed oil, soybean oil and safflower oil such that the fatty acid composition matches that of DAG oil.

Single dose ingestion studies on postprandial lipids after DAG ingestion in humans

Relations between hypertriglyceridemia and coronary heart disease (CHD) have been widely investigated[13] and triglyceride-rich lipoproteins (TRL), such as chylomicrons, very low-density lipoproteins (VLDL) and their remnants are considered to be independent risk factors for CHD.[14-16] Such TRL are increased mainly in the postprandial state, and many studies have been conclusively shown the relationship between postprandial hyperlipidemia and atherosclerosis.[17-20]

Studies of the effects of DAG ingestion on the postprandial response in humans are listed in Table 2. Taguchi *et al.*[21] showed that triglyceride concentrations in the chylomicron fraction were markedly lower after the ingestion of DAG than after that of TAG. Using single doses of 10, 20 or 44g of DAG, significant differences were observed in the serum amounts of triglycerides for all doses at 6 hours following consumption. Additionally, the 44g dose demonstrated a significant reduction in the IAUC (incremental area under the curve above baseline) of postprandial triglycerides.

Tada *et al.*[22] demonstrated that DAG has been shown to weaken the postprandial increase in remnant-like lipoprotein particles (RLP), which is a more potent risk factor of

cardiovascular diseases than whole serum triglyceride concentrations, using a single dose of 30g/m^2 of body surface area. Significant differences were also observed in the level of change in postprandial serum triglycerides at 2, 3 and 8 hours following consumption of test emulsions.

These two studies were performed using test fat emulsion. More practically, postprandial response of DAG vs. TAG ingestion has been studied using a mayonnaise type solidified dressing prepared from DAG oil or a typical breakfast in which a mayonnaise type DAG (10g DAG oil/60kg) had been incorporated.[23-24] In the latter study, subjects ingested 500 kcal of breakfast containing Protein (29.9g), Fat (18.8g) and Carbohydrate (50.8g) including 15g of mayonnaise with 10g of test oil. These studies were double blind placebo controlled crossover studies and the control was regular mayonnaise prepared with TAG oil with a fatty acid composition similar to DAG oil. Postprandial changes in serum triglyceride levels from the initial values were significantly low in the DAG ingestion group compared to the TAG group. Differences were more pronounced for changes in chylomicron triglyceride and RLP- triglyceride levels.

Postprandial hyperlipidemia is thought to be closely related with insulin resistance, and the effect of DAG on postprandial serum triglyceride was investigated in relation with insulin resistance. Takase *et al*.[25] reported that the reduction of postprandial increment of serum triglyceride strongly correlated with insulin resistance assessed by homeostasis model assessment (HOMA-R). In subjects with insulin resistance (HOMA-R>2.0), the postprandial lipidemia were reduced after DAG ingestion to about half of those after TAG ingestion.

In subjects with type II diabetes, the incremental areas under the curve (IAUC) for serum triglyceride and that for lipids in RLP with DAG ingestion were significantly smaller than those with TAG ingestion.[26] However, changes in serum levels of insulin, free fatty acids, and ketone bodies during fat loading were essentially the same for DAG and TAG.

The lower serum triglyceride levels after DAG ingestion may be the result of the slower rate of chylomicron formation after DAG ingestion compared with that of TAG. A possible mechanism for the reducing effect of DAG on postprandial lipidemia has been investigated in

Table 3. Studies of the effects of long-term DAG ingestion on body fat reduction and related risk factors in humans

Study	Subjects		Ingested dosage	Diet condition	Duration	Main outcomes	Ref.
Nagao et al.	Healthy male	n=19 (DAG) n=19 (TAG)	10g / day	target total fat 50g /day	16 weeks	body weight ↓ abdominal fat area ↓ hepatic fat content↓	28
Takei et al.	Healthy male	n=23 (DAG) N=20 (TAG)	10g / day	target total fat 50g /day	16 weeks	visceral fat area ↓	23
Maki et al.	Overweight or obese American	n=65 (DAG) n=62 (TAG)	15% of total energy	reduced-energy diet (2100-3350 kJ/d deficit)	24 weeks	body weight ↓ body fat mass ↓	29
Katsuragi et al.	Healthy male and female	n=109 (DAG)	ad-libitum	free living	9 months	waist circumference ↓ subcutaneous fat thickness ↓ HDL-cholesterol ↑	30
Otsuki et al.	Healthy male and female	n=60 (DAG)	ad-libitum	free living	2 years	BMI ↓ waist circumference ↓ number of risk factors ↓	31
Takase et al.	Healthy male and female	n=134 (DAG) n=143 (TAG)	ad-libitum	free living	1 year	body weight ↓	32
Matsuyama	Obese children	n=11 (DAG)	ad-libitum	free living	5 months	abdominal fat area ↓	33
Teramoto et al.	Patients on hemo-dialysis	n=10 (DAG)	9.8g / day		3 months	abdominal fat area ↓ VLDL lipoprotein ↓ HDL lipoprotein ↑	34
Yamamoto et al.	Type II diabetic patients with hypertriglyc-eridemia	n=8 (DAG) n=8 (TAG)	10g / day	nutritional counseling for diabetes	12 weeks	serum TG ↓ HbA1c ↓	35
Yamamoto et al.	Type II diabetic patients with hypertriglyc-eridemia	n=11 (DAG) n=13 (TAG)	ad-libitum	nutritional counseling for diabetes	3 months	waist circumference ↓ serum TG ↓ HDL-cholestreol ↑ LDL particle size ↑	36
Yamamoto et al.	Type II diabetic patients with nephropathy	n=8 (DAG) n=7 (TAG)	10g / day	nutritional counseling for diabetes	13 months	body weight ↓ serum TG ↓ serum creatinine →	37

