RESEARCH PAPER

An interaction effect between *glucokinase* gene variation and carbohydrate intakes modulates the plasma triglyceride response to a fish oil supplementation

Annie Bouchard-Mercier · Iwona Rudkowska ·
Simone Lemieux · Patrick Couture · Marie-Claude Vohl

Abstract A large inter-individual variability in the plasma triglyceride (TG) response to fish oil consumption has been observed. The objective was to investigate the gene–diet interaction effects between single-nucleotide polymorphisms (SNPs) within *glucokinase* (*GCK*) gene and dietary carbohydrate intakes (CHO) on the plasma TG response to a fish oil supplementation. Two hundred and eight participants were recruited in the greater Quebec City area. The participants completed a 6-week fish oil supplementation (5 g fish oil/day: 1.9–2.2 g EPA and 1.1 g DHA). Thirteen SNPs within *GCK* gene were genotyped using TAQMAN methodology. A gene–diet interaction effect on the plasma TG response was observed with rs741038 and CHO adjusted for age, sex and BMI ($p = 0.008$). In order to compare the plasma TG response between genotypes according to CHO, participants were divided according to median CHO. Homozygotes of the minor C allele of rs741038 with high CHO >48.59 % had a greater decrease in their plasma TG concentrations following the intake of fish oil ($p < 0.05$) than C/C homozygotes with low CHO and also than the other genotypes either with high or low CHO. The plasma TG response to a fish oil supplementation may be modulated by gene–diet interaction effects involving *GCK* gene and CHO.

Keywords Glucokinase · Carbohydrate · Fish oil · Triglyceride · Gene–diet interaction

Introduction

Glucokinase (*GCK*) gene encodes for GCK or hexokinase type IV which phosphorylates glucose to glucose-6-phosphate (Massa et al. 2011). *GCK* gene is expressed mainly in the liver and in pancreatic beta cells but also in neurons, the pituitary and the entero-endocrine K and L cells (Massa et al. 2011). GCK has a glucose-sensor role and regulates glucose disposal toward glycogenesis and TG synthesis (Iynedjian 2009). It is partly regulated by GCKR which forms an inhibitory complex with GCK at low glucose concentrations because of its binding with fructose-6-phosphate (Choi et al. 2013). At high glucose concentrations such as after a meal high in carbohydrates (CHO), fructose-1-phosphate binds with GCKR and releases GCK which enhances glucose metabolism leading to a greater glycolytic flux (Girard et al. 1997b; Iynedjian 2009). A few single-nucleotide polymorphisms (SNPs) within GCK have been reported to have an impact on type 2 diabetes risk, glycemia, beta cell function and plasma TG concentrations (Hu et al. 2010; Sotos-Prieto et al. 2013; Wang et al. 2013; Fu et al. 2013; Asselbergs et al. 2012).

The hypotriglyceridemic impact of marine omega-3 polyunsaturated fatty acids (n-3 PUFA) at doses around 3 g or more is well known (De 2011). This effect is even

A. Bouchard-Mercier · S. Lemieux · P. Couture · M.-C. Vohl (✉)
Institute of Nutrition and Functional Foods (INAF), Laval University, 2440 Hochelaga Blvd., Quebec G1V 0A6, Canada
e-mail: marie-claude.vohl@fsaa.ulaval.ca

A. Bouchard-Mercier · S. Lemieux · M.-C. Vohl
Department of Food Science and Nutrition, Laval University, 2425 de l'Agriculture St., Quebec G1K 7P4, Canada

A. Bouchard-Mercier · I. Rudkowska · P. Couture · M.-C. Vohl
Endocrinology and Nephrology, CHU de Québec Research Center, 2705 Laurier Blvd., Quebec G1V 4G2, Canada

