

Original Article

BMI status influences the response of insulin sensitivity to diacylglycerol oil in Chinese type 2 diabetic patients

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Present study was a post-hoc analysis and aimed to examine the influence of adiposity status on the response of insulin sensitivity to diacylglycerol (DAG) oil in type 2 diabetic patients. A total of 127 type 2 diabetic patients were recruited into a randomized double-blind controlled parallel trial in Hangzhou, China. Subjects were allocated to consume the same amount (25 mL/d) of DAG (n=66) or triacylglycerol (TAG) oil (n=61) with similar fatty acid compositions for 120 days. Marginally significant interaction was observed between BMI status (overweight versus normal weight) and test oils for fasting insulin (p -interaction=0.046) and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) (p -interaction=0.059). For normal weight subjects (BMI \leq 25), DAG group showed significant decrease of fasting insulin (-2.0, 95% CI: -3.90, -0.10; p =0.036) and HOMA-IR (-0.69, 95% CI: -1.36, -0.03; p =0.015), but not in the TAG group. No significant change of either trait in DAG or TAG group was observed for overweight subjects (BMI $>$ 25). In summary, the effect of DAG oil on insulin sensitivity in type 2 diabetic patients is influenced by the baseline BMI status. Type 2 diabetic patients may benefit from DAG oil in terms of insulin sensitivity improvement, however only when they are in normal body weight range.

Key Words: BMI, diacylglycerol, insulin sensitivity, randomized controlled trial, type 2 diabetes

INTRODUCTION

Diacylglycerol (DAG) is a natural component in various edible oils, such as soybean oil, corn oil, safflower oil and olive oil.¹ In the past decade, accumulating evidence from randomized controlled trials²⁻¹¹ suggested that DAG was beneficial for fasting and postprandial hyperlipidemia, and excess adiposity. Several meta-analysis showed that DAG, compared with triacylglycerol (TAG) oil, was efficacious for reducing body weight¹² and postprandial TAG concentration,¹³ and improving fasting TAG concentration in diabetic patients with hypertriglyceridemia.¹⁴ Insulin resistance is a marker of type 2 diabetes and risk factor of cardiovascular disease. A randomized double-blind controlled trial⁹ suggested that DAG oil consumption, compared with TAG oil, decreased insulin resistance and fasting insulin in type 2 diabetic patients. However, other DAG trials showed rather inconsistent results with regard to the improvement of insulin sensitivity.^{2,4,7,8}

Obesity is closely related with insulin resistance and type 2 diabetes,^{15,16} and obese diabetic subjects showed significantly different patterns of glucose metabolism compared with non-obese diabetic subjects.¹⁷ Thus, the response of insulin sensitivity to DAG oil may vary according to different adiposity status, which might contribute to the inconsistent association between DAG intake and insulin resistance. Therefore, we hypothesized that baseline adiposity status could influence the response of insulin sensitivity to DAG oil consumption. We have published the original data of a prior randomized clinical

trial in Clinical Nutrition,⁹ which mainly found that DAG oil improved insulin sensitivity in type 2 diabetic patients. The present study was a post-hoc analysis of the original data. We aimed to re-evaluate if the original finding that DAG oil improved insulin sensitivity was influenced by adiposity of study subjects. We firstly grouped the type 2 diabetic patients based on different baseline BMI status, and examined their response to DAG oil consumption, compared with TAG oil. Furthermore, we examined the interaction of the BMI status with test oils (DAG vs. TAG) for the change of insulin sensitivity in these patients.

