A new twist on an old vitamin: human polymorphisms in the gene encoding the sodium-dependent vitamin C transporter $^{1,2}$

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Encoded by the gene $SLC23A1$, the sodium-dependent vitamin C transporter 1 (SVCT1) plays a critical role in hepatic portal absorption and renal reabsorption of vitamin C (ascorbic acid). Through these functions, SVCT1 controls plasma vitamin C homeostasis, as recently shown in SVCT1 knockout mice (1). Despite massive loss of ascorbic acid from the circulation by urinary excretion, these mice survive due to increased endogenous vitamin C synthesis. An argument can therefore be made that factors altering SVCT1 activity may critically affect vitamin C homeostasis in humans, one of several mammalian species lacking ascorbic acid synthesis.

In this issue of the Journal, Timpson et al (2) report on a large cohort of >15,000 individuals combined from 5 independent observational studies in the United Kingdom to provide the first evidence that the $SLC23A1$ genotype affects plasma vitamin C status in humans. One of the 4 $SLC23A1$ single nucleotide polymorphisms (SNPs) examined, rs33972313, was associated with a highly significant reduction in plasma vitamin C concentrations (-5.98 μmol/L per modified allele). Remarkably, this effect was observed without adjustment for variables known to affect vitamin C status, such as dietary intake or cigarette smoking, and despite diverse study designs and differing methods used for plasma ascorbic acid analysis. These data, therefore, suggest that the rs33972313 SNP is a “nonconfounded proxy for variation in L-ascorbic acid at the population level” (2) that needs to be considered—potentially with other $SLC23A1$ genetic variants—in the design of future observational studies and randomized controlled trials investigating the role of vitamin C in humans.

A central question borne of this research is whether rs33972313 and other $SLC23A1$ variants modify chronic disease risk. Prior studies have found no correlation of SNPs in $SLC23A1$ with gastric cancer (3) or advanced colorectal cancer (4). One study did report a correlation of 2 $SLC23A1$ SNPs with decreased risk of lymphoma (5); one of these SNPs, rs6596473, was associated with a significant reduction in follicular lymphoma and is now shown by Timpson et al (2) to modestly but significantly increase plasma ascorbic acid concentrations (+2.86 μmol/L per modified allele in the British Women’s Heart and Health Study cohort). However, a limitation of these previous genetic studies (3–5) is that plasma vitamin C concentrations were not measured concurrently, and hence correlations with SNPs or disease risk could not be assessed.

Nevertheless, the notion that vitamin C affects chronic disease risk is supported by many epidemiologic studies, including those investigated by Timpson et al (2). For example, in the European Prospective Investigation into Cancer and Nutrition Norfolk Study, a 20-μmol/L increase in plasma ascorbic acid was correlated with a highly significant 20% decrease in relative risk of all-cause mortality, and similar inverse associations were observed for cardiovascular disease and ischemic heart disease (6). The British Regional Heart Study supported these findings by showing a significant decrease in markers of inflammation and endothelial dysfunction in relation to high plasma vitamin C concentrations (7). Furthermore, there is extensive evidence from randomized controlled trials that vitamin C supplementation restores normal endothelial function and vasodilation in individuals with coronary risk factors or established coronary artery disease (8).

Because the determinants of plasma vitamin C concentrations are multifactorial in nature, the effects of $SLC23A1$ genetic polymorphisms must be viewed in the context of diet and lifestyle factors known to influence vitamin C concentrations and disease risk. Although not the focus of their work, the data presented by Timpson et al (2) confirm that lower socioeconomic status, excessive alcohol consumption, and cigarette smoking are associated with significantly lower plasma vitamin C concentrations (2). As indicated above, the effects of the genetic variants studied were independent of all of these potential confounding factors (2), which underscores the pervasive nature of the rs33972313 genotype. Combining deleterious diet and lifestyle factors with $SLC23A1$ SNPs that negatively (rs33972313) or positively (rs6596473) affect plasma ascorbic acid status may amplify or reduce, respectively, an individual’s risk of developing vitamin C deficiency and adverse health outcomes.

Conversely, the limitations that a deleterious $SLC23A1$ gene variant places on plasma vitamin C status may be overcome by dietary means. If SVCT1-independent routes exist for intestinal vitamin C absorption, as suggested by current research in SVCT1 knockout mice (1), then increasing dietary consumption
or taking supplements of vitamin C may partially compensate for reduced SVCT1 activity. However, unlike intestinal absorption, renal reabsorption of vitamin C strictly depends on SVCT1 (1), and hence the urinary threshold and saturating steady state concentrations of plasma ascorbic acid in individuals with deleterious SL2C3A1 SNPs are unlikely to be affected by increased vitamin C intake.

To restore urinary threshold and plasma saturation concentrations, specific interventions that increase SLC23A1 expression might be necessary. Unfortunately, our current understanding of SVCT1 regulation is limited. Recent data suggest that SLC23A1 transcription is controlled by hepatocyte nuclear factor 1 (9) and thus may be linked to carbohydrate metabolism. Studies in rats also show that SLC23A1 transcription declines with age, resulting in lower plasma and tissue concentrations of ascorbic acid (10). Similar declines in SVCT1 may occur in humans, because higher vitamin C intakes are required by older adults to maintain plasma vitamin C concentrations comparable to those of young adults (11).

A better understanding of SVCT1 regulation offers the intriguing possibility that pharmaceutical drugs or dietary supplements may be developed that will overcome deficits in SVCT1 protein kinetics, thus raising plasma vitamin C status in SLC23A1 variant carriers and possibly in older adults. This could be more effective than merely increasing vitamin C intake, which does not increase SVCT1 expression. Because other SLC23A1 SNPs have been identified that may be even more deleterious than rs33972313 for human vitamin C status, eg, rs35817838 (1), understanding SVCT1 regulation and the role of vitamin C in chronic disease risk takes on even greater importance.

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REFERENCES