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COMMENTARY

Vitamin C deficiency: more than just a nutritional disorder

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Abstract Although vitamin C deficiency and scurvy are generally considered as pure nutritional disorders, only a minority of the vitamin C concentration is determined by food intake. In the presence of transition metals (iron and copper), the antiscorbutic factor shifts from an antioxidant to a pro-oxidant function. Haptoglobin (Hp) is a plasma α-2 glycoprotein characterized by 3 common phenotypes (Hp 1–1, Hp 2–1 and Hp 2–2). Its free hemoglobin (Hb)-binding capacity prevents Hb-driven oxidative damage. When the antioxidant capacity of Hp is insufficient, its role is taken over by hemopexin (heme-binding protein) and by vitamin C (free radical scavenger). The Hp 2–2 phenotype has a lower capacity to inhibit oxidation and vitamin C depletion. In this article, two consequences of this major finding are tackled. The Hp polymorphism is an important non-nutritional modifying factor in the pathogenesis of vitamin C deficiency and scurvy, which may explain the success of long-range human migration by the natural selection of some populations characterized by high Hp 1 allele frequencies. Moreover, we propose tailoring the recommended dietary allowance (RDA) values of vitamin C, taking into consideration the Hp phenotype dependency.

Keywords Haptoglobin · Polymorphism · Scurvy · Vitamin C

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Due to the lack of L-gulonolactone oxidase, human is one of the few species not capable of synthesizing the chemically instable ascorbic acid (vitamin C) (Chatterjee et al. 1961). This mutational loss, which probably took place in a remote primate ancestor of man (Gluecksohn-Waelsch 1963), causes a dependency on dietary vitamin C sources, but can also be considered as an advantage since ascorbic acid synthesis requires a lot of costly glucose reserves. On average, the human body loses approximately 3% of its vitamin C content per day, which is the percentual daily loss corresponding with the first-order elimination process of vitamin C assuming no intake. This severely limits the disease-free and survival time when subjects are on a diet poor in vitamin C, because this nutrient is a first-line antioxidant acting as a free radical scavenger. The half-life of ascorbic acid is approximately 16 days (Yung et al. 1978). In subjects without vitamin C intake, ascorbic acid is no longer detected in blood after 35–40 days

(Willet 1998). In 1939, a Harvard surgeon deliberately went on to a C-free diet, and although his blood vitamin level dropped rapidly, it was only after 12 weeks that he began to have feelings of fatigue (Crandon et al. 1940). In a larger British trial during World War II, it took 17–20 weeks for any signs to appear among 120 volunteers (No authors listed 1948). In a later trial using 4 American prisoners, using a purified liquid diet, skin changes appeared after 8–13 weeks and gum changes in 5–27 weeks (Hodges et al. 1969). So, the clinical symptoms due to vitamin C deficiency develop very slowly. Beside the conflicting results of the therapeutic use of ascorbic acid in a wide range of diseases (Cahill and El-Sohemy 2010), vitamin C deficiency and scurvy have always been a major health problem. The in vivo instability of this antiscorbutic factor is due to its proneness to oxidation. Although scurvy is generally regarded as a nutritional problem, only ±17% of the variance of the serum vitamin C concentration can be explained by vitamin C intake, as presented in the Third National Health and Nutrition Examination Survey. The influence of dietary vitamin C on serum ascorbic acid measurements in this study was complicated by the use of food frequency questionnaires that poorly report vitamin C levels (Hampl et al. 2004).

Several in vivo factors related to inflammation and oxidative stress have been demonstrated to influence the biological variation in vitamin C concentration in humans. Recent research showed that genetic polymorphisms coding for vitamin C transporter protein (SVCT) 1 (SLC23A1 gene) (Cahill and El-Sohemy 2009) and glutathione S-transferase (GST) (Cahill et al. 2009) may affect the concentrations of fasting serum ascorbic acid independent of diet. SVCT1 and SVCT2 genotypes modify the strength of the correlation between dietary vitamin C and serum ascorbic acid (Cahill and El-Sohemy 2009). GST enzymes have a protective capacity against vitamin C deficiency when dietary vitamin C is insufficient (Cahill et al. 2009). Another important factor, the acute phase protein haptoglobin (Hp) is characterized by a genetic polymorphism with three phenotypes (Hp 1–1, Hp 2–1, and Hp 2–2), which results from the expression of two alleles (Hp 1 and Hp 2) of the Hp gene on chromosome 16q22. The major biological function of Hp is binding and recycling of free hemoglobin (Hb) in plasma to prevent oxidative damage induced by heme iron following hemolysis (Langlois and Delanghe 1996). When the Hb-binding capacity of Hp is saturated, its antioxidant role is taken over by hemopexin (heme-binding protein) and by vitamin C.

