CHAPTER SEVEN

Dietary Vitamin C in Human Health

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Advances in Food and Nutrition Research, Volume 83
ISSN 1043-4526
https://doi.org/10.1016/bs.afnr.2017.11.006

Abstract

Vitamin C is essential to prevent scurvy in humans and is implicated in the primary prevention of common and complex diseases such as coronary heart disease, stroke, and cancer. This chapter reviews the latest knowledge about dietary vitamin C in human health with an emphasis on studies of the molecular mechanisms of vitamin C maintenance as well as gene–nutrient interactions modifying these relationships.

Epidemiological evidence indicates 5% prevalence for vitamin C deficiency and 13% prevalence for suboptimal status even in industrialized countries. The daily intake (dose) and the corresponding systemic concentrations (response) are related in a saturable relationship, and low systemic vitamin C concentrations in observational studies are associated with negative health outcomes.

However, there is no evidence that vitamin C supplementation impacts the risks for all-cause mortality, impaired cognitive performance, reduced quality of life, the development of eye diseases, infections, cardiovascular disease, and cancers. This might be related to the fact that prevention would not be realized by supplementation in populations already adequately supplied through dietary sources.

Recent genetic association studies indicate that the dietary intake might not be the sole determinant of systemic concentrations, since variations in genes participating in redox homeostasis and vitamin C transport had been associated with lowered plasma concentrations. However, impact sizes are generally low and these phenomena might only affect individual of suboptimal dietary supply.

1. INTRODUCTION

Vitamin C, existing in the two main forms of ascorbic and dehydroascorbic acid, is a ubiquitous metabolite in plants and animal. Eukaryotes, plants, fungi, and most animals can synthesize L-ascorbic acid (Drouin, Godin, & Page, 2011). Anthropoid primates, teleost fish, bats, passeriforme birds, and guinea pigs have lost this ability, and for these species it is an essential dietary component (Menniti, Knoth, & Diliberto, 1986; Ohta & Nishikimi, 1999). In humans, the ability to synthesize vitamin C was lost due to mutations in the L-gulonolactone oxidase (*GLO*) gene, that is responsible for catalyzing the synthesis of L-ascorbic acid from L-gulono-1,4-lactone, the last step in the ascorbic acid synthesis pathway in mammals (Nishikimi & Yagi, 1991). A profound lack of dietary supply will result in the deficiency disease scurvy, which can be fatal (Padayatty & Levine, 2016).

Due to the presence of scurvy, vitamin C's existence was known before its molecular discovery. In his 1753 work, *Treatise of the Scurvy*, James Lind noted that consumption of citrus fruit prevents scurvy, also known in Latin as scorbutus (Bartholomew, 2002). Hence, ascorbutus was the lack of

scorbutus (scurvy), and the molecular name of ascorbic acid originates there (Grzybowski & Pietrzak, 2013). The water-soluble L-ascorbic acid was discovered by Albert Szent-Györgyi in 1928 and characterized as the anti-scorbutic factor by Szent-Györgyi and King in 1932 (King & Waugh, 1932; Svirbely & Szent-Györgyi, 1932). The chemical structure of ascorbic acid was deduced by Walter Norman Haworth in 1933 (Carpenter, 2012). Since then vitamin C has been extensively researched with speculations regarding its many beneficial functions in the maintenance of health and the curing of disease (Padayatty et al., 2003; Padayatty & Levine, 2016).

This chapter aims to update on the latest knowledge about dietary vitamin C in human health. The many epidemiological or dietary intervention studies scrutinizing the effects of vitamin C consumption and/or supplementation on physiological parameters, biomarkers, and clinical end points are not being reviewed in great detail, since they have been reviewed elsewhere. For reviews on technical issues of research on vitamin C, such as adequate sampling and sensitivity of assays refer to Levine, Wang, and Rumsey (1999), on the role as a physiologic antioxidant refer to Padayatty et al. (2003). The main emphasis is placed on studies of the molecular mechanisms of vitamin C maintenance as well as gene–nutrient interactions modifying these relationships.

2. VITAMIN C: BASIC PHYSIOLOGY

The biological functions of vitamin C revolve around its ability to alter its redox state, which enables it to function as a cofactor for eight known human enzymes and as a water-soluble antioxidant (Padayatty & Levine, 2016). At the physiological pH of 7.4, vitamin C exists as the ascorbic acid anion (Fig. 1; Padayatty et al., 2003; Padayatty & Levine, 2016).

The reduced ascorbic acid loses electrons sequentially, with the loss of one electron forming the ascorbic acid radical. Compared to other radical species it has a long half-life of many seconds to minutes (Buettner, 1993) and has been measured in blood and extracellular fluid samples (Chen et al., 2007). The oxidized form of vitamin C, dehydroascorbic acid, results from the loss of a second electron and can be recycled into the reduced form through enzyme mediated or reductive metabolic pathways (Dhariwal, Shirvan, & Levine, 1991; Dhariwal, Washko, & Levine, 1990; Wang et al., 1997). Dehydroascorbic acid has a half-life of only minutes, after which it undergoes hydrolytic ring rupture, the resulting 2,3-diketogulonic acid cannot reform its precursor and is unable to continue its role in

