Review Article

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High Genetic Risk of Diabetes after a High-Carbohydrate Meal

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Abstract

The aim of our study was to evaluate postprandial metabolic changes in healthy men with a high genetic risk for diabetes, following two meals with high polynutrient content. Amount of change, the study was performed in 21 homozygous non-diabetic men carrying the high-risk genotype or locus rs7901695. During two challenges, subjects received standard 450 kcal isothermal liquid meals: HC contains many starchy substances, carbohydrates: 89% energy and normal carbohydrates NC, carbohydrates: 45% energy. Fasting and postprandial plasma samples were analyzed for metabolite profiles by non-targeted metabolites. Metabolic fingerprinting was performed on an ultra-high performance liquid chromatography system connected to an Funnel quadrupole time-of-flight mass spectrometer.

Keywords: Polynutrient • Plasma

Introduction

Type 2 diabetes is a heterogeneous metabolic disease with multifactorial etiology including genetic and environmental factors. Single nucleotide polymorphisms in the transcription 2 7-like gene have been shown to confer one of the strongest genetic predispositions to T2DM, mainly due to their influence on pancreatic β-cell dysfunction [1]. Some studies have reported defects in insulin secretion, some authors found insulin resistance and decreased insulin action, other authors found no decline in cell function and no relationship with insulin action. Simultaneously, the development of T2D may be regulated by exogenous factors, such as diet, and the extent to which exogenous factors influence disease outcome may be influenced by different patterns. Individual genes. Interactions between the TCF7L2 gene variant and metabolic parameters have been shown to impact β-cell function. In our previous study, we observed that SNPs in the TCF7L2 gene affect postprandial glucose and lipid utilization in non-diabetic men. The molecular and cellular mechanisms underlying the potential metabolic changes associated with the TCF7L2 SNP leading to the development of type 2 diabetes are still not fully understood [2-5]. Recently, measurements of a large number of metabolites have been successfully used to determine the metabolic signature of many diseases. Metabolomics is a useful method for identifying and quantifying or semi-quantitatively metabolic compounds that are ultimately associated with specific disorders. To our knowledge, the association between TCF7L2 SNPs and postprandial plasma metabolite profiles in healthy subjects has not yet been investigated. In addition, studies in healthy subjects are of great importance to better understand the effects of gene-diet interactions on human metabolism and on pathways associated with the development of metabolic diseases. Postprandial metabolic studies are relevant for characterizing individual responses to diet [6]. We hypothesize that healthy individuals with a high genetic risk for T2DM may exhibit an early metabolic disturbance that can be induced by eating a variety of meals, leading to the progression of metabolic dysfunction evolution and evolution of T2DM. Therefore, we recruited non-diabetic men with TCF7L2 SNPs and analyzed fasting and postprandial plasma metabolite concentrations in response to the stimulation tests of the meals rich in carbohydrates and normoglucic, aimed at identifying potential specific early disorders that may be involved in the future development of T2D. Our previous Haploview analysis in this study group indicates that the TCF7L2 SNPs examined in rs7901695, rs4506565 and rs7903146 are in very high linkage disequilibrium, thus for in-depth metabolic analysis Rather, the participants were divided based on the genotype [7].

Metabolic analysis

Metabolic fingerprinting was performed using a UHPLC 1290 Infinity system, Agilent Technologies connected to an iFunnel Q-TOF 6550 mass spectrometer, Agilent Technologies. The preparation, analysis, and data processing of plasma samples were performed according to the protocols described previously. In the quality assurance procedure, metabolic traits have good repeatability, i.e. those detected in >80% of the quality control samples and with a CV of 80% of the samples in at least one dataset were accepted and then perform dedicated filtering for each comparison. Metabolic features present in ≥80% of samples in the group were forwarded for statistical analysis. The AUC was calculated based on the relationship between time points and signal intensities for each metabolite. A statistical analysis was performed on the AUCs obtained and comparisons were made between the genotypes studied. The NC meal group was analyzed independently of the HC meal group [8]. The selection of statistically significant metabolites was made on the basis of partial least squares discriminant analysis models obtained by SIMCA software. Volcano plots are generated using the variable's significance in the projection and scaled P-load values as the correlation coefficient values; variables with VIP > 1.0 and absolute P > 0.4 were considered significant. In addition, for each significant metabolite, the P value was calculated in Matlab. Shapiro-Wilk test is used for normality tests, then depending on the distribution of data, t-test or Mann-Whitney test is performed. Multivariate statistically significant metabolites were determined by matching the spectral data of the reference compounds available in the public database with the MS tandem spectral data obtained for the metabolites present in plasma samples. Route analysis was performed using Metabo Analyst 3.0 [9].

Statistical analysis

Following ingestion of the NC meal, in HR genotyped men, lower postprandial AUC concentrations were observed for LysoPC O-18: 1, LysoPC O-16: 0, LysoPC16: 0, LysoPC O-18: 0 and PC 36: 5, while LysoPC 20 ASC after meals: 2, LysoPC 22: 6, CP 18: 1, and EP P-16: 0/22: 6 was significantly higher than individuals with the LR genotype. We also observed in HR genotype carriers significantly lower AUC for postprandial sphingomyelin plasma concentrations HC and 125–832% higher AUC for postprandial sphingomyelin concentrations after administration NC meal. The postprandial AUC of decenoylcarnitine and tetradecenoylcarnitine was lower after the NC meal, while the postprandial AUC of isobutyryl carnitine was lower after the HC meal in men in the HR genotype group. Our analysis also showed that the postprandial AUC of oleic acid, AA, keto-octadecadienoic acid, hexacosanedioic acid, hydroxyeicosatetraenoic acid, and hydroxydocosahexaenoic acid was significantly lower in HR genotyped subjects after eating the HC meal [10]. Men with HR genotype had lower AUCs for OA and AA, HETE, HDoHe, and keto-octadecadienoic acid concentrations after meals. In men with HR genotype, we observed lower AUC of postprandial leukotriene A4 and leukotriene B5 plasma concentrations after HC meal intake. Carriers of HR genotype had a >500% higher AUC of postprandial linoleamide concentrations after the NC meal, as well as a 367% higher AUC of postprandial eicosenamide and a 51% higher AUC of postprandial docosenamide concentrations after when taking HC meals. In addition, after eating the HC meal, we noted a lower AUC of postprandial pyroglutamic acid and uric acid levels in HR genotyped men.

Conclusion

The main limitation in our experience is the small sample size of the study, one of the reasons why LC-MS-based non-targeted metabolism can be performed in a limited, but limited sample set. The overall number of CC genotypes is about 6% and it is difficult to find healthy individuals carrying the genotype at risk. Despite the limitations, our results suggest that in nondiabetic HR genotype carriers, in a state where the usual parameters of glucose homeostasis have not been affected, there are subtle changes in mediating metabolic regulation that cannot be detected only by food challenge assays. Functional studies are needed to extrapolate from our findings and hypothesize effects on biochemical pathways, because despite the well-established effects of TCF7L2 SNPs on β-cell function, but there may be additional underlying pathways leading to its effect on glucose metabolism or a defense mechanism by which the carrier is at greatest genetic risk

still tolerate glucose. Further investigations may provide novel strategies for prevention and personalized dietary treatment involving the T2DM gene.

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