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Understanding the Genome: Implications for Human Nutrition?

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Editorial

The understanding of the role of vitamins has shifted in recent years from preventing overt deficiencies to helping achieve optimal health along the life course and decrease the risk of developing non-communicable diseases such as type 2 diabetes mellitus (T2D) or cardiovascular disease (CVD). Though such variables are considered when establishing dietary recommendations (See for example [1]), the genotype, which is emerging as an important modulator of the impact of a given (micro) nutrient on the metabolism, has so far not been included. However, new technologies allow assessing micronutrient-gene interactions and connecting nutrient status with genotypes, phenotypes and biomarkers. These developments stimulate a renaissance in nutrition science and vitamin research and provide opportunities for more individualized recommendations: Various polymorphisms have been described for genes encoding enzymes involved in the conversion of beta-carotene to vitamin A. Carriers of these polymorphism can have an up to 50% reduced enzyme activity, and have therefore an impaired ability to convert beta-carotene to vitamin A [2]. Given that beta-carotene is an important source of vitamin A, such polymorphisms make it more difficult to achieve adequate intakes and specific recommendations might be needed for these at risk groups [3].

The majority of vitamins or their metabolites act as coenzymes involved in >1000 biochemical reactions and there is increasing evidence that such enzymatic shortcomings can be compensated by higher doses of the relevant vitamin. For example, homozygous carriers of the common methylenetetrahydrofolate reductase (MTHFR) 677TT mutation synthesize up to 50% less active MTHFR [4]. It constitutes the most frequent cause of moderate hyperhomocysteinemia due to genetic factors [4] and results in an increased risk for elevated blood pressure [5], two risk factors for CVD [6]. In a recent clinical trial, supplementation with riboflavin was effective in lowering blood pressure in individuals with the MTHFR 677TT genotype, with potentially important implications for the primary prevention of CVD and stroke [7].

Thanks to increased knowledge on the role of genotypes, relationships between vitamins and health conditions are discovered that were not evident before: Epidemiological data suggested a link between oxidative stress, CVD and the antioxidant vitamin E, yet clinical trials failed to demonstrate a benefit of vitamin E in preventing vascular complications of diabetes mellitus [8]. It was subsequently shown that the risk of CVD in T2D patients was five times higher if they had a dysfunctional allelic mutation in a gene encoding for haptoglobin [9]. Supplementation with vitamin E in these individuals was able to compensate the impaired antioxidant function of haptoglobin, thereby reducing their risk of stroke, myocardial infarction and cardiovascular mortality [10]. No such benefit was observed in patients with other haptoglobin genotypes. Given that up to 40% of the European population and 90% of the Indian population carry this polymorphism (haptoglobin 2-2) [11,12], the potential of this discovery is of great significance for the care of diabetic patients.

The relationship between vitamin E and CVD is found to be more complex as further polymorphisms are discovered: After a 10 year follow-up, 400 mg vitamin E had no impact on CVD mortality in a cohort of healthy women [13]. However, it was then proposed that a polymorphism in the gene encoding for the catechol-*O*-methyltransferase (COMT) was linked to increased risk of CVD, possibly via its effect on homocysteine levels [14]. When the COMT genotype was taken into account in the afore mentioned study, daily doses of vitamin E led to a non-significant increase in the CVD risk in homozygotes for the valine allele, but to a significantly reduced risk in homozygotes for the methionine substitution of valine.

These examples show that while our current recommendation might be a good approximation of the vitamin requirements of the population as a whole, there are significant sub groups that might benefit from a more targeted approach. Currently, adherence to dietary guidelines is notoriously poor [15] and the genotype may be an opportunity to consider in the future: A recent study found that giving people dietary guidance based on information on their genetic profile led to an improvement in nutritional habits [16]. At this stage, it is difficult to predict whether in the future, there will still be recommendations for the general population only distinguishing between gender and age groups or whether guidance will be given for specific genotypic subgroups. However, many questions remain to be resolved before our understanding of these complex and often interlinked processes is sufficient to be translated into concrete guidelines.

It is for example becoming increasingly clear that the efficiency of enzymes is not only reduced by genetic mutations, but also by epigenetic modulations early in life: In rats, vitamin B12 restriction during pregnancy and early life led to a change in body composition, metabolic profile and activity of enzymes involved in the glucose metabolism [17]. Even though the mechanisms are not entirely understood, it appears as if epigenetic processes such as DNA methylation in the offspring as a result of maternal or even paternal diet play an important role [18]. A recent study in the Gambia for example showed different DNA methylation pattern in blood of infants whose mothers had received periconceptional micronutrient supplements compared to those whose mothers received a placebo [19]. These changes can have far reaching consequences for the offspring: Indian children who were born to mothers with high folic acid but low vitamin B12 levels, were more likely to be adipose at age 6, thereby increasing their risk of developing T2DM [20]. It is conceivable that such changes have a further impact on what constitutes as optimal vitamin intakes later in life. Answering such questions may be possible as the technologic advances and enables us to map and monitor a person's genetic and epigenetic make up. This

may help to better understand the specific vitamin requirements at various stages of the life course.

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