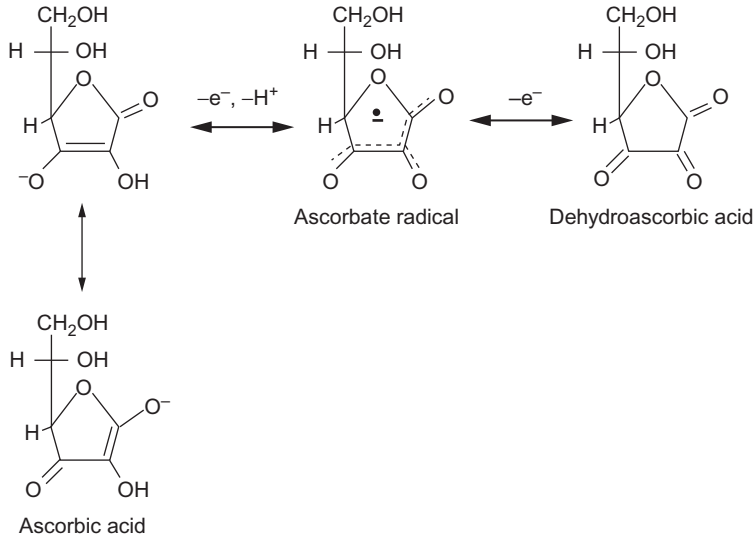

Fig. 1 The three states of vitamin C. The reduced ascorbic acid exists at the physiological pH of 7.4 as the ascorbic acid anion. The ascorbic acid radical results from the loss of one electron and is a stable radical species, indicated by the *dot*. Dehydroascorbic acid results from the loss of another electron and is the oxidized form of vitamin C, which can be recycled into ascorbic acid through reduction by glutathione or glutathione utilizing enzymes.

vitamin C metabolism. Ascorbic acid and dehydroascorbic acid utilize distinct pathways for cellular entry, while ascorbic acid utilizes sodium-dependent membrane transporters, dehydroascorbic acid utilizes facilitative glucose transporters.

Eight human enzymes are known to utilize ascorbic acid as a cofactor, three participate in collagen hydroxylation (Kivirikko & MyllylÄ, 1985; Peltonen, Halila, & Ryhänen, 1985; Peterkofsky, 1991; Prockop & Kivirikko, 1995) and two in carnitine biosynthesis (Dunn, Rettura, Seifter, & Englard, 1984). Of the three enzymes which participate in collagen hydroxylation, one is necessary for biosynthesis of the catecholamine norepinephrine (noradrenaline) (Kaufman, 1974; Levine et al., 1992), one is necessary for amidation of peptide hormones (Eipper, Milgram, Husten, Yun, & Mains, 1993; Eipper, Stoffers, & Mains, 1992), and one is involved in tyrosine metabolism (Englard & Seifter, 1986; Lindblad, Lindstedt, & Lindstedt, 1970). Details about these enzymes and their functional role are described by Padayatty and Levine (2016).

As a major water-soluble antioxidant in mammalian physiology, ascorbic acid scavenges potentially harmful oxidizing free radicals and can be irreversibly oxidized in this process, unless it is recycled (Frei, England, &

Ames, 1989; Frei, Stocker, England, & Ames, 1990), which leads to increased dietary requirements in situations of oxidative stress. Through redox sensing it also contributes to differential gene expression and mRNA translation, which could also contribute to the prevention of oxidative damage of intracellular proteins and DNA (Hitomi & Tsukagoshi, 1996; Padayatty et al., 2003; Qiao & May, 2011; Sram, Binkova, & Rossner, 2012). Plasma ascorbic acid contributes to the reduction of extracellular oxidants, increased endothelium-dependent vasodilatation, and reduced low-density lipoprotein oxidation (Ceriello et al., 2013; Polidori, Mecocci, Levine, & Frei, 2004; Richards, Crecelius, Larson, & Dinenno, 2015; Traber & Stevens, 2011).

In the intestinal tract ascorbic acid increases nontransferrin-mediated absorption of iron by reducing ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}) and also enhances transferrin-mediated uptake of iron via intracellular reduction of iron (Hallberg, Brune, & Rossander, 1989; Lane, Chikhani, Richardson, & Richardson, 2013a, 2013b; Lane & Richardson, 2014).

Related to the above described biological functions, vitamin C has a role in energy-yielding metabolism, collagen synthesis, nonheme iron absorption, and normal functioning of the nervous system. In spite of our knowledge on vitamin C physiology, significant uncertainties remain in the quest to link individual variability in vitamin C metabolism to improved and individualized recommendations. This chapter will update the latest knowledge on the genetic variability influencing vitamin C utilization and therefore recommendations.

It is well established that a severe dietary undersupply of vitamin C will result in scurvy, and many deficiency symptoms are reflected in the functions of ascorbic acid as a cofactor of known enzymes, such as defects in collagen leading to structural weakening in connective tissue (Padayatty & Levine, 2016). However, ascorbic acids role in the prevention or treatment of common and complex diseases is still uncertain. Even the widely held assumption that ascorbic acid is one of the major biological antioxidants and therefore has a prominent role in disease prevention has not been definitively validated (Padayatty et al., 2003; Padayatty & Levine, 2016).

3. CURRENT BENCHMARKS OF VITAMIN C STATUS AND DIETARY RECOMMENDATIONS

Plasma concentrations serve as the most readily available biomarker for vitamin C status. Values below 11 μmol/L specify deficiency coincide with the clinical symptoms of scurvy (Lykkesfeldt & Poulsen, 2010; Robitaille &

Hoffer, 2016). The highest concentrations observed in pharmacokinetic studies are between 70 and 80 μmol/L (Levine et al., 1996; Levine, Wang, Padayatty, & Morrow, 2001), seldom more than 100 μmol/L has been reported (Padayatty & Levine, 2016), and concentrations plateau in that range even during very high dietary supplementation. However, concentrations as low as 28 μmol/L are considered adequate (Hoffer, 2010), and consequently values between 11 and 28 μmol/L indicate marginal deficiency (often referred to as hypovitaminosis C), where scurvy is absent but the risk for chronic diseases is elevated.

The recommended dietary allowance (RDA) for vitamin C has been developed over the years, and the current recommendations in the United States and Canada are set to 90 mg/day for adult men and 75 mg/day for adult women. They are based on maintaining near-maximal neutrophil concentrations and to elicit antioxidant protection (Monsen, 2000). Recommendations stratified by age and metabolic status are summarized in Table 1.