observed among individuals with plasma TG concentrations within normal values (<1.7 mmol/L) and at lower marine n-3 PUFA doses (<2 g) (Caslake et al. 2008). However, an important inter-individual variability in the plasma TG response to marine n-3 PUFA has been reported (Caslake et al. 2008; Cormier et al. 2012; Minihane et al. 2000). Approximately 30 % of the individuals do not lower their plasma TG concentrations following the intake of marine n-3 PUFA (Cormier et al. 2012; Madden et al. 2011). The reduction in de novo lipogenesis pathway is one of the mechanisms which may explain the hypotriglyceridemic effect of n-3 PUFA (Harris and Bulchandani 2006). Among healthy individuals, the proportion of free fatty acids from de novo lipogenesis contributing to the free fatty acids pool that are incorporated into the VLDL-TG assembly is relatively small ($\sim$5 %) (Vedala et al. 2006). However, among hypertriglyceridemic obese individuals with or without type 2 diabetes, the contribution of de novo lipogenesis increases to around 13–14 % (Vedala et al. 2006). De novo lipogenesis is modulated by high dietary carbohydrate (CHO) intakes which increase the activity of GCK, the production of acetyl-CoA and malonyl-CoA, therefore stimulating de novo lipogenesis (Girard et al. 1997a; Iynedjian 2009). Thus, we hypothesized that SNPs within *GCK* gene could have an impact on the plasma TG response to a fish oil supplementation and these impacts could be modulated by gene–diet interaction effects with dietary CHO.

Methods

Participants

A total of 254 unrelated participants were recruited to participate in this clinical trial from the greater Quebec City metropolitan area between September 2009 and December 2011 through advertisements in local newspapers as well as by electronic messages sent to university students/employees (Bouchard-Mercier et al. 2013). Briefly, to be eligible, participants had to be non-smokers and free of any thyroid or metabolic disorders requiring treatment such as diabetes, hypertension, severe dyslipidemia and coronary heart disease. A total of 210 participants completed the n-3 PUFA supplementation period. However, plasma TG concentrations were available for 208 participants, and thus, the analyses were conducted on 208 participants. No differences in the descriptive characteristics were observed between the participants included in these analyses and the participants who did not complete the study or for which plasma TG concentrations values were missing. The experimental protocol was approved by the ethics committees of Laval University Hospital Research Center and Laval University. This clinical trial was registered at clinicaltrials.gov

(NCT01343342). Informed written consent was obtained from all the study participants.

Study design and diets

The study design and diets have been described previously (Bouchard-Mercier et al. 2013). Briefly, participants followed a run-in period of 2 weeks. Individual dietary instructions were given by a trained dietitian to achieve the recommendations from Canada's Food Guide in order to standardize dietary intakes. Some specifications were given regarding the n-3 PUFA dietary intake: not exceed two fish or seafood servings per week, prefer white flesh fishes instead of fatty fishes (examples were given) and avoid enriched n-3 PUFA dietary products such as some milks, juices, breads and eggs. Subjects were also asked to limit their alcohol consumption during the protocol; two regular drinks per week were allowed. In addition, subjects were not allowed to take n-3 PUFA supplements (such as flax-seed), vitamins or natural health products during the protocol.

After the 2-week run-in period, each participant received a bottle containing n-3 PUFA capsules for the next 6 weeks. They were instructed to take five capsules (1 g of fish oil/capsule) per day (Ocean Nutrition, Nova Scotia, Canada), providing a total of 5 g of fish oil (1.9–2.2 g EPA and 1.1 g DHA) per day.

Participants completed two 3-d food records, before and after the n-3 PUFA supplementation period. Thus, the first food record reflected dietary intakes of the week prior to the beginning of the supplementation period and for the second food record the week prior to the end of the supplementation period. All foods and beverages consumed on 2 representative weekdays and 1 weekend day were weighed or estimated and recorded in food diaries. Dietary intake data were analyzed using Nutrition Data System for Research software version 2011 developed by the Nutrition Coordinating Center (NCC), University of Minnesota, Minneapolis, MN.