MATERIAL AND METHODS

Subjects and study design

The present study is based on a post-hoc analysis of a randomized double-blind controlled parallel trial. The inclusion and exclusion criteria of the diabetic patients have been described for this trial.⁹ A total of 127 type 2 diabetic patients (40-65 y) were included in the intervention, and were randomized into DAG (n=66) and TAG (n=61) group, matched by gender and age. These subjects

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were firstly placed into the same oil (TAG) for 14 days as a run-in period. Then, they were randomized into DAG or TAG group (25 mL/d per subject) and consumed corresponding oil for 120 days. To provide an accurate measurement of the test oils, a 25 mL measure spoon was provided for all the subjects, and these oils were used to substitute part of their cooking oils. Subject compliance and daily oil intake were measured by calculating the used oil bottles (590 mL/bottle) they returned after the intervention. All the recruited subjects were required to maintain their usual dietary habit and physical activity during the study period. All the subjects (except for eight subjects, four in each group) were taking at least one type of the following anti-diabetic medications: glipizide, acarbose, insulin or protamine zinc insulin, and other medication (such as metformin, gliquidon and repaglinide). The study design was approved by the Ethics Committee of the Affiliated Second Hospital, Zhejiang University. All the subjects gave informed consent forms before participating.

Characteristics of test oils

Both DAG and TAG oils were provided by Kao Corporation, Tokyo, Japan. The fatty acid compositions (percentage of total fatty acid) of the DAG were similar as that of TAG. Briefly, 16:0, 18:0, 18:1, 18:2n-6, 18:3n-3, 20:0, 20:1 fatty acid composition (%) in DAG oil was 3.0, 1.1, 32.9, 53.6, 8.8, 0.2 and 0.1, respectively; while it was 4.0, 1.4, 30.6, 54.6, 8.8, 0.3 and 0.1 for TAG oil. 16:1 composition in DAG oil was lower than that in TAG oil (0.3 vs 4.2). The ratio of n-3: n-6 was identical (0.16) between the two oils. The glyceride composition of DAG and TAG oils were 2.3 and 0.3 for mono, 86.1 and 0.4 for diglycerides, and 11.6 and 99.3 for triglycerides, respectively.

Treatment of blood samples and biochemical analysis

Blood samples were collected at day 0, 60 and 120 after an overnight fast when the subjects attended the Affiliated Second Hospital and Affiliated Sir Run Run Shaw Hospital of Zhejiang University. Common anthropometric parameters, including weight, height, waist circumference, and blood pressure were measured at each visit. Overweight was defined as baseline BMI > 25 kg/m².¹⁸

Fasting biochemical parameters were measured with commercial kits on an auto-biochemical analyzer (Olympus AU 2700, Japan). Blood glucose was measured by hexokinase method using commercial kits (Fenghui Medical Sci& Tech Cooperation, China); Fasting insulin and leptin were measured with commercial radioimmunoassay kits (Linco Research, Inc., St Louis, MO, USA). Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) (calculated as: fasting insulin × fasting glucose/22.5) was used to assess insulin resistance. The fatty acid composition of test oils was determined by capillary gas-liquid chromatography with an Agilent 60 m×0.25 mm×0.25 μm column.⁹

Statistical analysis

STATA software (version 12.0, StataCorp LP, College Station, TX, USA) was used to perform the data analyses. All biochemical and anthropometric variables were exam-

ined for normal distribution. HOMA-IR, insulin, glucose, leptin were log transformed to achieve normality before statistical analysis. As fasting insulin and leptin data was only measured before (day 0) and after (day 120) the intervention, our analyses were based on the two time points. Student's t test was used to examine the difference of baseline biochemical and anthropometric parameters between overweight and normal weight subjects. Paired t test was used to examine the change of HOMA-IR or related traits within each oil group. Linear regression models were used to analyze the difference of the change of HOMA-IR or related traits between the two oil groups, adjusting for age, sex, study center and baseline value of corresponding trait. An interaction term was added into the linear regression model to examine the possible interaction between baseline adiposity status and test oils. Baseline BMI was expressed as either a continuous variable or a categorical variable (overweight versus normal weight) for the estimate of interaction. All the values were expressed as mean±SD. Two tailed *p*-values < 0.05 were considered as significant.

RESULTS

Among all the participants, 8 subjects did not complete the study, 7 subjects consumed less than 7 mL/d of oil or have suspect dietary records. Thus, 112 subjects were included in our final analysis. In the DAG group, there were 44 normal weight subjects and 16 overweight subjects, and there were 32 normal weight subjects and 20 overweight subjects in the TAG group. Overweight subjects had significantly higher baseline levels of LDL-cholesterol, TAG, fasting insulin, HOMA-IR, leptin, systolic and diastolic blood pressure, and lower level of HDL-cholesterol (Table 1).