RDAs differ widely across the world, however, which reflects the lack of underlying scientific evidence. For example, for adults in the United Kingdom 40 mg/day are recommended, while in France and Belgium the benchmark lies at 110 mg/day (Birlouez-Aragon, Fieux, Potier De Courcy, & Hercberg, 2001), and in Germany at 110 mg/day for males and at 95 mg/day for females (Bechthold, Leschik-Bonnet, Strohm, & Heseker, 2015).

Table 1 Recommended Dietary Allowances (RDAs) for Vitamin C in the United States and Canada

Age	Male (mg)	Female (mg)	Pregnancy (mg)	Lactation (mg)
0–6 Months	40[a]	40[a]		
7–12 Months	50[a]	50[a]		
1–3 Years	15	15		
4–8 Years	25	25		
9–13 Years	45	45		
14–18 Years	75	65	80	115
19+ Years	90	75	85	120
Smokers	Individuals who smoke require 35 mg/day more vitamin C than nonsmokers			

[a]Adequate intake (AI) is issued on a less validated scientific basis.
Recommended dietary allowances (RDAs) are issued if a strong scientific basis exists (Monsen, 2000).

Due to the large variability in RDAs worldwide, it has been suggested that vitamin C intakes above current RDAs could contribute to the prevention of chronic diseases, in particular cardiovascular diseases (CVDs)—principally coronary heart disease (CHD) and stroke—and certain cancers (Frei, Birlouez-Aragon, & Lykkesfeldt, 2012).

4. VITAMIN C STATUS IN THE GENERAL POPULATION

Studies describing the relationship between dietary intake and the plasma concentrations of vitamin C generally show that both low intake and plasma concentrations are common. Available data from the United States show mean plasma ascorbic acid concentrations of 48 μmol/L in males and 54.8 μmol/L in females (Schleicher, Carroll, Ford, & Lacher, 2009). However, 8.2% of males and 6% of females had plasma vitamin C concentrations below the deficiency threshold of 11 μmol/L. Among men, 18% of smokers had values below this threshold, while only 5.3% of nonsmokers had such low values. Among women, 15.3% of smokers and 4.2% of nonsmokers had similarly low values (Schleicher et al., 2009).

Around 5.5% of the Canadian general population who did not use supplements had deficient plasma vitamin C concentrations of less than 11 μmol/L (Fig. 2; Langlois, Cooper, & Colapinto, 2016), while approximately 11.6% of smokers, 5.8% overweight individuals had deficient vitamin C concentrations. About 13.5% of nonsupplement users had marginal deficient plasma vitamin C concentrations between 11 and 28 μmol/L, while 17.6% of smokers, 9% of nonsmokers, 17% of obese individuals, 8.2% of overweight individuals had marginal deficient plasma vitamin C concentrations (Langlois et al., 2016).

Even in industrialized countries, marginal deficiency or hypovitaminosis C can have a prevalence of about 15% of the general population (Lindblad, Tveden-Nyborg, & Lykkesfeldt, 2013), 30% of cigarette smokers (Pfeiffer, Sternberg, Schleicher, & Rybak, 2013; Schectman, Byrd, & Hoffmann, 1991), and 60% of hospitalized individuals (Evans-Olders, Eintracht, & Hoffer, 2009; Fain et al., 2003; Gan, Eintracht, & Hoffer, 2008; Gariballa & Forster, 2006; Hunt, Chakravorty, Annan, Habibzadeh, & Schorah, 1994; Teixeira, Carrie, Genereau, Herson, & Cherin, 2001; Wang et al., 2013; Zhang, Robitaille, Eintracht, & Hoffer, 2011). The exact health implications of marginal deficient vitamin C status remain unknown, but clinical symptoms may include fatigue or mood disruption (Crandon, Lund, & Dill, 1940; Wang et al., 2013; Zhang et al., 2011),

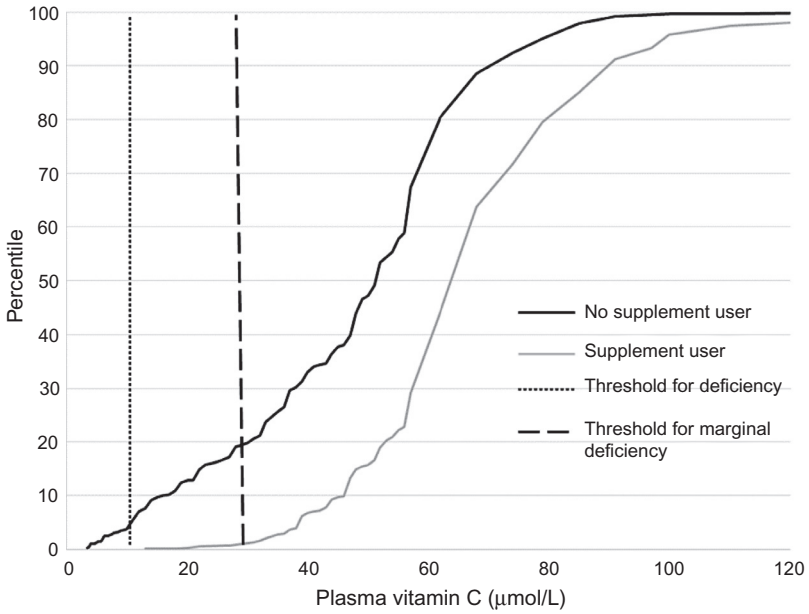

Fig. 2 Plasma vitamin C concentrations of Canadians. *Data sourced from the 2012/2013 Canadian Health Measures Survey (Langlois, K., Cooper, M., & Colapinto, C. K. (2016). Vitamin C status of Canadian adults: Findings from the 2012/2013 Canadian Health Measures Survey.* Health Reports*, 27(5), 3–10).*

decreased immunity (Anthony & Schorah, 1982; Hemila & Louhiala, 2007; Hunt et al., 1994), impaired wound healing (Blass et al., 2013; Lund & Crandon, 1941; Sorensen et al., 2010), localized pain (Shibuya, Humphers, Agarwal, & Jupiter, 2013), and CVD (Frei et al., 2012; Juraschek, Guallar, Appel, & Miller, 2012; Padayatty & Levine, 2000; Rodrigo et al., 2013; Vita et al., 1998).