Biochemical parameters

The morning after a 12-h overnight fast and 48-h alcohol abstinence, blood samples were collected from an antecubital vein into vacutainer tubes containing EDTA. Plasma was separated by centrifugation ($2,500 \times g$ for 10 min at 4 °C), and samples were aliquoted and frozen for subsequent analyses. Plasma total cholesterol (total-C) and plasma TG concentrations were measured using enzymatic assays (Burstein and Samaille 1960; McNamara and Schaefer 1987). Infranatant ($d > 1.006$ g/ml) with heparin-manganese chloride was used to precipitate VLDL and LDL and then determine HDL-cholesterol concentrations

Fig. 1 Linkage disequilibrium (LD) plot of tSNPs within *GCK* gene. LD plots were generated by HaploView software version 4.2 using R^2 LD values
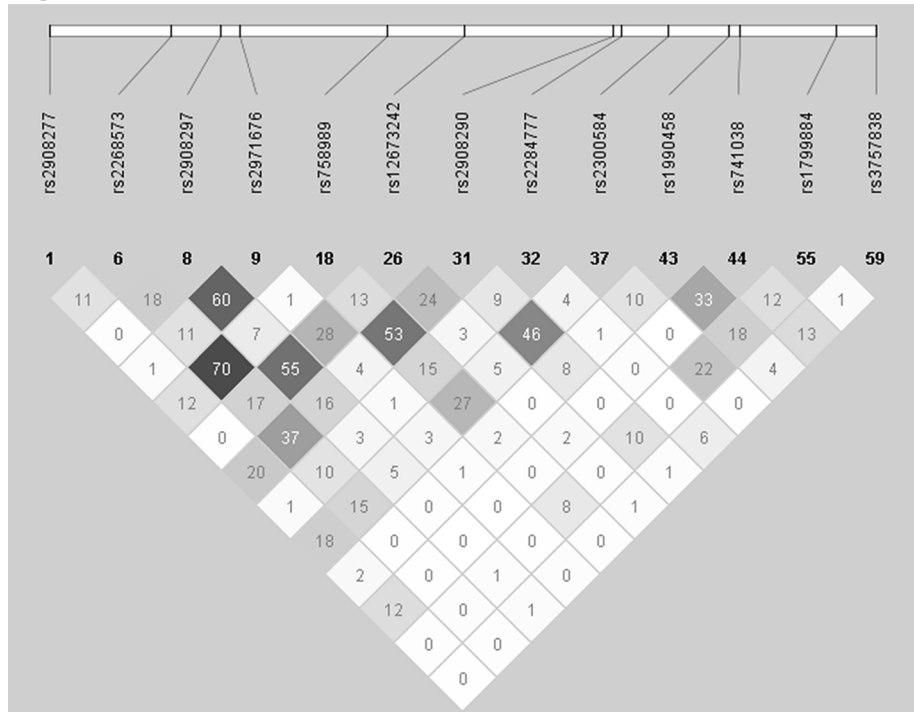

Table 1 Descriptive characteristics of the study participants

Variables	Baseline ($n = 208$)	Pre ($n = 208$)	Post ($n = 208$)	p^{a}
Age (years)	30.82 ± 8.66	–	–	
Sex (men/women)	96/112	–	–	
BMI (kg/m^2)	27.84 ± 3.73	27.81 ± 3.74	27.90 ± 3.85	0.005
Fasting glucose (mmol/L)	4.95 ± 0.52	4.95 ± 0.46	5.05 ± 0.49	0.0003
Fasting insulin (pmol/L)	82.51 ± 35.61 ($n = 206$)	87.15 ± 75.70	83.63 ± 40.81 ($n = 207$)	0.98
Total-C (mmol/L)	4.82 ± 1.01	4.75 ± 0.90	4.72 ± 0.94	0.48
LDL-C (mmol/L)	2.79 ± 0.87 ($n = 207$)	2.76 ± 0.81	2.78 ± 0.85	0.42
HDL-C (mmol/L)	1.46 ± 0.39	1.44 ± 0.36	1.47 ± 0.40	0.005
Triglycerides (mmol/L)	1.23 ± 0.64	1.21 ± 0.63	1.02 ± 0.52	<0.0001
Dietary intakes				
Energy (kcal)	–	$2,273 \pm 590$ ($n = 207$)	$2,186 \pm 566$	0.006
Fat intake (%)	–	32.59 ± 6.04 ($n = 207$)	35.30 ± 6.27	<0.0001
CHO (%)	–	50.51 ± 7.16 ($n = 207$)	48.61 ± 7.75	0.0009
Protein intake (%)	–	17.36 ± 3.32 ($n = 206$)	16.95 ± 3.17	0.12

Mean ± SD

[a] p values were calculated with paired t tests

(HDL-C) (Albers et al. 1978). The equation of Friedewald was used to estimate LDL-cholesterol concentrations (LDL-C) (Friedewald et al. 1972). Non-HDL-C was calculated by subtracting HDL-C from total-C.