In normal weight subjects, DAG oil significantly decreased fasting insulin (-2.0, 95% CI: -3.90, -0.10) and HOMA-IR (-0.69, 95% CI: -1.36, -0.03) after the intervention, while it was not changed for TAG oil (Table 2). The changes in fasting insulin (*p*=0.003) and HOMA-IR (*p*=0.006) after the intervention were significantly different between the DAG and TAG oil groups. In contrast, among overweight subjects there was no significant difference for the change in fasting insulin and HOMA-IR between DAG and TAG intervention observed. In addition, marginally significant interactions for the change in fasting insulin (*p*-interaction=0.046) and HOMA-IR (*p*-interaction=0.059) were detected between baseline BMI status (as a categorical variable) and test oils. We further assessed the interaction of BMI status as a continuous variable with test oils for fasting insulin and HOMA-IR. Consistently, significant and marginally significant interactions were observed for fasting insulin (*p*-interaction=0.026) and HOMA-IR (*p*-interaction=0.078), respectively. With the increase of baseline BMI, the predicted beneficial decreases of fasting insulin (*p*-trend=0.002) and HOMA-IR (*p*-trend=0.004) were significantly diminished in DAG group (Figure 1).

Body weight (*p*=0.038) and BMI (*p*=0.054) were significantly decreased in DAG group compared with TAG group only among overweight subjects, but not among normal weight subjects (Table 2). To examine the influence of the change of BMI on the observed interaction

and group difference, we added net change of BMI into all the regression models. But no difference was observed with and without the adjustment of net BMI changes (data not shown). No significant difference or interaction between the two oil groups for other metabolic traits was observed.

DISCUSSION

DAG oil is well known for its beneficial effect on adiposity and postprandial hyperlipidemia,^{12,13} but its influence on insulin sensitivity is rather inconsistent among different populations. The present study revealed that baseline BMI status influenced the response of insulin sensitivity to DAG oil in Chinese type 2 diabetic patients. DAG oil improved the insulin sensitivity only among normal weight patients. The beneficial effect of DAG oil on insulin sensitivity was attenuated or even abolished with the increase of the patients' baseline BMI.

The different structures and metabolic characteristics between DAG and TAG oil determine their different effects on weight control, lipid and glucose metabolism. DAG oil is mainly in the form of 1,3-DAG, its metabolites by 1,3-lipase action are glycerol and free fatty acids; while TAG oil is hydrolyzed to 2-monoacylglycerol and free fatty acids in the small intestinal lumen. DAG oil mainly involves glycerol-3-phosphate pathway for the reconstruction of chylomicron TAG, which is less active than the 2-monoacylglycerol pathway (mainly for the metabolism of TAG oil). Animal studies¹⁹⁻²¹ suggested that DAG oil intake activated pathways involved in the fatty acid β -oxidation and suppressed the pathways for fatty acid synthesis, thus affecting energy metabolism. The results of present study were in line with human studies.²²⁻²⁵ Hibi et al²⁵ reported that DAG oil consumption for two weeks stimulated both fat oxidation and resting metabolic rate, thereby contributing to the greater weight loss and reduction of body fat compared with TAG oil consumption. Consistently, greater weight loss was observed in DAG group compared with TAG group in the present randomized trial. Nevertheless, compared with TAG group, the weight loss in DAG group was more evident in the overweight subjects than in normal weight

subjects. This may be because overweight subjects had more excess body fat, and were more subject to the thermogenic effects of DAG oil.

In addition to its effect on body weight, DAG oil consumption improved insulin sensitivity in normal weight diabetic patients in the present study. Previous intervention studies^{4,9} indicated that DAG oil improves glucose metabolism in type 2 diabetic patients. Rodent models^{20,26-28} also showed that DAG oil consumption improves the glucose metabolism and prevents diet-induced impaired glucose tolerance compared with TAG oil. The mechanisms relating DAG oil to insulin sensitivity may involve the reduction of body fat and weight loss, as obesity is closely related with insulin resistance and type 2 diabetes.^{15,16} Nevertheless, the influence of DAG oil on insulin sensitivity may not be solely attributed to its anti-obesity effect, as suggested by the significant interaction between BMI status and test oils in the present study.

