Replication of a Gene-Diet Interaction at CD36, NOS3 and PPARG in Response to Omega-3 Fatty Acid Supplements on Blood Lipids: A Double-Blind Randomized Controlled Trial

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ABSTRACT

Background: Modulation of genetic variants on the effect of omega-3 fatty acid supplements on blood lipids is still unclear.

Methods: In a double-blind randomized controlled trial, 150 patients with type 2 diabetes (T2D) were randomized into omega-3 fatty acid group (n = 56 for fish oil and 44 for flaxseed oil) and control group (n = 50) for 180 days. All patients were genotyped for genetic variants at CD36 (rs1527483), NOS3 (rs1799983) and PPARG (rs1801282). Linear regression was used to examine the interaction between omega-3 fatty acid intervention and CD36, NOS3 or PPARG variants for blood lipids.

Findings: Significant interaction with omega-3 fatty acid supplements was observed for CD36 on triglycerides (p-interaction = 0.042) and PPARG on low-density lipoprotein-cholesterol (p-interaction = 0.02). We also found a significant interaction between change in erythrocyte phospholipid omega-3 fatty acid composition and NOS3 genotype on triglycerides (p-interaction = 0.042), total cholesterol (p-interaction = 0.013) and ratio of total cholesterol to high-density lipoprotein cholesterol (p-interaction = 0.015). The T2D patients of CD36-G allele, PPARG-G allele and NOS3-A allele tended to respond better to omega-3 fatty acids in improving lipid profiles. The interaction results of the omega-3 fatty acid group were mainly attributed to the fish oil supplements.

Interpretation: This study suggests that T2D patients with different genotypes at CD36, NOS3 and PPARG respond differentially to intervention of omega-3 supplements in blood lipid profiles.

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1. Introduction

There has been a pronounced progress in the field of nutrigenetics or gene-diet interaction in the past decade, thanks to the great achievement in the identification of novel genetic variants related to diseases in large-scale epidemiological studies and international consortium [1–4]. The goal of gene-diet interaction is to tailor one’s diet based on his genetic background in contrast to the traditional “one-size-fits-all” dietary recommendation. Although the concept of gene-diet interaction is appealing, and progress within recent years is encouraging, lack of...
replication has become a major barrier affecting the acceleration of the field and its translation into practice [1,4,5].

Omega-3 (or n-3) fatty acids, both marine (C20:5n-3, C22:5n-3, C22:6n-3) and plant based (C18:3n-3), could improve blood lipid profiles and decrease risk of cardiovascular diseases [6–9]. Some intervention studies suggest that effects of omega-3 fatty acids on blood lipids could be modified by genetic variants and supports the existence of gene-diet interaction for omega-3 fatty acids with regard to the lipid outcomes [10–12]. In a systematic review, Corella et al. [13] suggested that only three genes (CD36, NOS3 and PPARγ) showed interactions with omega-3 fatty acids to affect the levels of blood lipids in the intervention studies, while no replication among trials has been reported so far.

Therefore, the aim of the present study was, to use a well-conducted randomized controlled trial to replicate the previous findings from intervention studies about the interaction of genetic variants (single-nucleotide polymorphisms, SNP) at CD36, NOS3 and PPARγ with omega-3 fatty acid intervention for the blood lipids.

2. Materials and Methods

2.1. Study Population and Design

This study was based on a double-blind randomized controlled trial. The trial was registered at ClinicalTrials.gov (No. NCT01857167), and approved by the Ethics Committee of College of Biosystem Engineering and Food Science at Zhejiang University. All participants gave written informed consent.

The inclusion and exclusion criteria, and the detailed procedures of the trial has previous been reported [14]. Briefly, the inclusion criteria were fasting blood glucose < 7.0 mmol/L or on use of diabetic medications, participants between 35 and 80 years for men or between postmenopausal and 80 years for women; the exclusion criteria were having familial hyperlipidemia or with blood triglycerides > 4.56 mmol/L, having a history of hepatic or kidney disease or any type of cancer, or participation in another clinical trial within 30 days.