SNPs selection and genotyping

As described previously (Bouchard-Mercier et al. 2013), SNPs were selected with the International HapMap Project

SNP database (HapMap Data Rel 28 Phase II + III, August 10, on National Center for Biotechnology Information (NCBI) B36 assembly, dbSNP b126). The chromosomal region selected was chr7:44149895-44198063, which included 2,500 bp upstream and 500 bp downstream of *GCK* gene. Tag SNPs (tSNPs) were determined with the tagger procedure in HaploView software version 4.2 with minor allele frequency (MAF) of >0.05 and pairwise tagging $R^2 \geq 0.80$. For each gene, a minimum of 85 % of the

most common SNPs had to be captured by tSNPs. Afterward, as shown in Fig. 1, linkage disequilibrium (LD) plot was generated with Haploview software version 4.2. All tSNPs were genotyped within INAF laboratories with the TAQMAN methodology (Livak 1999), as described previously (Cormier et al. 2012). Briefly, genotypes were determined using ABI Prism SDS version 2.0.5 (Applied Biosystem, Foster City, CA, USA). All SNPs were successfully genotyped with a call rate of 100 % ($n = 208$).

Statistical analyses

Hardy–Weinberg equilibrium was tested with the ALLELE procedure of SAS version 9.3 using Fisher's exact test ($p < 0.01$). When the genotype frequency for homozygous individuals of the minor allele was <5 %, carriers (heterozygotes and homozygotes) of the minor allele were grouped.

Variables non-normally distributed were logarithmically transformed (BMI, plasma TG and insulin). Differences were assessed using analyses of variance (ANOVAs) with the GLM procedure in SAS and the type 3 sum of squares for unbalanced study design. To examine the impact of gene–diet interaction effects on the plasma TG response, the interaction term (SNP × CHO) was added into the ANOVA model. The plasma TG response was calculated as followed: ((post-supplementation plasma TG − pre-supplementation plasma TG)/pre-supplementation plasma TG × 100). The model was adjusted for the effects of age, sex and BMI. To take into account the effects of multiple testing, the simpleM procedure described by Gao et al. (2008) was used. The number of effective independent test determined by the procedure of Gao et al. (2008) was eight, and only one environmental factor (CHO) was studied. Thus, p values lower than 6.25×10^{-3} were considered significant ($p = 0.05/(8 \times 1)$). All statistical analyses were performed using SAS statistical software version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Results

Descriptive characteristics of the study population and tSNPs

As previously observed (Thifault et al. 2013), the baseline, pre- and post-supplementation descriptive characteristics including dietary intakes of the study participants are presented in Table 1. Briefly, BMI, fasting glucose and HDL-C slightly increased ($p = 0.005$, $p = 0.0003$ and $p = 0.005$, respectively), whereas plasma TG decreased ($p < 0.0001$) following the fish oil supplementation. For dietary intakes,

Table 2 Pre-supplementation plasma TG concentrations according to genotype of tSNPs within *GCK* gene