4.1 Associations of Vitamin C and Health Outcomes in Observational Studies

Since outcomes in major common and complex diseases are potentially modified by the vitamin C status, large-scale observational studies have examined these relationships. In the following sections the major observations for the most detrimental common and complex diseases, namely, CVD and cancers, are summarized. It should be noted that men with marginal deficient serum vitamin C concentrations below 28 μmol/L had a 57%

higher risk of all-cause mortality after 12–16 years of follow-up than men with the highest vitamin C concentrations above 74 μmol/L, creating the rationale to try to relate this to today's major health problems.

4.2 The Relation of Vitamin C to CVDs in Human Observational Studies

Many epidemiological studies assessed the association between dietary vitamin C intake and the risks of common and complex diseases. However, some of these observational studies did not consider biomarkers of vitamin C status such as plasma concentrations. The following section summarizes studies reporting on the biomarkers of vitamin C status, thereby eliminating the uncertainty of dietary assessments.

Serum vitamin C concentrations above 45 μmol/L (45.4 and 79.5 μmol/L) lowered the risk of CVD by about 25% compared to individuals with concentrations under 23 μmol/L (Simon, Hudes, & Tice, 2001). Similarly, a 33% lowered risk for CHDs was associated in subjects with mean plasma vitamin C concentrations of 77 μmol/L compared to those with 27 μmol/L (Boekholdt et al., 2006). Moreover, plasma vitamin C concentrations were inversely related to mortality from all causes and CVD (Khaw et al., 2001), where each 20 μmol/L increase in plasma vitamin C was associated with a 20% and 30% reduction in all-cause and CVD mortality, respectively. Concurring evidence was reported for associations of increased vitamin C plasma or serum concentrations (means ranging from 49.5 to 85.2 μmol/L) and decreased CVD risks (Langlois, Duprez, Delanghe, De Buyzere, & Clement, 2001; Nyyssonen, Parviainen, Salonen, Tuomilehto, & Salonen, 1997; Simon, Hudes, & Browner, 1998). Consistent with these findings, in young type 1 diabetic patients, poor vitamin C status was found to be associated with an increase in several early cardiovascular risk markers (Odermarsky, Lykkesfeldt, & Liuba, 2009).

A recent systematic review on the relationship between vitamin C and heart health concluded that in populations with already adequate vitamin C intake, further supplementation with vitamin C did not correlate with the risk of CVD (Moser & Chun, 2016). However, if dietary supply was suboptimal, risks for CVD were elevated (Moser & Chun, 2016).

Older adults with plasma vitamin C concentrations above 28 μmol/L had 30% less deaths from strokes (Gale, Martyn, Winter, & Cooper, 1995), and a 42% lower incidence of stroke occurred when plasma concentrations were above 66 μmol/L compared to individuals with vitamin C concentrations

below 41 μmol/L (Myint et al., 2008). Similarly, subjects with vitamin C concentrations above 64 μmol/L had a 41% lower risk of stroke than those with vitamin C below 40 μmol/L (Yokoyama et al., 2000). Echoing these data, individuals with plasma concentrations below 28 μmol/L had a twofold increased risk of stroke compared to individuals with concentrations above 65.0 μmol/L.

Contrary to the positive effects reported, CVD mortality increased upon vitamin C supplementation in postmenopausal women with diabetes (Lee, Folsom, Harnack, Halliwell, & Jacobs, 2004), indicating that cases of specific pathologies should be viewed separate from the general population.

In conclusion, observational studies have produced mixed results regarding the relationship of vitamin C and CVDs. Generally, no relationship between vitamin C and CVD risk was observed at optimal plasma vitamin C concentrations, but suboptimal concentrations seem to be associated with elevated CVD risks.

4.3 The Relation of Vitamin C to Cancers in Human Observational Studies

More limited evidence exists for a relationship between vitamin C status and the prevention of certain cancers. In a case–control study, individuals with plasma concentrations above 51 μmol/L had a 45% lower risk of gastric cancer compared to individuals with concentrations below 29 μmol/L (Jenab et al., 2006). Men with serum vitamin C concentrations below 28 μmol/L had a 62% higher risk of cancer-related deaths after 12–16 years of follow-up than men above 73.8 μmol/L (Loria, Klag, Caulfield, & Whelton, 2000). Men with mean plasma vitamin C concentrations of 73 μmol/L had a 53% reduced cancer mortality compared to those of 21 μmol/L (Khaw et al., 2001).

Very low vitamin C status was also reported for cases of multiple myeloma (Sharma, Tripathi, Satyam, & Kumar, 2009) and unspecified advanced cancers, where it was associated with increased inflammation and lower survival (Mayland, Bennett, & Allan, 2005). However, in those case–control studies it was undetermined if reduced concentrations are the consequence of rather than the cause of the reported associations.

In conclusion, observational studies indicate that vitamin C plays a role in the prevention of gastric cancer, while the role in the prevention of other cancers is indicated, but requires further validation.

4.4 Human Intervention Studies Supplementing Vitamin C

The epidemiologic associations between adequate vitamin C status and decreased risk of CVD and cancers inspired controlled intervention studies to determine if a causal relationship exists. Those intervention studies regularly used vitamin C supplementation in combination with other "antioxidant vitamins" (most often vitamin E and β-carotene), or as part of a multivitamin–mineral mix, which would complicate the interpretation of positive findings. However, if intervention studies report no effect of vitamin C supplementations then they would be considered ineffective.