several animal studies. Kondo *et al*.[27] reported the that the main digestive product of DAG is 1-monoacylglycerol, which is poorly re-esterified into triglyceride in the cells of the intestinal lining, and it is thought to be one of the probable causes of the discriminative postprandial response of DAG.

Long-term ingestion study on body fat reduction in humans

Studies of the effects of long-term DAG ingestion on body fat reduction and related risk factors in humans are listed in Table 3. Three double-blinded randomized placebo-controlled studies were conducted in overweight or obese Japanese and American. Nagao *et al*.[28] conducted a comparative study of DAG oil and TAG oil consumption in 38 healthy Japanese men under a controlled fat intake. In subjects consuming approximately 10g/d DAG oil (approximately 5% of total calories) in 50g/d total fat intake for 16 weeks, significantly greater reductions in body weight ($p<0.01$) and body fat area ($p<0.01$) and waist circumference ($p<0.05$) were observed. In a similar manner, Takei *et al*.[23] confirmed significant visceral fat reduction in DAG treatment which was provided in mayonnaise type solidified dressing. In a US population, 131 overweight/obese subjects consuming 15% of total energy from DAG oil for 6 months as part of a mildly hypocaloric diet (500 to 800 kcal/d deficit from the energy requirement calculated based on body weight, sex, activity level and age) revealed a greater extent of body weight and body fat loss.[29] DAG oil was supplied as the oil ingredient for food items which included mayonnaise, crackers, muffins and instant soups, etc.

These studies were conducted under properly controlled diet condition. However, it is very important to evaluate the efficacy of diacylglycerol on weight reduction and maintenance in a free-living environment, because diacylglycerol is used as ordinary cooking oil in consumer's home. Three large scale, long-term, ad-libitum free-living studies were reported. Two of them were single-blinded uncontrolled studies. Katsuragi *et al*.[30] reported that waist circumference and subcutaneous fat were significantly decreased from baseline in ad-libitum consumption of DAG for 9 month. Otsuki *et al*.[31] conducted 2 year ad-libitum study in 60 Japanese subjects (51 males and 9 females) whose body mass index (BMI) was greater than 25kg/m^2 and/or serum triglyceride level was greater than 150 mg/dL. Although it was an ad-libitum, free-living study, energy consumption did not change in study period, but BMI and waist circumference were significantly reduced from baseline. Total number of risk factors (waist circumference, blood pressure, triglyceride, HDL-cholesterol, glucose) was significantly decreased from baseline in subject who had more than 3 risk factors at baseline. Also, one double-blinded randomized placebo-controlled study in ad-libitum, free-living condition was performed.[32] Three-hundred twelve overweight or obese and/or hyperlipidemic Japanese men (n=174) or women (n=138) aged 22 to 73 years were randomly assigned to the DAG group (n=155) or TAG group (n=157) for 12 months. Participants replaced their usual cooking oil with the assigned test oil and used it at home. Of the 312 initial participants, 134 (86%) in the DAG group and 143 (91%) in the TAG group completed the 12-month study period. In the intention-to-treat analysis, body weight decreased in the DAG group as compared with the TAG group and there was a significant difference in body weight at 12 months (-0.90kg, $p=.002$). After 1 year, 21% of the participants (28/134) decreased their BMI by more than 1 unit in the DAG group but less than 10% (14/143) did so in the TAG group ($p=.016$ by $\chi 2$ test). In these ad-libitum free-living studies, study duration is much longer than controlled trial, however, similar body weight reduction was observed in DAG treatment. It may suggest that the practical use of DAG in daily life gives modest body fat reduction and may be useful for healthy body weight management.