Blood DNA was isolated by using the QIAamp DNA Blood Mini Kits (Qiagen, Valencia, CA, USA). The selected SNPs were genotyped using the standard protocol recommended by the MassARRAY RS1000 (Sequenom, San Diego, CA, USA) manufacturer, and the data were analyzed by Typen 4.0 Software (Sequenom) [15], with an average genotyping success rate of 98%.

2.2. SNP Selection and Genotyping

SNPs rs1527483 at CD36, rs1799983 at NOS3, and rs1801282 at PPARγ were selected for genotyping based on the prior evidence [13]. Blood DNA was isolated by using the QiAamp DNA Blood Mini Kits (Qiagen, Valencia, CA, USA). The selected SNPs were genotyped using the standard protocol recommended by the MassARRAY RS1000 (Sequenom, San Diego, CA, USA) manufacturer, and the data were analyzed by Typen 4.0 Software (Sequenom) [15], with an average genotyping success rate of 98%.

2.3. Measurement of Blood Lipids, Erythrocyte Phospholipid Fatty Acids, and Other Parameters

Fasting blood samples were collected at baseline and the end of the intervention. Serum high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and triglycerides (TG) were measured by commercially available kits with HIFACHE 7020 chemistry analyzer using enzyme-based colorimetric test supplied by Diasys Diagnostic Systems (Shanghai) Co., Ltd. Erythrocyte phospholipid fatty acid composition was measured by gas chromatography, as has been described previously [14]. Body weight and height were measured by trained nurses at baseline and the end of the intervention. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters.

2.4. Statistical Analyses

All the statistical analyses were conducted using Stata (version 14; StataCorp, College Station, TX, USA). All the lipid variables (HDL-C, LDL-C, TC, TC/HDL-C, and TG) were checked for normal distribution and were natural log-transformed if not normally distributed (for TG only). Dominant models were used to assess the genetic effects and the gene-diet interactions in the present study, as to maximise the sample size in each genetic group. At baseline, the association between blood lipids and genetic variants at CD36, NOS3 and PPARγ was examined by linear regression models, adjusted for age, sex, study center and BMI.

As the primary analysis, we examined the interaction of genetic variants at CD36, NOS3 and PPARγ with omega-3 fatty acid supplements on the change in blood lipids during the intervention based on the complete case analysis. We used general linear model to test the genotype-by-intervention interaction as independent predictors of change in blood lipids, adjusting for sex, age, study center, BMI and baseline value of the corresponding outcome trait. To increase the sample size and the power to detect the interaction, we combined fish oil and flaxseed oil group into one omega-3 fatty acid supplement group, as erythrocyte phospholipid C20:5n-3 and C22:6n-3 were increased in both fish oil and flaxseed oil groups as reported previously [14]. Quanto 1.2.4 (University of Southern California) was used to estimate the detectable effect size of genotype-by-diet interactions. For example, this study had 80% power to detect significant gene-diet interaction effect sizes (for rs1527483) of 0.27 mmol/L, 0.85 mmol/L, 0.97 mmol/L, 1.05, and 0.9 mmol/L for change in HDL-C, LDL-C, TC, TC/HDL-C ratio and TG under a dominant model, respectively.

In a secondary analysis, we examined the interaction between change in erythrocyte phospholipid omega-3 fatty acids (sum of C18:3n-3, C20:5n-3, C22:5n-3 and C22:6n-3, as a continuous variable) and NOS3 genotypes for the change in lipid outcomes using the general linear model, adjusting for age, sex, study center, BMI and baseline value of the corresponding outcome trait. We conducted this secondary analysis because original paper reporting this gene-fatty acid interaction was based on the interaction between change in plasma total omega-3 fatty acids and NOS3 variant on change in TG in an intervention study [10].