Many clinical studies have used interventions with vitamin C in relation to specific outcomes in patients populations, such as HIV (Guwatudde et al., 2015), type 2 diabetes (Shateri et al., 2016), depressive disorders (Sahraian, Ghanizadeh, & Kazemeini, 2015), and end-stage renal diseases (Biniaz, Sadeghi Shermeh, Ebadi, Tayebi, & Einollahi, 2014; Shateri et al., 2016). Those small and targeted studies will not be discussed in this chapter, which rather focuses on large-scale long-term studies on health outcomes in the general population. Within these intervention studies, cardiovascular outcomes and cancers had been a targeted most often.

4.5 Human Intervention Studies and Health Outcomes in Common and Complex Diseases

Major human intervention trials with vitamin C did not show improvements in all-cause mortality (Hercberg, Galan, Preziosi, et al., 2004), eye health (age-related macular degeneration, age-related cataract, lens opacity, or vision loss) (Age-Related Eye Disease Study Research Group, 2001; Christen et al., 2012), cognitive performance (Grodstein et al., 2013), infections (Avenell et al., 2005; Girodon et al., 1999; Graat, Schouten, & Kok, 2002), and overall quality of life (Avenell et al., 2005).

One clinical trial of moderate size reported the improvement of serum pepsinogen concentrations, which serve as a biomarker for the progression of gastric mucosal atrophy during *Helicobacter pylori* infection in a group highly supplemented with vitamin C (500 mg/day) vs the low-supplemented group (50 mg/day) (Sasazuki et al., 2003).

In conclusion, vitamin C supplementation did not modify all-cause mortality, cognitive performance, overall quality of life, the development of eye diseases, and infections.

4.6 Human Intervention Studies and Cardiovascular Outcomes

Major coronary events and fatal or nonfatal vascular events (2002) as well as incidences of myocardial infarction, stroke, coronary revascularization, or CVD death (Cook, Albert, Gaziano, et al., 2007) were not affected by supplementation with vitamins C + E + β-carotene. Similar supplementation with vitamins C + E + β-carotene + Zn + Se did not protect from ischemic CVD and all-cause mortality (Hercberg et al., 2004). Vitamin C combined with vitamin E did not reduce any cardiovascular events, myocardial infarction, stroke, or death from CVDs (Sesso, Buring, Christen, et al., 2008) and did not affect atherosclerotic lesions and carotid artery intima-media thickness (Salonen et al., 2003) or changes in minimum lumen diameter of coronary arteries (Waters, Alderman, Hsia, et al., 2002). Moreover, cerebrovascular diseases were not reduced upon daily supplementation with 14 vitamins and 12 minerals (Li et al., 1993).

Overall, the attempt to prove causal relationships in controlled clinical feeding trials has negative results for CVDs (Moser & Chun, 2016).

4.7 Human Intervention Studies and Cancer Outcomes

Vitamin C supplementation did not affect incidences or outcomes for major gastrointestinal cancers or overall cancer mortalities in the majority of studies. Specifically, supplementation with vitamin C and molybdenum (Blot et al., 1993), or vitamins C + E + β-carotene + zinc + selenium (Hercberg et al., 2004) did not reduce overall cancer incidence and disease-specific mortality. Similarly, interventions with vitamin C, vitamin E, β-carotene, and selenium did not reduce gastric cancer and overall cancer mortality (You et al., 2001). Daily supplementation with 14 vitamins and 12 minerals did reduce esophageal and gastric cancer deaths or total cancer incidences (Li et al., 1993). Occurrences of colorectal adenomas (Gaziano, Sesso, Christen, et al., 2012; Greenberg et al., 1994) or the progression of multifocal nonmetaplastic atrophy or intestinal metaplasia (Correa et al., 2000) were not correlated with multivitamin–mineral and β-carotene + vitamins C + E supplementation, respectively.

Vitamin C combined with vitamin E did not reduce the risks for prostate and total cancer (Gaziano, Glynn, Christen, et al., 2009); similarly, multivitamin supplementation did not reduce the risk for prostate, colorectal, and other site-specific cancers, however, reduced the risk of total cancer (Gaziano et al., 2012).

One solitary study reported that the positive association between red and processed meat intakes and breast cancer risk was eliminated upon supplementation with vitamins C + E + β-carotene + zinc + selenium (Pouchieu et al., 2014). Otherwise, all major intervention studies failed to prove a positive modification of cancer incidences and outcomes.

4.8 Human Intervention Studies and the Importance to Consider the Dose–Concentration Relationship for Vitamin C

Most evidence reported from large epidemiological cohorts, dietary intervention studies, as well as meta-analyses remain ambiguous, with many reporting that vitamin C supplementation had little or no effect on outcome measures (Moser & Chun, 2016; Padayatty & Levine, 2016). Specifically, most intervention studies do not show positive effects, while low systemic vitamin C concentrations in observational studies are associated with negative health outcomes. The explanation for this phenomenon might lay in the saturable relationship between daily intake (dose) and the corresponding systemic concentrations (response). In individuals with depleted plasma vitamin C, concentrations increase only modestly after small doses of up to 30 mg/day but increase more rapidly upon larger doses up to 100 mg/day reaching a plateau at about 200 mg/day (Fig. 3). Consequently, in studies where the control and treatment groups already have an adequate supply at baseline, plasma and cellular concentrations might not differ even upon interventions with high doses of vitamin C, eliminating the chance of

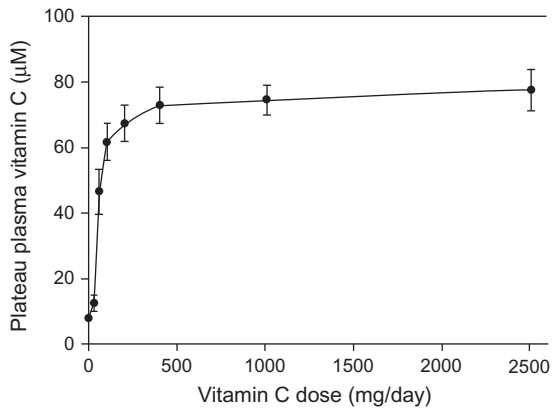

Fig. 3 Vitamin C concentrations as a function of the dose (Levine et al., 2001).

any demonstrable effects. Therefore, the effect of any supplementation would only be observed in groups undersupplied through the basal diet.