Overweight diabetic patients did not benefit from DAG oil in terms of insulin sensitivity improvement, although significant weight loss was observed amongst these subjects. Furthermore, the interaction did not change when net BMI change was adjusted in the statistical models. This indicated that the influence of DAG oil on insulin sensitivity may be partly independent of the change of BMI during the intervention. These results are in agreement with the previous trial,⁴ which found that DAG oil, compared with TAG oil, decreased glycohemoglobin A1c, a marker of long-term blood glucose status. But no significant change of BMI was observed.

Overweight subjects usually have more severe insulin resistance and impaired glucose metabolism, as observed in this study, thus their glucose metabolism may differ considerably from that of the normal weight subjects. Chung et al,¹⁷ reported that when obesity is present in type 2 diabetic patients, the insulin-stimulated glucose uptake was lowered by 35%-40%, together with decreased intracellular substrate availability, lower oxidative rate and non-oxidative glucose metabolism. Therefore, the significantly abnormal glucose metabolism in overweight diabetic patients may abolish the beneficial effects of DAG oil on insulin sensitivity. Reduction of

Table 1. Baseline characteristics of the included type 2 diabetic patients according to their BMI status[†]

	Normal weight (n=76)	Overweight (n=36)	<i>p</i> -value
Male (%)	31 (40.8%)	16 (44.4%)	0.714
Age, y	53.0±6.0	53.4±7.3	0.758
Body weight, kg	57.8±8.6	74.6±8.7	<0.001
Height, cm	163±7.6	166±8.2	0.094
BMI, kg/m ²	21.7±1.9	27.2±1.4	<0.001
Waist circumference, cm	78.7±7.5	91.8±6.5	<0.001
SBP, mmHg	126±13.8	134±14.1	0.007
DBP, mmHg	77.1±9.9	82.4±1.6	0.009
Total Cholesterol, mmol/L	4.66±0.82	4.96±1.03	0.090
HDL-Cholesterol, mmol/L	1.39±0.39	1.16±0.32	0.003
LDL-Cholesterol, mmol/L	2.2±0.54	2.49±0.70	0.017
Triacylglycerol, mmol/L	1.29±0.84	1.84±0.99	<0.001
Glucose, mmol/L	7.48±2.40	7.79±2.00	0.340
Insulin, mU/L	12.9±9.5	19.9±23.8	0.009
HOMA-IR	4.46±4.14	7.48±10.5	0.009
Leptin, μ g/L	6.97±4.88	9.45±6.68	0.038

[†]Values are mean±SD, or n (%). SBP: systolic blood pressure; DBP: diastolic blood pressure; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance.

Table 2. Effect of DAG oil consumption on body weight, insulin resistance and related traits in type 2 diabetic patients with different baseline BMI status[†]

