Nutrition, Metabolism & Cardiovascular Diseases (2012) 22, 449–455

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journal homepage: www.elsevier.com/locate/nmcd

Nutrition, Metabolism & Cardiovascular Diseases

Perilipin polymorphism interacts with saturated fat and carbohydrates to modulate insulin resistance☆

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Received 2 April 2010; received in revised form 20 August 2010; accepted 1 September 2010

KEYWORDS
Perilipin;
Gene-nutrient interaction;
Insulin resistance;
Replication

Abstract *Background and aims:* Macronutrient intakes and genetic variants have been shown to interact to alter insulin resistance, but replications of gene–nutrient interactions across independent populations are rare, despite their critical importance in establishing credibility. We aimed to investigate a previously demonstrated saturated fat and carbohydrate interaction for insulin resistance for perilipin (*PLIN1*), a regulator of adipocyte metabolism.
Methods and results: We investigated the previously shown interaction for *PLIN1* 11482G > A (rs894160) on insulin resistance in US men ($n = 462$) and women ($n = 508$) (mean ± SD, 49 ± 16 years). In multivariable linear regression models, we found an interaction ($P < 0.05$) between the ratio of saturated fat to carbohydrate intake as a continuous variable and *PLIN1* 11482G > A for HOMA-IR (homeostasis model assessment of insulin resistance) in women. For carriers of the minor allele but not for non-carriers, as the ratio of saturated fat to carbohydrate intake increased, predicted HOMA-IR increased ($P = 0.002$). By dichotomizing the ratio of saturated fat to carbohydrate intake into high and low, we found significant interaction terms for insulin and HOMA-IR ($P < 0.05$). When the ratio of saturated fat to carbohydrate was high, insulin and HOMA-IR were higher in minor allele carriers ($P = 0.004$ and $P = 0.003$, respectively), but did not differ when the ratio was low. Similar patterns or trends were observed when saturated fat and carbohydrate were dichotomized into high and low as individual macronutrients.

☆ This work was supported by the National Institutes of Health, National Institute on Aging, Grant Number 5P01AG023394-02 and NIH/NHLBI grant number HL54776 and NIH/NIDDK DK075030 and contracts 53-K06-5–10 and 58–1950-9–001 from the U.S. Department of Agriculture Research Service. C.E. Smith is supported by T32 DK007651-19.

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0939-4753/$ - see front matter
doi:10.1016/j.numecd.2010.09.003

Conclusions: Replication of the previously reported interaction between macronutrient intakes and *PLIN1* genotype for insulin resistance reinforces the potential usefulness of applying genotype information in the dietary management of insulin resistance.

The prevalence of insulin resistance is growing globally in conjunction with increased obesity prevalence [1] and a sedentary lifestyle [2], but glucose metabolism may also be modified by dietary macronutrients [3,4]. The role of fat quantity and specific types of fatty acids (e.g., saturated, monounsaturated (MUFA), omega-3) in modulating glucose metabolism has been extensively explored, often in the context of obesity and metabolic syndrome [5–10]. However, high fat meals have been shown to alter insulin concentration and insulin sensitivity even in healthy individuals with normal glucose and lipid metabolism [7,10]. Saturated fat may be particularly detrimental to glucose metabolism [9], at least in overweight individuals [11].

While the evidence for a role of saturated fat in glucose metabolism is strong, results are not conclusive. In some studies, polyunsaturated and omega-3 fatty acids [5,12] or MUFA appear to play a larger role [6,7]. These inconsistencies may be related to macronutrient substitutions and displacement among various fatty acid types. Alternatively, genetic variation in regulators of lipid metabolism is another potential source of variability in sensitivity of glucose metabolism to particular fatty acids.

One such metabolic regulator is perilipin, the most abundant protein surrounding the triglyceride droplet in adipocytes, where it regulates adipocyte metabolism and lipolysis [13]. Perilipin interacts with hormone-sensitive lipase to facilitate lipolysis of triglyceride, but also acts as barrier to inhibit triglyceride hydrolysis by preventing lipase access [14,15]. One particular common variant, *PLIN1* 11482G > A, has been extensively investigated and has been associated with altered adipocyte perilipin content, altered lipolysis rates and differences in plasma free fatty acid concentrations following weight loss [13,16]. Although established primarily as a modifier of obesity risk in women or in predominantly female populations [17–19], the same *PLIN1* SNP (single nucleotide polymorphism) 11482G > A was also shown to modulate susceptibility to insulin resistance in women [20]. Specifically, the relationship between the 11482G > A variant and insulin resistance was observed in the context of high saturated fat/low carbohydrate intake, suggesting that *PLIN1* genotype could be a potential source of variability in the response of glucose metabolism to dietary macronutrients.

While evidence relating *PLIN1* variants to obesity has accumulated from studies in several independent populations, relationships between *PLIN1*, macronutrient intake and insulin resistance have been reported in women in a single, although large and multi-ethnic, study of Asians [20]. Confirmation of genetic associations and interactions described in one population is infrequently established in independent populations, although replication is considered essential to establishing scientific credibility. Recent recommendations published by a genotype–phenotype association working group emphasize the scarcity of replication studies and propose that positive replication is best achieved by examining the same phenotype and SNP using a similar study design [21]. In the current study, we examined associations between *PLIN1* 11482G > A insulin resistance and BMI, and potential interactions with saturated fat and carbohydrate intake in a White population living in the US.

Methods

Study population

Study subjects were recruited from three-generational pedigrees from the ongoing National Heart Lung and Blood Institute Family Heart Study to participate in the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) Study. The GOLDN study was designed to evaluate genetic factors that modulate dietary and fenofibrate responses, and its methods have been previously described in Ref. [22]. Study sites were located in Minnesota and Utah and the predominantly White subjects were of Northern European origin. Criteria for exclusion included age <18 years, triglyceride >16.5 mmol/L, myocardial infarction within six months, and history of hepatic, renal, gall bladder, pancreatic or malabsorptive disease or insulin use. Study protocol approval was obtained from the Human Studies Committee of Institutional Review Board at the University of Minnesota, University of Utah, and Tufts Medical Center. All participants provided written informed consent. Questionnaires were used to collect demographic, lifestyle, medical history, medication and dietary data. The original sample size targeted for the study was approximately 1200. Complete biochemical data (fasting and post-prandial) were obtained from 1118 individuals.

Laboratory and anthropometric measurement methods

Laboratory methods have been previously described in detail in Ref. [22]. Venous blood was drawn after an overnight fast. Glucose concentration was measured using a hexokinase-mediated reaction on the Hitachi 911 (Roach Diagnostic). A commercial kit using a radioimmunoassay (Linco Research, St. Charles, MO) was used for insulin. Insulin resistance (fasting glucose X fasting insulin/22.5) was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) method. Anthropometric data were measured using standard techniques. Height was measured using a stadiometer and weight using a beam balance.

Dietary intake and lifestyle habits

Dietary intake was estimated by use of the Diet History Questionnaire, a food frequency questionnaire that consists