This phenomenon is exemplified by a recent meta-analysis on the effects of vitamin C supplementation on glycemic control, where overall no effects were observed on biomarkers of dysglycemia, as measured by glucose, HbA1c, and insulin concentrations (Ashor et al., 2017). However, in patients with type 2 diabetes, the high blood glucose concentrations were reduced upon vitamin C supplementation (Ashor et al., 2017), which could be attributed to improvements in the low vitamin C status of diabetic individuals (Chen et al., 2006; Tu et al., 2015).

5. GENETIC INFLUENCES ON VITAMIN C METABOLISM AND DISEASE PATHOLOGY

An individual's vitamin C status depends on the absorption, distribution, and metabolism of ascorbic acid where all of these processes may vary depending on genetic variations. Two genes encoding sodium-dependent ascorbic acid transporters have been identified, and polymorphisms in these have been associated with reduced systemic vitamin C concentrations and several diseases. The associations of polymorphisms in the ascorbic acid transporter genes to biomarkers of the vitamin C status and the disease associations will be discussed in separate sections, since it is currently unclear how they correlate. Polymorphisms in two glutathione *S*-transferases (GSTs) and haptoglobin had been associated with reduced vitamin C status and those will be summarized in separate sections; however, the disease associations for these genes will not be discussed, since their direct involvement in the ascorbic acid metabolism is unclear and correlations to the vitamin C status speculative at best.

5.1 Genetic Variations in the SLC23A1 Gene Associated to Altered Vitamin C Status

The *SLC23A1* gene encodes the sodium-dependent ascorbic acid transporter SVCT1 (SLC23A1) which plays a key role in the renal reabsorption of vitamin C (Daruwala, Song, Koh, Rumsey, & Levine, 1999; Tsukaguchi et al., 1999; Wang et al., 2000). Genetic variations in *SLC23A1* could lower the renal threshold for ascorbic acid reabsorption and therefore increase urinary losses and decrease steady-state plasma and body vitamin C concentrations (Corpe et al., 2010).

Five alleles of single nucleotide polymorphisms (SNPs, variations with frequencies over 1%) in the *SLC23A1* gene have been associated with lowered serum ascorbic acid concentrations; however, some genotypes showed mixed results with elevated concentrations in one study and decreased concentrations in others.

The average serum ascorbic acid concentrations were 5.3 μmol/L lower for SNP rs4257763-GG homozygotes in a setting indicating suboptimal values across this cohort (Cahill & El-Sohemy, 2009).

The SNP rs33972313-G, rs10063949-A, and rs6596473-C alleles were associated with 4.2, 2.9, and 2 μmol/L reductions in circulating concentrations of L-ascorbic acid, respectively (Timpson et al., 2010). These findings could not be replicated for the SNP rs10063949-A allele, but were replicated for the rs33972313-G and rs6596473-C alleles with associated reductions of 8.3 and 1 μmol/L, respectively (Timpson et al., 2010). A subsequent pooled analysis across five studies associated each additional rs33972313-G allele with a 6 μmol/L reduction in circulating vitamin C. In stark contrast to these results, the rs33972313-G allele was associated with a 3.1-μmol/L elevation in plasma vitamin C concentrations (Kobylecki, Afzal, Smith, & Nordestgaard, 2015), where GG homozygotes showed increases of 7.3 μmol/L and AG heterozygotes 4.1 μmol/L plasma vitamin C concentrations, respectively. Similarly, rs33972313-GG homozygotes had plasma ascorbic acid concentrations 6 μmol/L higher than those of GA heterozygotes, while AA homozygotes were found in this study (Duell et al., 2013).

SNP rs11950646-GG homozygotes had 8 μmol/L lower plasma vitamin C concentrations compared to AA heterozygotes, while a 3-μmol/L decrease in plasma vitamin C concentrations was observed in GA heterozygotes (Duell et al., 2013), indicating an allele dosage effect.

To conclude, emerging evidence indicates a role of genetic polymorphisms in the modulation of biomarkers of vitamin C status. However, the inconsistencies in the results need to be addressed in future controlled trials.

5.2 Genetic Variations in the SLC23A1 Gene Associated With Common and Complex Diseases

Several variations in the *SLC23A1* gene have been associated with increased risks of certain types of cancers, Crohn's disease, spontaneous preterm delivery, and aggressive periodontitis.

An 80% elevated risk of non-Hodgkin lymphoma was demonstrated for homozygotes for rs6596473-C/C and rs11950646-G/G (Skibola et al., 2008). A 150% increase in the risk for Crohn's disease was associated with the rs10063949-A/G heterozygotes and a 307% increase with G/G homozygotes, clearly showing an allele dosage effect (Amir Shaghaghi, Bernstein, Serrano Le, El-Gabalawy, & Eck, 2014). Certain haplotypes in *SLC23A1* gene were associated with increased risk of spontaneous preterm delivery (Erichsen et al., 2006). The rare allele of rs6596473 was associated with aggressive periodontitis (De Jong et al., 2014).

Overall, evidence of associations in the SLC23A1 gene with common and complex diseases is currently emerging but lacks enough depth to conclude on the validity.

5.3 Genetic Variations in the SLC23A2 Gene Associated to Altered Vitamin C Status

Three SNPs in the *SLC23A2* gene have been associated with lowered serum ascorbic acid concentrations. Plasma vitamin C concentrations were decreased by 5 μmol/L in SNP rs6053005-CC homozygotes and 4.3 μmol/L in CT heterozygotes compared to TT homozygotes (Duell et al., 2013). They were also decreased by 6 μmol/L in carrier of the SNP rs6133175-A allele (Duell et al., 2013). Moreover, rs1279386-GG homozygotes had approximately 1.1 μg/mL lower plasma vitamin C concentrations than the other genotypes (Zanon-Moreno et al., 2011).

