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Commentary

Dietary Supplementation with L-Arginine, Single Nucleotide Polymorphisms of Arginase 1 and 2, and Plasma L-Arginine

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There are ~3 million single nucleotide polymorphisms (SNPs) between 2 unrelated individuals, with each SNP representing a single modification in the genomic code and cumulatively representing 0.1% human genetic diversity. Although many of these differences are silent, relatively recent data suggest that around half of the various responses to dietary agents could be related to genetic variation, a field coined as nutrigenetics. These variations are of considerable interest in improving the health of individuals and collectively mitigating the risk of chronic disease. In this issue of the Journal, Hannemann et al. (1) describe a possible functional relation between arginase isoforms, important in the urea cycle and nitric oxide (NO) production and produced by SNPs of arginase 1 and 2, and circulating plasma arginine concentrations in individuals with or without dietary supplementation.

L-Arginine is the amino acid substrate for numerous enzymatic pathways involved in the regulation of vascular tone, immune activation, and cell growth and is metabolized by nitric oxide synthase (NOS) to NO and citrulline and by arginase to urea and ornithine (2). Ornithine is a substrate for the synthesis of polyamines and proline, whereas citrulline, a coproduct of the NOS reaction, is used for the synthesis of arginine via the citrulline-NO cycle (3). Intracellular concentrations of arginine are maintained by endogenous sources such as intracellular protein degradation or by endogenous synthesis, primarily in the kidney, and plasma concentrations are regulated via endogenous synthesis, protein biosynthesis, dietary uptake, and enzymatic metabolism (2).

In humans, 2 isoforms of arginase exist, arginase type 1 (ARG1) and type 2 (ARG2), which are encoded by different genes and differ in tissue distribution, intracellular location, and in molecular and immunochemical characteristics (4, 5). Hepatic ARG1 is a cytosolic enzyme and ARG2 is a mitochondrial enzyme that is expressed in most tissues including the kidney. ARG2 appears to control the availability of the arginine used for NO synthesis and is necessary for the synthesis of ornithine. ARG1 functions largely in the terminal step of the urea cycle in which arginine is converted to urea and ornithine (6).

Arginine-dependent NO impacts the immune, neuronal, and cardiovascular systems and is a potent vasodilator critical for vascular tone, blood pressure modulation, vascular permeability, and angiogenesis (7–9). SNPs in the ARG1 gene are clinically associated with cardiovascular diseases such as hypertension, cardiomyopathy, myocardial infarction, and carotid intima media thickness, and upregulation of arginase is implicated in vascular dysfunction (10, 11). Thus, dietary supplementation with L-arginine could be warranted.

The study by Hannemann et al. is the first to describe an association between genotypes of ARG1 and ARG2 with consequent circulating plasma concentrations of L-arginine. The data indicate that an SNP in ARG1 was significantly associated with L-arginine concentrations in those using dietary supplements of L-arginine. However, an SNP in ARG2 was significantly associated with L-arginine plasma concentrations in those not taking dietary supplements. Collectively, the haplotype was further associated with circulating plasma concentrations for the collective group. Given that NOS and arginase compete for their common substrate, arginine, greater expression and/or activity of one results in lower activity of the other due to limitations in L-arginine bioavailability.

In the study by Hannemann et al., 374 adults were analyzed for the 2 most prevalent SNPs in the ARG1 [rs2246012 (T/C) and rs2781667 (C/T)] and ARG2 genes [rs3742879 (A/G) and rs2759757 (G/C)] and their associations with blood L-arginine concentrations, which were stratified into tertiles (low, <42 μmol/L; medium, 42–114 μmol/L; high, >114 μmol/L). The typical range of L-arginine plasma concentrations is 82–114 μmol/L in males and 72–88 μmol/L in females, suggesting strongly that there were responder and nonresponder phenotypes within the cohort (12). It is noteworthy that the allelic frequencies of the 4 SNPs did not significantly differ from the expected allelic frequency based on the European reference population within the 1000 Genomes Project, a comprehensive public catalogue of human variation and genotype data (info@1000genomes.org). The associations of haplotypes for both the ARG1 and ARG2 genes were also analyzed and compared with blood L-arginine concentrations in individuals supplementing or not with dietary L-arginine.