tSNPs	Genotype	Plasma TG concentrations (mmol/L)	p^a
rs2268573	C/C	1.26 ± 0.69	0.90
	A/C	1.19 ± 0.65	
	A/A	1.17 ± 0.47	
rs2908297	G/G	1.22 ± 0.66	0.97
	A/A+A/G	1.17 ± 0.47	
rs2971676	C/C	1.21 ± 0.65	0.76
	T/T+C/T	1.21 ± 0.45	
rs758989	A/A	1.27 ± 0.74	0.53
	A/G	1.21 ± 0.63	
	G/G	1.12 ± 0.47	
rs12673242	T/T	1.22 ± 0.66	0.81
	C/C+C/T	1.18 ± 0.47	
rs2908290	C/C	1.27 ± 0.75	0.80
	C/T	1.13 ± 0.49	
	T/T	1.22 ± 0.51	
rs2284777	A/A	1.23 ± 0.61	0.17
	G/G+A/G	1.15 ± 0.67	
rs2300584	T/T	1.24 ± 0.69	0.68
	C/C+C/T	1.15 ± 0.50	
rs1990458	G/G	1.16 ± 0.65	0.13
	A/G	1.18 ± 0.56	
	A/A	1.42 ± 0.77	
rs741038	T/T	1.26 ± 0.63	0.48
	C/T	1.18 ± 0.62	
	C/C	1.11 ± 0.65	
rs1799884	G/G	1.24 ± 0.65	0.28
	A/A+A/G	1.15 ± 0.59	
rs2908277	C/C	1.22 ± 0.64	0.87
	T/T+C/T	1.18 ± 0.58	
rs3757838	T/T	1.24 ± 0.65	0.07
	A/A+A/T	1.00 ± 0.36	

Mean ± SD

[a] p values of the GLM models are adjusted for age, sex and BMI

total daily energy intakes (including fish oil supplements) and CHO (expressed as percentage of energy intakes) decreased ($p = 0.006$ and $p = 0.0009$, respectively) and total fat intakes (expressed as percentage of energy intakes) increased ($p = <0.0001$) following the fish oil supplementation.

The selected SNPs are presented in Online Resource 1. All SNPs were in Hardy–Weinberg equilibrium ($p < 0.01$). Figure 1 presents the LD plot. Briefly, thirteen tSNPs covered 86 % of the known genetic variability within *GCK* gene (including 2,500 bp upstream and 500 bp downstream *GCK* gene).

Table 3 Gene–diet interaction effects on the plasma TG response to fish oil

tSNPs	Genotype	β (interaction term)	P genotype[a]	P CHO[a]	P interaction effect[a]
rs2268573	C/C	0	0.94	0.05	0.96
	A/C	0.0740 ± 0.5332			
	A/A	-0.1084 ± 0.6796			
rs2908297	G/G	0	0.54	0.27	0.40
	A/A+A/G	0.4819 ± 0.5730			
rs2971676	C/C	0	0.73	0.23	0.70
	T/T+C/T	0.2427 ± 0.6239			
rs758989	A/A	0	0.62	0.04	0.67
	A/G	0.4084 ± 0.5660			
	G/G	-0.0393 ± 0.5978			
rs12673242	T/T	0	0.14	0.68	0.09
	C/C+C/T	1.0556 ± 0.6198			
rs2908290	C/C	0	0.65	0.07	0.65
	C/T	0.3690 ± 0.4906			
	T/T	-0.2902 ± 0.8764			
rs2284777	A/A	0	0.48	0.04	0.50
	G/G+A/G	-0.3345 ± 0.4975			
rs2300584	T/T	0	0.38	0.04	0.36
	C/C+C/T	-0.4474 ± 0.4880			
rs1990458	G/G	0	0.09	0.07	0.07
	A/G	1.1604 ± 0.5029			
	A/A	0.4946 ± 0.7105			
rs741038	T/T	0	0.01	0.0004	0.008
	C/T	0.3766 ± 0.4779			
	C/C	-2.4272 ± 0.9010			
rs1799884	G/G	0	0.73	0.05	0.78
	A/A+A/G	-0.1385 ± 0.4847			
rs2908277	C/C	0	0.97	0.08	0.83
	T/T+C/T	-0.1151 ± 0.5440			
rs3757838	T/T	0	0.18	0.03	0.19
	A/A+A/T	-1.0834 ± 0.8202			

Mean ± SD

[a] p values of the GLM models are adjusted for age, sex and BMI

The impact of CHO and tSNPs on pre-supplementation plasma TG concentrations

No gene–diet interaction effects on pre-supplementation plasma TG concentrations were observed (data not shown). Pre-supplementation CHO intake was positively associated with pre-supplementation plasma TG concentrations ($r = 0.19$, $p = 0.007$). Pre-supplementation plasma TG concentrations according to genotype are presented in Table 2. Briefly, no differences in plasma TG concentrations were observed according to genotypes. A trend ($p = 0.07$) was observed for rs3757838, for which individuals carrying the A allele had lower plasma TG concentrations than T/T homozygotes.