If a significant interaction (p < 0.05) was detected, we conducted a stratified analysis by the genotype groups and by intervention groups using the general linear model. In addition, we also separately examined the effects of different omega-3 fatty acid group (i.e. fish oil and flaxseed oil group) on blood lipids by the tested genotypes.
In a post-hoc analysis, we generated a genetic score summing number of the omega-3 responsive allele across the 3 SNPs (rs1527483-G allele, rs1799983-A allele and rs1801282-G allele). Carriers of these alleles in the respective SNP or patients with a higher genetic score showed a better response to omega-3 fatty acids in improving lipid profiles in the present study. We examined the interaction of this genetic score (as a continuous variable) with omega-3 fatty acid intervention on blood lipids using general linear model, adjusting for age, sex, study center, BMI and baseline value of the corresponding outcome trait. We subsequently conducted stratified analysis if a significant interaction (p < 0.05) was observed.

3. Results

After the intervention, there were 94 patients (53 in fish oil and 41 in flaxseed oil group) left in the omega-3 fatty acid supplement group, and 45 patients in corn oil control group. The minor allele frequency of rs1527483 (A allele, CD36), rs1799983 (A allele, NOS3), and rs1801282 (G allele, PPARG) was 0.223, 0.073 and 0.057, respectively, and all SNPs were consistent with Hardy-Weinberg equilibrium (p > 0.05). The population characteristics by the genotypes and the intervention group were presented at Table 1. At baseline, no difference in age, BMI or lipid traits was observed among the different genotypes of the three SNPs.

For CD36 SNP rs1527483, we found a significant interaction (p-interaction = 0.042) of the genotype with serum TG levels. Omega-3 supplements marginally decreased TG levels among rs1527483-GG carriers (p = 0.067), but not among A allele carriers (p = 0.19) (Table 2). When we separated fish oil and flaxseed oil group, TG was decreased significantly among rs1527483-GG carriers after fish oil supplements (p = 0.031), but not flaxseed oil supplements (p = 0.39). No interaction was observed for other lipid outcomes.

We did not find any significant interaction between NOS3 SNP rs1799983 and omega-3 fatty acid supplements on lipid traits (Table 3). In our secondary analysis, we found that change in erythrocyte phospholipid omega-3 fatty acids had significant interaction with rs1799983 on serum TG (p-interaction = 0.042), TC (p-interaction = 0.013) and TC/HDL-C (p-interaction = 0.015) (Fig. 2). In the low omega-3 fatty acid change group (<1.38%, calculated based on the median level of the omega-3 fatty acid change), rs1799983 A allele carriers had increased change in TG (p = 0.035), TC (p = 0.02) and TC/HDL-C (p = 0.035) compared with CC carriers, while no difference was found in the high omega-3 fatty acid change group (≥1.38%).

For PPARG SNP rs1801282, we observed that omega-3 supplements interacted with the SNP to modulate LDL-C levels (p-interaction = 0.02). Stratified analysis suggested that GG/GC allele carriers had a significantly higher increase in LDL-C with CC carriers in the control group (p = 0.022), but no difference was observed in the total omega-3 group, fish oil or flaxseed oil group (Table 4).

We observed a significant interaction between the genetic score and omega-3 fatty acid supplements on TG levels (p-interaction = 0.04) (Fig. 3), not for other lipids. Among the control group, serum TG levels were significantly higher (p = 0.008) in high genetic score group compared with low genetic score group, while no difference was observed among omega-3 supplement group. Omega-3 supplements significantly decreased serum TG levels compared with control only among participants with a high genetic score (p = 0.026), and only fish oil (p = 0.009), not flaxseed oil, decreased TG in the subgroup analysis. (See Fig. 3).

4. Discussion

In the present study, we successfully replicated the interaction of genetic variants at CD36, NOS3 and PPARG with omega-3 fatty acids on blood lipids. The T2D patients with CD36 major allele GG genotype, but not A allele carriers, displayed a decreased TG concentration in...
response to the omega-3 intervention. Carriers of the PPARG minor G allele, compared with those carrying CC genotype, showed increased levels of LDL-C among control group, but not among the omega-3 intervention group. We also replicated the interaction between erythrocyte omega-3 fatty acid change and NO3 variant on blood lipids that rs1799893 minor A allele carriers responded better to high erythrocyte omega-3 fatty acid in improving lipid profiles. A genetic score generated based on the three SNPs demonstrated a combined effects of the three SNPs for their interactions with omega-3 supplements on blood lipids. The effect of the omega-3 supplement group was mainly attributed to the fish oil supplements.