Current evidence might indicate a role of *SLC23A2* polymorphism in the regulation of steady-state plasma vitamin C concentrations, but at present, research is only emerging thus it is premature to make any concrete conclusions.

5.4 Genetic Variations in the SLC23A2 Gene Associated With Common and Complex Diseases

Several variations in the SLC23A2 gene had been associated with the risk of six types of cancer, birth complications, CHD, and glaucoma.

Reduced risks for gastric cancer were reported for SNP rs12479919-AA homozygotes (Wright et al., 2009), and the haplotype for the common alleles of SNPs rs6139591 + rs2681116 + rs14147458 was inversely associated with gastric cancer (Wright et al., 2009). Similarly, the genotype rs6116569-C/T and the two haplotypes, CGTC (rs6052937, rs3787456, rs6116569, rs17339746) and ATC (rs6139587, rs6053005, rs2326576), in

the *SLC23A2* gene were associated with the risk for gastric cancer (Duell et al., 2013).

The haplotype G-C for SNPs rs4987219 + rs1110277 was associated with a reduction in the risk of colorectal adenoma (Erichsen et al., 2008).

SNP rs12479919-CT heterozygosity interacted with SCARB1 (scavenger receptor class B 1) rs4765621 genotypes to elevate the risk for bladder cancer (Andrew et al., 2009).

The risks for non-Hodgkin lymphomas were elevated by 80% for genotypes rs6133175-GG, rs1715364-CC, rs1715385-AA, rs1776948-AA, and rs6139587-AA, as well as the two haplotypes rs1776948 + rs6139587-AA and rs1715385 + rs6133175 + rs1715364-AAC (Skibola et al., 2008). SNPs rs6133175-G and rs1776948-A elevated the risk for chronic lymphocytic leukemia by about 20% (Casabonne et al., 2017). The haplotype analysis of rs1715364 + rs6133175 supported the genotype results.

The risk of head and neck cancer following HPV16 infections was decreased for rs4987219-C/C homozygotes (Chen et al., 2009).

Elevated risks for spontaneous preterm birth were observed in carrier of the minor T allele of SNP rs6139591, showing 1.7- and 2.7-fold elevations for hetero- and homozygotes, respectively (Erichsen et al., 2006).

A 5.4-fold elevated risk of acute coronary syndrome was reported in women with the rs6139591-T/T genotype with low-dietary vitamin C (Dalgard et al., 2013). Moreover, women with the rs1776964-T/T genotype and high intake of vitamin C had a 3.4-fold increased risk of acute coronary syndrome, compared with C/C homozygotes with low intake. This might indicate that the genotype effects may not be completely compensated by a high dietary intake of vitamin C (Dalgard et al., 2013).

The risk for open-angle glaucoma was elevated by 1.7-fold in rs1279386-G/G homozygotes, potentially echoing the lower plasma vitamin C concentration observed for this genotype (Zanon-Moreno et al., 2011).

To conclude, reports on genetic associations of *SLC23A2* variations mostly consist of observation from single studies, which calls for replications in similar or larger studies in order to validate those results.

5.5 Genetic Variations in the GSTM1 and GSTT1 Genes Associated to Altered Vitamin C Status

GSTs are phase 2 enzymes which conjugate glutathione to xenobiotics for the purpose of detoxification. The two major isoforms, GSTT1 and GSTM1, are involved in oxidative stress pathways through the utilization and conjugation of glutathione (Block, Shaikh, Jensen, Volberg, & Holland, 2011),

and their genes are deleted in ~20% and ~50% of the human population. The capacity of GSTO to recycle dehydroascorbic acid has been demonstrated (Linster & Van Schaftingen, 2007), but the participation of the GSTT1 and GSTM1 enzymes in the recycling of dehydroascorbic acid has not been proven. However, if they do not participate directly, they could spare the biochemical ascorbic acid consumption indirectly through recycling of other antioxidants.

For individuals carrying GSTT1 and GSTM1 null genotypes (**0/*0* gene is nonfunctional) a rare diet–gene interaction was reported: individuals had an increased risk of vitamin C deficiency when their dietary supply did not meet current recommendations (Cahill, Fontaine-Bisson, & El-Sohemy, 2009). Specifically, the risk of serum ascorbic acid deficiency in marginal vitamin C supply was elevated approximately 12-fold for the *GSTT1*0/*0* genotype but was only increased approximately twofold for carriers of the *GSTT1*1* allele. Moreover, the risk of serum ascorbic acid deficiency with marginal vitamin C intake was approximately fourfold elevated for the *GSTM1*0/*0* genotype, while it was approximately twofold for carriers of the *GSTM1*1* allele. Individuals with both nonfunctional genotypes had an approximately 15-fold elevated risk of serum ascorbic acid deficiency in marginal vitamin C supply compared to an approximately twofold risk for subjects with both functional genotypes. Serum ascorbic acid concentrations were decreased by approximately 10 μmol/L for individuals with both nonfunctional genotypes in marginal supply (Cahill et al., 2009).

Plasma vitamin C concentrations in *GSTM1*0/*0* homozygotes were decreased by 2.1 μmol/L in the general population and by 5.3 μmol/L in asbestos factory workers (Horska et al., 2011). In workers of a rock wool plant GSTT1**0/*0* homozygotes showed 9.5 μmol/L lower concentrations. Homozygotes for GSTM1/GSTT1 deletions had a vitamin C level that was 6.42 μmol/L lower.