Long-term effects of DAG consumption in various clinical conditions were reported. As well as adult obesity, childhood obesity is serious worldwide problem. Matsuyama[33] conducted 5 month study in obese children (n=11, age 7-17) and reported that the abdominal fat area was significantly reduced after DAG treatment. However, body weight and BMI did not decrease because subjects were in growth process. Long-term study for patients on hemodialysis with type IIb or type IV hyperlipidemia was reported by Teramoto *et al*.[34] In patients on hemodialysis**,** abnormality in lipid metabolism is observed frequently, and thought to be closely related to incidence of CHD. After 3 months DAG consumption, visceral fat area, serum triglyceride and Lp(a) were significantly lower and HDL-cholesterol was significantly higher from baseline.

Yamamoto *et al*. reported three clinical studies for type II diabetic patients in various stages.[35-37] In the two studies in type II diabetic patients with hypertriglyceridemia, serum triglyceride were significantly improved in DAG treatment. Other lipid metabolism was also improved. Other study was performed in patients with nephropathy. Consistent with former studies, serum triglyceride was significantly reduced in DAG treatment. The DAG group maintained their serum creatinine level during the 13 months study period, whereas the control TAG group was significantly increased from baseline. The delayed progression of renal failure by DAG may be related to improvement of hypertriglyceridemia, which is a predictor of progressive renal dysfunction. From these results, DAG consumption incorporated with nutritional counseling may be useful for diet therapy for diabetic complications.

Single dose ingestion studies on energy expenditure and fat utilization in humans

If certain food contributes to weight reduction, it is reasonable to suppose it may affect on energy balance between intake and expenditure via suppression of absorption, enhancement of energy expenditure or appetite suppression.

Taguchi *et al*.[38] reported that diacylglycerol does not differ in digestion and absorption route as compared with triacylglycerol and the physiologic fuel value is similar to that of triacylglycerol. Therefore, the nutritional effect of diacylglycerol does not depend on digestibility or reduced energy content.

In humans, the influence of DAG oil versus conventional oil on 36-h energy expenditure and substrate

utilization was reported using healthy 12 women.[39] The study was carried out using human respiratory chamber and the respiratory quotient (RQ) calculated from measurements of expired carbon dioxide and consumed oxygen are used to estimate contribution of fat or carbohydrate as an energy utilization. Although consumption of DAG in place of TAG did not alter energy expenditure, a significant decrease in RQ (-0.006, $p<0.05$) and a significant increase in fat oxidation were observed following consumption of a eucaloric diet containing 12% of total energy from DAG (16% energy from DAG oil) over 36 hours compared to TAG oil. This increase in fat oxidation corresponds to 4.9 g/d on day 1 and 4 g/d on day 2. In same study, appetite after DAG treatment was significantly lower. They discussed such lower appetite in relation with higher plasma ketone bodies (β-hydroxybutylate) arise from higher hepatic fat oxidation.

Saito *et al.*[40] focused on the diet induced thermogenesis and fat utilization after DAG or control TAG ingestion. Thirteen healthy male subjects ingested 4240 KJ diet containing 30g of DAG or TAG and breath samples were collected for up to 5 hours after meal. Change in energy expenditure from fasting tended to be higher ($p<0.1$) at 3 hours after DAG meal compared with TAG meal. Change in RQ was significantly lower at 2 and 5 hours after DAG meal compared with TAG meal. These results suggested that the meal containing DAG may stimulate postprandial fat utilization and diet induced energy expenditure.

Conclusions

Regarding safety, DAG oil has been approved as GRAS by the FDA in the United States. Health benefits have also been evaluated by the Japanese Ministry of Health and Welfare as a "Food for Specified Health Use". The approved claims are: 1) A lower elevation in postprandial triglyceride concentrations in the blood. 2) Less likely to be stored as body fat.

Characteristic features of DAG in postprandial and long-term effects have been widely investigated by several clinical studies compared to TAG. In humans, DAG oil consumption decreases postprandial serum triglycerides and enables greater degrees of body fat and body weight loss compared to conventional oil. Some studies revealed that lipid profile and risk factors were also improved along with body fat reduction. These effects were investigated not only studies in healthy overweight adult but also in subject with various clinical conditions. Especially, utilizability in diet therapy for diabetic patients has gotten a lot of attention recently.

Although some studies suggested possible metabolic effects on energy and fat utilization, which may closely related to the long-term efficacy of DAG, further studies are still needed to confirm its mechanism and increasing the reliability of DAG oil for consumption under various conditions.

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