Hp phenotypes show important structural and functional differences. Hp 1–1 is a small dimeric protein (86 kDa), whereas Hp 2–1 and Hp 2–2 show polymeric forms (up to 900 kDa). Iron status is affected by Hp polymorphism as Hp 2–2 is less efficient in the clearance of Hb from the circulation. As a consequence, Hp 2–2 individuals show iron retention in macrophages and present higher serum iron and ferritin concentrations and increased transferrin saturation compared with the other Hp phenotypes (Langlois et al. 2000).

The iron delocalization pathway, selectively occurring in Hp 2–2 subjects, has important biological consequences. Iron withholding is an important example of nutritional immunity in the defense against infectious diseases (Weinberg 1984; Kristiansen et al. 2001). Hp acts as a natural bacteriostat by preventing the utilization of Hb by pathogenic bacteria which require iron for their growth. The iron-restrictive environment in body fluids established by Hp–Hb binding is part of the non-specific defense against bacterial invasion. Hp polymorphism plays a role in a number of bacterial and viral infections (Kasvosve et al. 2010). In the early history of mankind, a successful mutation took place, which proved to be beneficial in terms of conservation of iron, although it had a major impact on vitamin C stability in vivo (Kamel and ‘Umar 1975).

Nowadays, scurvy is still classified as a nutritional disorder or avitaminosis instead of a genetic disease. In humans, the vitamin C status is not only determined by diet but also by the environment, lifestyle, biological and pathological conditions (Langlois et al. 2009; Pincemail et al. 2011; Lowik et al. 1993; Galan et al. 2005; Vioque et al. 2007; Johnston et al. 2006). In this paper, we will focus on the link between the vitamin C status and the Hp polymorphism by discussing the three following hypotheses:

(1) The stability of vitamin C depends on the iron status and the Hp polymorphism.
(2) Success of long-range human migration has been strongly determined by Hp polymorphism. Due to natural selection, some populations characterized by high Hp 1 allele frequencies are much less prone to scurvy.
(3) The recommended dietary allowance (RDA) values of vitamin C might be strongly Hp phenotype dependent.

Scurvy is one of the genetic metabolic anomalies that has been with us since prehistory, as it was already reported by the Egyptians (1550 BC) and Hippocrates (460 BC–380 BC) (Hirsch 1885; Bourne 1949; Carpenter 1986). In his *Handbook of geographical and historical pathology*, Hirsch described in detail the scurvy outbreaks among Europeans between 1556 and 1873 (the expedition by Cartier in the sixteenth century, the Dutch expedition to Novaya Zemlya (1594–1596), the US Army outpost Fort Atkinson in 1819, Perth prison in the nineteenth century) (Langlois et al. 2009; Delanghe et al. 2007). Nutritional availability of ascorbic acid is geographically dependent.

Although relative losses by scurvy were relatively lower in Europe, it is clear that the majority of described scurvy outbreaks were situated in Europe. However, there is a strong geographical bias in this description. A particular susceptibility of East and South East Asians toward scurvy has been reported (Delanghe 2007; Hirsch 1885; Torck 2005; Torck 2009). A medical report from the eighteenth-century documenting outbreaks in Chinese army garrisons operating in the north of the country mentions rates of affected troops amounting to 80 and 90% (Torck 2009). Furthermore, Japanese sailors were particularly susceptible to scurvy during drifting accidents in the Pacific. Among castaways, mortality rates as high as 50 and 78% have been reported in nineteenth-century records (Delanghe et al. 2007). Moreover, in early modern Japan (nineteenth century), there is a description of the Tsugaru soldiers with up to 72% mortality from scurvy (Walker 1999; Matsuki 1981). It is important to point out that these occurrences date back to a time frame in the context of which the diet of the Japanese population is generally considered to be nutritionally balanced, stable, and thus, in quality not likely to be inferior to contemporary European diets (Hanley 1991).