In direct contrast to the above reported results, serum vitamin C concentrations were 5 μmol/L higher in GSTM**0/*0* homozygotes (Block et al., 2011). However, the dual deletions of GSTM1**0/*0* and GSTT**0/*0* were not associated with serum vitamin C concentrations. The association of vitamin C concentrations with the probability of being GSTM1**0/*0* was allele dosage dependent (Fig. 4), where subjects in the highest quartile of vitamin C concentrations were 2.6 times as likely to be GSTM1**0/*0*. SNPs did not modify any associations between dietary vitamin C intake and serum ascorbic acid, as reported in the previous paragraph (Block et al., 2011;

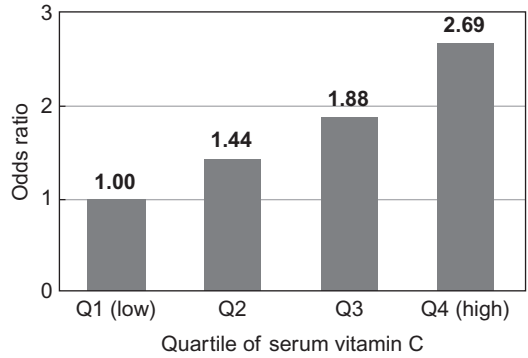

Fig. 4 Odds ratios for being GSTM1 null, by quartile (Q) of serum vitamin C, adjusted for age, sex, and BMI. 95% CIs: Q2 (0.80, 2.58), Q3 (1.04, 3.40), Q4 (1.46, 4.93). *P*-trend = 0.001. Median serum vitamin C: Q1 (41.46 μmol/L), Q2 (59.07 μmol/L), Q3 (67.59 μmol/L), Q4 (82.93 μmol/L) (Block et al., 2011).

Cahill et al., 2009). Furthermore, no associations with plasma vitamin C concentrations have been reported for GSTM1/T1 polymorphisms (Yuan et al., 2012).

Conflicting results of the associations of GSTT1 and GSTM1 null genotypes with circulating ascorbic acid concentrations do not allow deducing any causal relationships. In contrast to GSTO and glutaredoxin, the participation of the GSTT1 and GSTM1 enzymes in the recycling of dehydroascorbic acid has not been proven (Linster & Van Schaftingen, 2007); however, it is necessary to confirm the mechanistic relevance of any of the reported genetic variations.

5.6 Genetic Variations in the Haptoglobin Gene Associated to Altered Vitamin C Status

The haptoglobin protein binds free hemoglobin in the plasma, inhibits its oxidative activity, and therefore acts as an antioxidant. The haptoglobin gene allele Hp2 comprises a 1.7-kb partial duplication which does not have the same potency as the Hp1 allele, and its presence could therefore cause excessive metabolic consumption of ascorbic acid (Guthrie et al., 2014).

A 12-μmol/L decrease in serum ascorbate concentrations in the general population has been reported for Hp2-2 homozygotes (Delanghe et al., 1998), and a reduction of approximately 40 μmol/L was reported for male but not for female Hp2-2 homozygotes (Na et al., 2006). Similarly, serum ascorbic acid concentrations in HIV patients were approximately 11 μmol/L lower for Hp2-2 homozygotes (Delanghe et al., 1998). No differences in

plasma ascorbic acid were observed between subjects with the Hp2-1 and Hp1-1 alleles (Delanghe et al., 1998; Na et al., 2006). In contrast, haptoglobin genotype was not associated with vitamin C concentrations in another cohort (Guthrie et al., 2014).

For individuals carrying the Hp2-2 genotype, a rare diet–gene interaction was reported: they had an increased risk of vitamin C deficiency when their dietary intake did not meet current recommendations (Cahill & El-Sohemy, 2010). Of the subjects who reported not meeting the RDA for vitamin C, those with the Hp2-2 genotype had 5.7 μmol/L lower average serum ascorbic acid concentrations than individuals with the Hp1 allele. Hp2-2 homozygotes had a 4.7-fold elevated risk for deficiency when they did not meet their RDA, while this was 1.7-fold for carriers of the Hp1 allele.

In conclusion, ascorbic acid oxidation might be increased in Hp2-2 homozygotes. However, the correlations with impaired iron status and lowered vitamin concentrations are unclear, and diet–gene interactions of haptoglobin alleles may extend beyond vitamin C regulation and should be examined with respect to the role of haptoglobin in iron status as well (Michels, Hagen, & Frei, 2013).

5.7 Conclusions From Large-Scale Observational/Intervention and Genetic Association Studies: Implications for Future Research

Around 5% of the general population in industrialized countries has deficient plasma vitamin C concentrations and about 13% have marginal deficient concentrations. Severe deficiency will lead to scurvy, while marginal deficiency is associated to elevated risks of all-cause mortality, CVD, and gastric cancer in observational studies.

Supplementation of Vitamin C did not reduce the risks for all-cause mortality, impaired cognitive performance, reduced quality of life, the development of eye diseases, infections, CVDs, and cancers. It is suggested that these results related to the fact that additional supplementation did not elevate systemic vitamin C level in individuals already in optimal supply.

Recent genetic association studies indicate that dietary intake is not the sole determinant of systemic vitamin C levels. Polymorphisms in two ascorbic acid transporter genes (*SLC23A1* and *SLC23A2*) are associated with lower system ascorbic acid concentrations. Common variations in three genes participating in the redox (*GSTM1* and *GSTT1*) and

antioxidant metabolism (*haptoglobin*) are also associated with lower system ascorbic acid concentrations. The impact sizes are moderate, with reductions ranging between 5 and 10 μmol/L, which leads to the speculation that these variations would only be relevant in situations of suboptimal dietary intake, as defined by the current RDAs. However, although impact sizes of common polymorphism are expected to be low, epistatic interactions of multiple common variants can dramatically increase effect sizes (Abdullah, Jones, & Eck, 2015).

It is anticipated that future research will address these relations, specifically if epistatic effects of common polymorphism will predispose individuals to marginal systemic vitamin C concentrations even if they achieve current intake recommendations.

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