	DAG oil				TAG oil				<i>p</i> -value within group*		<i>p</i> -value between groups*
	Before intervention	After intervention	Change	95% CI	Before intervention	After intervention	Change	95% CI	DAG	TAG	
Normal weight subjects (n=44 for DAG group; n=32 for TAG group)											
Body weight, kg	57.1±7.48	55.9±7.11	-1.22	(-1.76, -0.68)	58.7±9.99	58.0±9.44	-0.77	(-1.43, -0.11)	<0.001	0.025	0.139
Waist circumference, cm	79.7±7.15	78.5±6.88	-1.20	(-1.93, -0.47)	77.3±7.86	77.1±7.34	-0.18	(-0.87, 0.52)	0.002	0.607	0.085
BMI, kg/m ²	21.7±1.60	21.2±1.55	-0.46	(-0.66, -0.26)	21.7±2.29	21.4±2.15	-0.27	(-0.51, -0.02)	<0.001	0.033	0.179
Glucose, mmol/L	7.48±2.47	7.08±2.28	-0.40	(-0.78, -0.02)	7.48±2.35	7.46±2.81	-0.02	(-0.63, 0.59)	0.066	0.621	0.422
Insulin, mU/L	11.8±6.74	9.82±3.44	-2.00	(-3.90, -0.10)	14.4±12.2	18.0±22.7	3.60	(-2.26, 9.45)	0.036	0.107	0.003
HOMA-IR	3.82±2.07	3.11±1.45	-0.69	(-1.36, -0.03)	5.29±5.78	7.32±14.7	2.03	(-2.33, 6.39)	0.015	0.264	0.006
Leptin, µg/L	7.93±5.60	6.64±3.79	-1.29	(-2.62, 0.05)	5.65±3.32	6.31±4.93	0.66	(-0.85, 2.17)	0.190	0.890	0.994
Overweight subjects (n=16 for DAG group; n=20 for TAG group)											
Body weight, kg	73.3±8.62	72.0±9.47	-1.31	(-2.28, -0.34)	75.7±8.82	75.5±8.97	-0.18	(-0.85, 0.50)	0.012	0.594	0.038
Waist circumference, cm	91.4±6.24	90.3±6.32	-1.11	(-2.33, 0.11)	92.1±6.77	92.2±6.69	0.08	(-0.99, 1.15)	0.072	0.877	0.110
BMI, kg/m ²	27.2±1.45	26.7±1.92	-0.50	(-0.87, -0.13)	27.2±1.46	27.1±1.42	-0.07	(-0.32, 0.18)	0.011	0.551	0.054
Glucose, mmol/L	7.20±2.29	7.13±2.04	-0.07	(-0.77, 0.64)	8.27±1.64	8.24±2.25	-0.03	(-0.69, 0.62)	0.988	0.597	0.974
Insulin, mU/L	19.1±24.07	24.0±26.51	5.64	(-0.47, 11.7)	20.5±24.2	23.6±20.1	3.08	(-6.45, 12.6)	0.110	0.191	0.522
HOMA-IR	6.63±9.69	7.78±9.36	1.41	(-0.46, 3.28)	8.11±11.3	9.78±10.9	1.67	(-2.92, 6.26)	0.130	0.289	0.526
Leptin, µg/L	10.2±6.73	11.9±8.31	0.87	(-4.41, 6.15)	8.86±6.76	11.9±10.4	3.05	(0.21, 5.89)	0.699	0.013	0.675

[†]Values are mean±SD, or n (%). DAG: diacylglycerol; TAG: triacylglycerol; HOMA-IR: homeostasis model assessment of insulin resistance.