The impact of tSNPs, CHO and gene–diet interaction effects on the plasma TG response

A trend for an inverse relationship between the plasma TG response and post-supplementation CHO was observed ($r = -0.14$, $p = 0.05$). This association was also observed between the plasma TG response and pre-supplementation CHO ($r = -0.19$, $p = 0.008$). As shown in Table 3, gene–diet interaction effects on the plasma TG response were observed with rs741038 and post-supplementation CHO expressed as percentage of energy consumption and adjusted for age, sex and BMI ($p = 0.008$) and was significant after correction for multiple testing only when pre-supplementation plasma TG concentrations were included
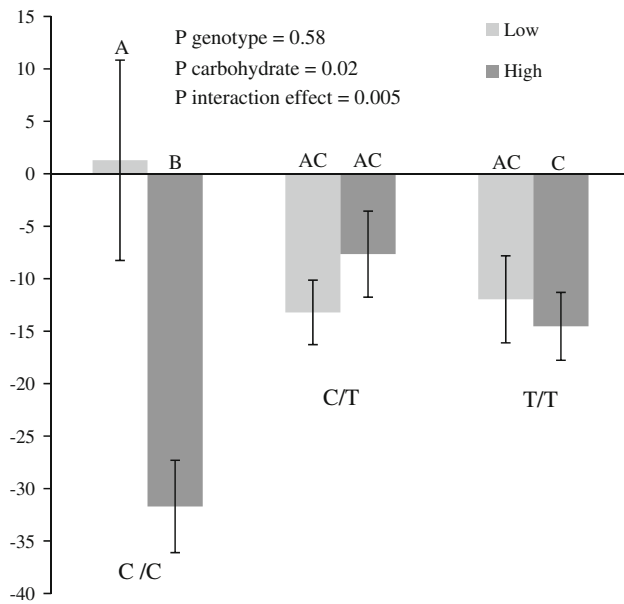
Fig. 2 The plasma TG response (%) according to median CHO and rs741038 genotype. The plasma TG response following fish oil supplementation (mean ± SE). Means with *different letters* are significantly different (assessed by an ANOVA). CHO are separated according to the median value: ≤48.59 (*low in light color*) and >48.59 % (*high in dark color*). Number of participants: low CHO and C/C genotype ($n = 13$), high CHO and C/C genotype ($n = 10$), low CHO and C/T genotype ($n = 44$), high CHO and C/T genotype ($n = 49$), low CHO and T/T genotype ($n = 47$), high CHO and T/T genotype ($n = 45$)

into the model as a confounding variable ($p = 0.001$). A trend for a gene–diet interaction effect was also observed for rs1990458 ($p = 0.07$) when age, sex and BMI were included in the model. None of the other SNPs were associated with the plasma TG response either alone or in interaction with CHO. To further explore the impact of rs741038 and CHO, participants were divided on the basis of CHO using the median value and genotype. As shown in Fig. 2, homozygotes for the minor C allele of rs741038 with high CHO >48.59 % had a greater decrease in plasma TG concentrations following the intake of fish oil than C/C homozygotes with low CHO intake ($p = 0.002$), than C/T heterozygotes with either low or high CHO ($p = 0.03$ and $p = 0.005$, respectively) and than T/T homozygotes with either low or high CHO intakes ($p = 0.02$ and $p = 0.04$, respectively).

Discussion

In this study, gene–diet interaction effects on the plasma TG response to fish oil were observed between *GCK* gene and CHO. The intake of CHO modified the plasma TG response to fish oil depending on the genotype of rs741038