There was a significantly higher prevalence of the minor allele of ARG1 rs2246012 (intron variant IVS2 + 333; Chr6:131,577,068) in supplement users with higher blood L-arginine concentrations. L-Arginine concentration was ~264 μmol/L in supplement users homozygous for the minor allele of ARG1 rs2246012 and ~70 μmol/L in unsupplemented

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Abbreviations used: ARG, arginase; NO, nitric oxide; NOS, nitric oxide synthase; SNP, single nucleotide polymorphism.

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participants homozygous for the minor allele of ARG2 rs3759757. The ARG1 haplotype was also significantly associated with blood L-arginine concentrations in supplement users, as was the combined ARG1/ARG2 haplotype in the collective cohort.

In contrast, arginine concentrations were higher in homozygous carriers of the major allele ARG1 (rs2781667) and the association was weaker for unsupplemented subjects. Interestingly, there were no significant differences in plasma arginine concentrations between ARG2 genotypes in dietary supplement users. In addition, arginine concentrations were significantly lower in those homozygous for the minor allele of ARG2 (rs3759757) and not supplementing, but the ARG2 (rs3742879) allele was not significantly associated with circulating arginine concentrations. In those not supplementing, there was a higher frequency of the major allele of ARG2 rs3759757 but no other correlations with other measured biomarkers.

Collectively, it appears that genetic variants in ARG1 are most relevant and predictive for determining bioavailability of dietary supplemented L-arginine, whereas ARG2 variants influence the endogenous circulating pool, many components of which could be inaccessible to arginase depending on intracellular locations (13). Moreover, the observation that SNPs in the ARG1 gene are associated with plasma concentrations in users of dietary supplements could explain the inefficaciousness in some individuals.

Intestinal and hepatic first-pass metabolism of arginine to ornithine and urea by hepatic ARG1 and ARG2 can hinder bioavailability from dietary supplements. ARG1 SNP 6012 showed significant association with plasma arginine in supplement users but a weak inverse association for ARG1 rs2781667. However, dietary supplementation with L-citrulline increased plasma L-arginine concentrations more rapidly and prolonged these concentrations compared with an equivalent dose of L-arginine, suggesting greater efficacy (14). This supports supplementation with citrulline alone or with L-arginine instead of L-arginine alone although the observed safe level of dietary arginine is ~20 g/d (15, 16).

This study is the first to describe a possible functional relation between ARG1 and ARG2 SNPs, as well as haplotypes, and plasma L-arginine concentrations. It appears that ARG1 is associated with blood L-arginine concentrations in L-arginine supplement users, whereas ARG2 is associated with blood L-arginine concentrations in unsupplemented participants. Genetic variability in ARG1 could explain variation in circulating L-arginine concentrations during dietary supplement use, and inconsistent study results reported in the literature. However, information gleaned from this study could permit more individual-specific recommendations regarding dietary supplementation with L-arginine.

There are limitations to this study that merit attention. First, the sampling for this study did not permit control for anthropometric and epidemiological characteristics contributing to variability. Second, the relatively low frequencies of minor alleles could hinder subgroup analyses. Also, the data presented are observational associations and lack any indications of specific mechanisms involved in the process. Lastly, because this is one of the first studies to explore a functional relation between ARG1 and ARG2 SNPs and blood L-arginine concentrations, corroboration is needed.

Collectively, however, the results further the notion that personalized nutrition and the use of nutrigenetics, an aspect of personalized nutrition, should focus on the various phenotypic responses, that is, plasma arginine concentrations, to a specific diet, dietary supplement, or nutraceutical depending on the genotype of the individual.

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