**p*-values were adjusted for age, sex, study center and baseline value of corresponding trait.

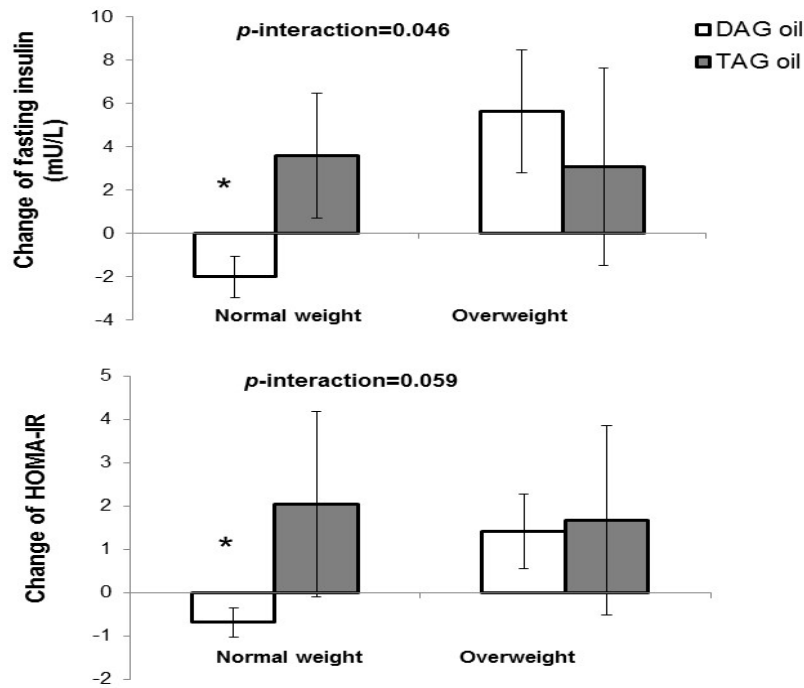


Figure 1. Changes of fasting insulin and HOMA-IR after DAG oil consumption in type 2 diabetic patients with different baseline BMI status. Significant differences for the change of fasting insulin ($p=0.003$) and HOMA-IR ($p=0.006$) between DAG and TAG oil groups were observed in normal weight subjects, but not in overweight subjects. Marginally significant interactions between baseline BMI status (as a categorical variable) and test oils were observed for both fasting insulin (p -interaction=0.046) and HOMA-IR (p -interaction=0.059), after adjusting for age, sex, study center and baseline value of corresponding trait. Data are expressed as mean \pm SE.

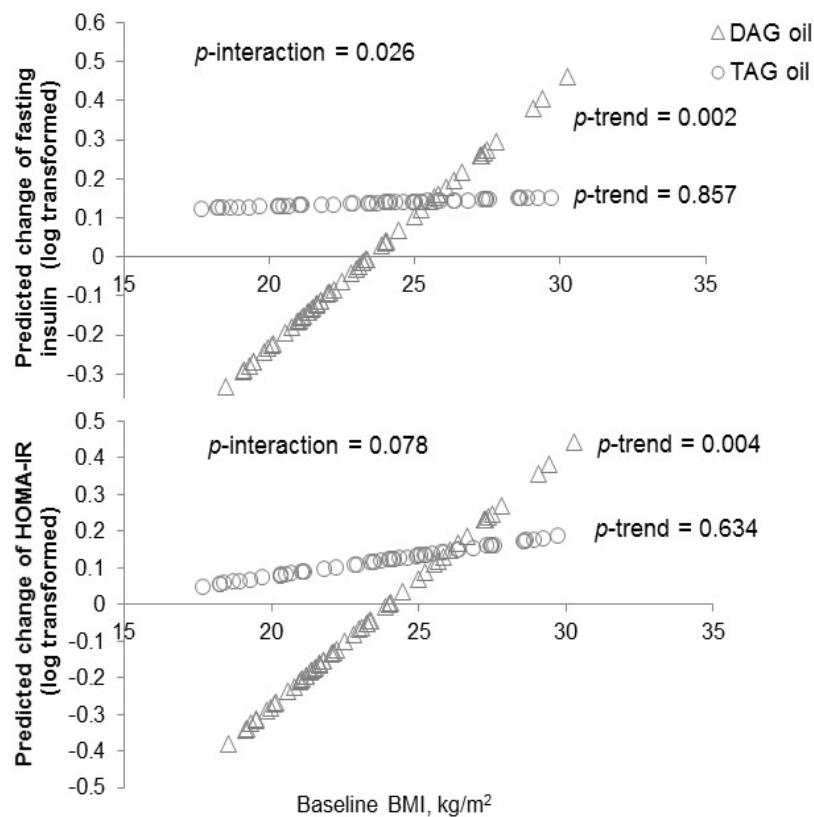


Figure 2. Predicted changes of fasting insulin and HOMA-IR after DAG oil consumption by baseline BMI levels. Significant and marginally significant interactions between baseline BMI and test oils were found for the changes of both fasting insulin and HOMA-IR, respectively. With the increase of baseline BMI, the beneficial decreases of fasting insulin and HOMA-IR diminished significantly in DAG oil group. The predicted changes of fasting insulin and HOMA-IR were calculated with linear regression models, after adjusting for age, sex, study center and baseline value of corresponding trait.

body fat could not reverse the impact of the severely impaired glucose metabolism, which already existed in these overweight diabetic patients. The observed interaction between BMI status and test oils may explain the inconsistent data in previous intervention studies^{4,7,9} with regard to the effect of DAG on insulin sensitivity and glucose metabolism in type 2 diabetic patients.