within *GCK* gene. For C/C homozygotes, low CHO intakes were associated with an increase in plasma TG concentrations, whereas when CHO intakes were high, they had the greatest decrease in their plasma TG concentrations following the fish oil supplementation of all genotype groups. The SNP rs741038 is an intronic SNP with no potential regulatory impact and is not in LD with rs1799884 or rs2070971 which have been associated previously with plasma TG levels, fasting glucose and/or type 2 diabetes risk (Asselbergs et al. 2012; Holmkvist et al. 2008; Sotos-Prieto et al. 2013; Webster et al. 2009; Hu et al. 2010; Wang et al. 2013). However, it is possible that rs741038 is in LD with other unknown functional SNPs. Moreover, the association between rs1799884 and plasma TG concentrations was not confirmed by our results (Sotos-Prieto et al. 2013). Hishida et al. (2012) have investigated the impact of gene–diet interaction effect on the risk of dyslipidemia defined as elevated plasma TG and/or low HDL-C concentrations and did not observe interaction effects with *GCK* gene rs1799884 and the intakes of energy, fat, CHO or alcohol. A recent meta-analysis has shown that the association between rs1799884 and type 2 diabetes varies according to ethnic populations and could be more important among Caucasians than among Asians (Fu et al. 2013). In a large-scale gene-centric meta-analysis, the intronic SNP rs2070971 within *GCK* gene was associated with plasma TG concentrations (Asselbergs et al. 2012).

In the liver, *GCK* gene expression is regulated by the presence of insulin (Iynedjian et al. 1988; Iynedjian 2009). This mechanism involves the long-term regulation of *GCK* gene transcription and translation (Moore et al. 2012). The induction of *GCK* gene expression by insulin may be modulated by dietary components such as dietary PUFA which decrease *GCK* gene expression induction (Jump et al. 1994). Moreover, the long-term consumption of a diet high in fat and in fructose among dogs has shown to also decrease GCK protein and its activity in the liver as well as glycogen storage, but not mRNA abundance (Coate et al. 2010, 2011; Moore et al. 2012). It has been observed that *GCK* mRNA abundance is positively correlated with the liver TG content (Peter et al. 2011). An increased *GCK* gene expression was also positively associated with expression levels of lipogenic enzymes and de novo lipogenesis index (Peter et al. 2011). It has been observed that compared to a high-fat/low-CHO diet, a low-fat/high-CHO diet led to increases in de novo lipogenesis which was correlated with the increase in plasma TG concentrations among both normoinsulinemic and hyperinsulinemic individuals (Schwarz et al. 2003). In this study, there was a positive correlation between pre-supplementation CHO and plasma TG concentrations. However, following the intake of fish oil, an inverse relationship between CHO (both pre-

and post-supplementation) and the plasma TG response was observed. Thus, it is possible that higher pre-supplementation CHO leads to higher GCK activity and, therefore, enhances the potential of fish oil to decrease its activity and affect plasma TG concentrations.

The variability observed in the plasma TG response to fish oil could be attributable to factors such as poor compliance. However, compliance rates were high (94 %) (Bouchard-Mercier et al. 2013), and thus, poor compliance could not explain the variability observed. Sex is another factor that may modulate the plasma TG response to fish oil (Caslake et al. 2008); however, no sex effect (or statistical interaction with sex) was observed in this cohort (Thifault et al. 2013). In our previous work, differences between responders and non-responders to fish oil intake according to the plasma TG response in the modulation of the expression levels of many genes involved in glycerophospholipid, sphingolipid, arachidonic acid and linoleic acid metabolisms were observed (Rudkowska et al. 2012). It is possible that pre-supplementation gene expression levels, depending on the dietary intakes or other environmental parameters, may affect the plasma TG response to fish oil.

Conclusion

A gene–diet interaction effect between GCK gene and CHO on the plasma TG response following fish oil intake among overweight individuals has been observed. For homozygotes of the minor allele, higher CHO intakes led to important decreases in plasma TG concentrations following the fish oil supplementation. However, when their intake of CHO was lower, they slightly increased their plasma TG concentrations. Still, for homozygotes of the minor allele with lower CHO intakes, plasma TG concentrations were within normal values. Thus, they are unlikely to be at increased cardiovascular disease risk following fish oil supplementation. These results need to be replicated among other populations. In the future, considering dietary carbohydrate intakes and the genetic background before recommending fish oil to reduce plasma TG concentrations may be of importance to identify subgroups of the population that may not respond as predicted. These results reinforce the importance of considering inter-individual variability in the response to fish oil supplementation. It will also be necessary to achieve a global understanding of the impacts of several gene–diet interaction effects on the plasma TG response to fish oil before taking this knowledge into clinical practice.

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