In a prior intervention study, 111 healthy Caucasian men took 1.71 g fish oil supplements.

### Table 2

| Total omega-3 supplements | Fish oil supplements | Flaxseed oil supplements | Control |
|---------------------------|----------------------|--------------------------|---------|
| AA/AC (n = 10)            |          |                       |         |
| Baseline                  | 1.10 (0.20) | 1.00 (0.22) | 0.99 (0.21) | 0.99 (0.21) |
| After intervention        | 1.10 (0.20) | 1.00 (0.22) | 0.99 (0.21) | 0.99 (0.21) |

### Table 3

| Total omega-3 supplements | Fish oil supplements | Flaxseed oil supplements | Control |
|---------------------------|----------------------|--------------------------|---------|
| AA/AC (n = 10)            |          |                       |         |
| Baseline                  | 1.10 (0.20) | 1.00 (0.22) | 0.99 (0.21) | 0.99 (0.21) |
| After intervention        | 1.10 (0.20) | 1.00 (0.22) | 0.99 (0.21) | 0.99 (0.21) |

### Table 4

| Total omega-3 supplements | Fish oil supplements | Flaxseed oil supplements | Control |
|---------------------------|----------------------|--------------------------|---------|
| AA/AC (n = 10)            |          |                       |         |
| Baseline                  | 1.10 (0.20) | 1.00 (0.22) | 0.99 (0.21) | 0.99 (0.21) |
| After intervention        | 1.10 (0.20) | 1.00 (0.22) | 0.99 (0.21) | 0.99 (0.21) |

### Table 5

| Total omega-3 supplements | Fish oil supplements | Flaxseed oil supplements | Control |
|---------------------------|----------------------|--------------------------|---------|
| AA/AC (n = 10)            |          |                       |         |
| Baseline                  | 1.10 (0.20) | 1.00 (0.22) | 0.99 (0.21) | 0.99 (0.21) |
| After intervention        | 1.10 (0.20) | 1.00 (0.22) | 0.99 (0.21) | 0.99 (0.21) |

### Table 6

| Total omega-3 supplements | Fish oil supplements | Flaxseed oil supplements | Control |
|---------------------------|----------------------|--------------------------|---------|
| AA/AC (n = 10)            |          |                       |         |
| Baseline                  | 1.10 (0.20) | 1.00 (0.22) | 0.99 (0.21) | 0.99 (0.21) |
| After intervention        | 1.10 (0.20) | 1.00 (0.22) | 0.99 (0.21) | 0.99 (0.21) |
by the omega-3 supplements compared to the other genotype group. The functional SNPs in CD36 gene responsible for the observed interaction are still not clear and warrant further investigation.

NOS3 gene encodes nitric oxide synthase 3, metabolizing L-arginine to nitric oxide. Homozygotes (AA carriers) of the NOS3 SNP rs1799983 (also known as Glu298Asp) A minor allele have increased risk of cardiovascular diseases [10]. In a randomized trial among 450 individuals with metabolic syndrome, carriers of the rs1799983 A allele showed a greater response to increased plasma omega-3 fatty acid levels in terms of reduction in TG levels [10]. In a cross-sectional analysis of 248 participants, increased omega-3 fatty acid levels were positively associated with endothelial function only in rs1799983 A allele carriers, but not in the CC genotype carriers [27]. In another postprandial study among 30 rs1799983 A allele carriers and 29 rs1799983 C allele carriers, only women with rs1799983 A allele were responsive to the beneficial effect of omega-3 fatty acids on endothelial function [28].

The above literature together with the findings from the present study suggest that rs1799983 minor A allele carriers might achieve more benefits in terms of improved lipids and other cardiovascular profiles in response to a higher omega-3 fatty acid exposure, compared to those with CC genotype. The above observed interaction is biological plausible. The minor A allele was suggested to be associated with endothelial function only in rs1799983 A allele carriers, but not in the CC genotype carriers [27]. In another postprandial study among 30 rs1799983 A allele carriers and 29 rs1799983 C allele carriers, only women with rs1799983 A allele were responsive to the beneficial effect of omega-3 fatty acids on endothelial function [28].