Type 2 diabetes continues to be one of the most common chronic diseases worldwide, causing substantial economic burdens for society and individuals.²⁹ Dietary approaches are considered to be an effective and sustainable way for the prevention and control of type 2 diabetes.³⁰ DAG oil has sparked great interest among researcher for its health effects, including the improvement of lipid and glucose metabolism, as well as the control of body weight. However, the beneficial effects of DAG oil on insulin sensitivity and glucose metabolism in type 2 diabetic patients are less well-studied. The present study for the first time revealed that the effect of DAG oil on insulin sensitivity was dependent on the baseline adiposity status of the type 2 diabetic patients. This suggests that reduction of body weight should be considered as a priority, rather than targeting insulin sensitivity directly when we intend to treat overweight or obese type 2 diabetic patients. In this respect, DAG remains a good food resource for these patients, given its protective role in weight control. Our study indicated that DAG oil is beneficial for normal weight diabetic patients in terms of improved insulin sensitivity, and for overweight diabetic patients in terms of reduction of body weight.

The main limitation of the present study includes its moderate sample size and post-hoc nature of the analysis. In addition, the interaction of BMI with DAG oil on insulin sensitivity is firstly detected in this study and still lacks of replication in other studies. Larger randomized controlled trials are warranted for the replication of the present findings. Furthermore, the precise mechanism for the effect of DAG oil on insulin sensitivity, independent of anti-obesity effect, is still unclear and needs further investigation.

In conclusion, the present study indicated that baseline BMI status influenced the response of insulin sensitivity to DAG oil consumption in Chinese type 2 diabetic patients. With the increase of baseline BMI, the beneficial effect of DAG oil on insulin sensitivity was diminished, and no effect was observed among the overweight patients. Replication is warranted in larger trials.

AUTHOR DISCLOSURE

We thank the Affiliated 2nd Hospital and Affiliated Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, China, for recruiting patients and for the use of their facilities. We thank Kao Corporation, Kokyo, Japan, for providing the test oils. This study was funded by the National Natural Science Foundation of China (81273054); by the PhD Programs Foundation of Ministry of Education of China (20120101110107); by the National Program on Key Basic Research Project of China (973 Program: 2011CB504002); by the National High-Tech R&D Program of China (863 Program, N20080753). The authors' contributions were as follows: JSZ and DL designed the research and wrote the paper; all co-authors help interpret the data. DL had primary responsibility for the final content. All authors approved the

final manuscript. The authors have declared no conflict of interest.

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Original Article

BMI status influences the response of insulin sensitivity to diacylglycerol oil in Chinese type 2 diabetic patients

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BMI状态影响中国2型糖尿病患者的胰岛素敏感性对甘油二酯的应答

本项二次分析的目的是探讨在中国2型糖尿病患者中进行甘油二酯的干预时，患者的肥胖状态对其胰岛素敏感性变化的影响。此项随机双盲对照试验共在中国杭州纳入了127名2型糖尿病患者，所有患者被随机分配到两个组，分别食用相同体积（25 mL/d）及相似脂肪酸含量的甘油二酯（n=66）和甘油三酯（n=61），持续120天。对空腹胰岛素（ p -交互=0.046）和空腹胰岛素抵抗指数（ p -交互=0.059），BMI状态（超重vs 正常体重）和两种油类干预都有边缘性显著的交互作用。在正常体重患者中（BMI \leq 25），甘油二酯干预能够使空腹胰岛素（-2.0, 95% CI: -3.90, -0.10; p =0.036）和胰岛素抵抗指数水平（-0.69, 95% CI: -1.36, -0.03; p =0.015）显著下降，但甘油三酯没有该作用。在超重患者中，甘油二酯和甘油三酯干预对两种指标都没有显著影响。综上所述，甘油二酯对2型糖尿病患者胰岛素敏感性的影响受患者基线BMI状态的影响。当2型糖尿病患者处于正常体重范围内时，食用甘油二酯可能对其胰岛素敏感性的改善有益处。

关键词：BMI、甘油二酯、胰岛素敏感性、随机对照试验、2型糖尿病