The above literature together with the findings from the present study suggest that rs1799983 minor A allele carriers might achieve more benefits in terms of improved lipids and other cardiovascular profiles in response to a higher omega-3 fatty acid exposure, compared to those with CC genotype. The above observed interaction is biological plausible. The minor A allele was suggested to be associated with a
lower NOS3 activity and lower NOS3 protein enrichment in the caveolar membrane fraction [29], while inhibition of NOS was found to be associated with an increase in circulating TG and cholesterol [29]. Dietary omega-3 fatty acid supplements could increase basal endothelial NO production and also increase NOS3 mRNA and protein levels [29]. Moreover, omega-3 fatty acids were shown to regulate caveolar microenvironment, including the distribution and translocation of NOS in caveolar [30,31]. Therefore, it is possible that omega-3 fatty acid supplements compensate the disrupted NOS3 activity caused by the rs1799983 minor A allele, whereas the homozygotes of the C major allele might not get additional benefit given its normal NOS3 activity in caveolar.

PPARG encodes peroxisome proliferator-activated receptor-gamma, which is a transcription factor that regulates various genes involved in lipid storage, adipogenesis and insulin sensitization [32]. Animal model showed that the rs1801282 variant, as an important modulator in metabolic control, was strongly subject to the influence of dietary factors or gene-diet interaction [33]. This concept was further confirmed in human studies, where the interaction of the rs1801282 with dietary fat intake has been reported in various populations [11,34–38]. In a controlled trial among 150 individuals, participants were randomized to consume fish oil supplement or placebo oil for 3 months. In that trial, rs1801282 G allele carriers had a greater decrease in serum TG in response to the omega-3 fatty acid supplements, compared with the CC carriers [11]. SNP rs1801282 G allele carriers had higher levels of LDL-C compared with CC carriers in a previous meta-analysis among Asian populations [39]. We found consistent association in the control group, but not in the omega-3 group. We hypothesized that the deleterious effect of rs1801282 G allele on LDL-C was attenuated by omega-3 fatty acids supplements.

There are several limitations in the present study. First, the sample size of the present study is moderate, limiting the statistical power of detecting a gene-diet interaction. Second, the combined intervention group has a double sample size than the control group. However, the impact of the difference in sample size on the interaction analysis should be minimal, as we have also examined the interaction for fish oil and flaxseed oil separately compared with control group and the results of fish oil is consistent with the combined intervention group across different tested genes. Third, potential false positive results may occur due to multiple testing, although we intends to replicate the gene-diet interaction in previous reports and the tests are hypothesis driven. We further demonstrate the existence of the interaction by using a generic score of the 3 tested SNPs. Fourth, our study is based on a Chinese population with T2D and the generalizability to other ethnicities or healthy populations may be limited. The major strength of the present study is that it is based on a well-conducted double-blind randomized controlled trial, which lasts for 180 days with good participant compliance as measured by erythrocyte fatty acid composition.

In conclusions, using a double-blind randomized controlled trial, we replicated the interaction between omega-3 fatty acids and genetic variants at CD36, NOS3 and PPARG on blood lipids reported in previous intervention study. These replications suggest that the effects of omega-3
fatty acids on blood lipids may vary by genetic variation at CD36, NOS3, PPARG genes, and a personalized diet recommendation based on certain genetic make-up to improve blood lipid profiles may work specifically for omega-3 fatty acid intake. Nonetheless, this study is still quite preliminary, and more trials with larger sample size are warranted.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

The author’s responsibilities were as follows: DL (Principal Investigator) and JSZ: designed the study; LW, HY, LF, YY, LY, JF, ML: conducted the clinical trials in study centers; JC, KL, JT: contributed to IC data collection and sample measurements; JSZ analyzed data and performed statistical analysis: JSZ, JC, CQ, DL: wrote paper; DL and JSZ had primary responsibility for final content. All authors contributed to the manuscript review and approved the final version.

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