Although the scorbutic syndrome has been merely regarded as a pure nutritional disturbance, differences in Hp phenotype distribution may offer a plausible explanation for these historical findings, which are furthermore supported by solid in vitro and in vivo biochemical evidence (Delanghe et al. 2007). In human evolution, the Hp 2 allele originated in South Asia, which explains the highest Hp 2 and the lowest wild-type Hp 1 allele ($\sim$0.25) frequencies in the local population (Fig. 1). The human species is currently in a state of transient gene equilibrium, in which the mutant Hp 2 allele has been generally favored during evolution. Among Western European populations, Hp 1 and Hp 2 allele frequencies are $\sim$0.40 and 0.60, respectively (Langlois and Delanghe 1996). However, there are some regions where populations can be found presenting with high Hp 1 allele frequencies (Table 1), e.g., the indigenous populations of Latin America (Hp 1 allele frequency: 0.58–0.78). Amerind populations showing very high Hp 1 allele frequencies amazingly proved to be capable of crossing the ocean on simple rafts without any advanced shipbuilding knowledge or technology (Heyerdahl 1995). The advantage of Hp 1–1 as a genetic factor favoring survival in long-distance sea voyages is illustrated by the Hp phenotype distribution among the indigenous populations of remote islands. Easter Island is one of the remotest places on earth. Its indigenous Rapa Nui population is characterized by the highest Hp 1 allele frequency (0.86) known (Delanghe et al. 2007). Undoubtedly, early immigrants of Easter Island and Northern Canada have been subject to a challenging vitamin C depletion (scurvy) during the long voyage. Documents from the eighteenth and nineteenth centuries indicate that scurvy caused by vitamin C deficiency was not observed among the Inuit in contrast to a serious illness observed among Arctic explorers (Fediuk 2000). Madagascar has a mixed population of African and proto-Indonesian origin. The Hp 1 allele frequency of the island's population is remarkably higher than the one of the constituting founding populations, which is pleading for a genetic selection based on Hp phenotype during the migration (Buettner-Janusch et al. 1973). Finally, in the Awyu population of Papua New Guinea, which is also characterized by a predominance of the Hp 1 allele, no events of scurvy have been reported. In this area, the regions with the highest Hp 1 allele frequency (>0.85) are Frederik Hendrik Island (West Irian) and the region north of it, which is a big contrast in Hp allele frequencies with the aboriginals from Northern Australia. Looking at the other gene maps of New Guinea, there is no similar gradient. Hp polymorphism seems to be an independent genetic factor (Klein 1954; Hill et al. 1986; Cavalli-Sforza et al. 1994).

Based on those findings, the effect of Hp polymorphism upon vitamin C metabolism offers a plausible, though speculative explanation how during the course of human history, some populations characterized by a high Hp 1 allele frequency have been able to migrate successfully over long distances and can survive on a vitamin C poor diet (Delanghe et al. 2007). This suggestion is further supported by the results of the Toronto Nutrigenomics and Health Study. In this study, Cahill and El-Sohemy showed a gene–diet interaction on the serum ascorbic acid concentration. In contrast to carriers of the Hp 1 allele with a greater antioxidant capacity, Hp 2–2 subjects had an increased risk of deficiency if they did not meet the RDA for vitamin C (Cahill and El-Sohemy 2010). Hp acts to prevent the oxidative and toxic effects of the iron-containing heme in Hb (Na et al. 2005). The ascorbic acid stability in body fluids is lower in Hp 2–2 individuals (Cahill and El-Sohemy 2010; Delanghe et al. 2007; Sadrzadeh and Eaton 1988; Langlois et al. 1997). Hp 2–2 subjects are less efficient in removing free Hb from the plasma, which may favor an iron-mediated vitamin C depletion (Langlois et al. 1997; Delanghe and Langlois 2002). Furthermore, the ability of Hp 2–2 polymers to sieve into the extravascular compartment is restricted by their high molecular mass. Parts of Hb-derived iron are delocalized and accumulated in inert, poorly accessible iron storage compartments (Delanghe et al. 2007). Complexes of Hb and multimeric Hp 2–2 exhibit a higher affinity for the Hb scavenger receptor CD163, which accounts for a substantial transfer of iron into macrophages, than complexes of Hb and the Hp 1–1 phenotype do (Kristiansen et al. 2001). Iron loading of macrophages

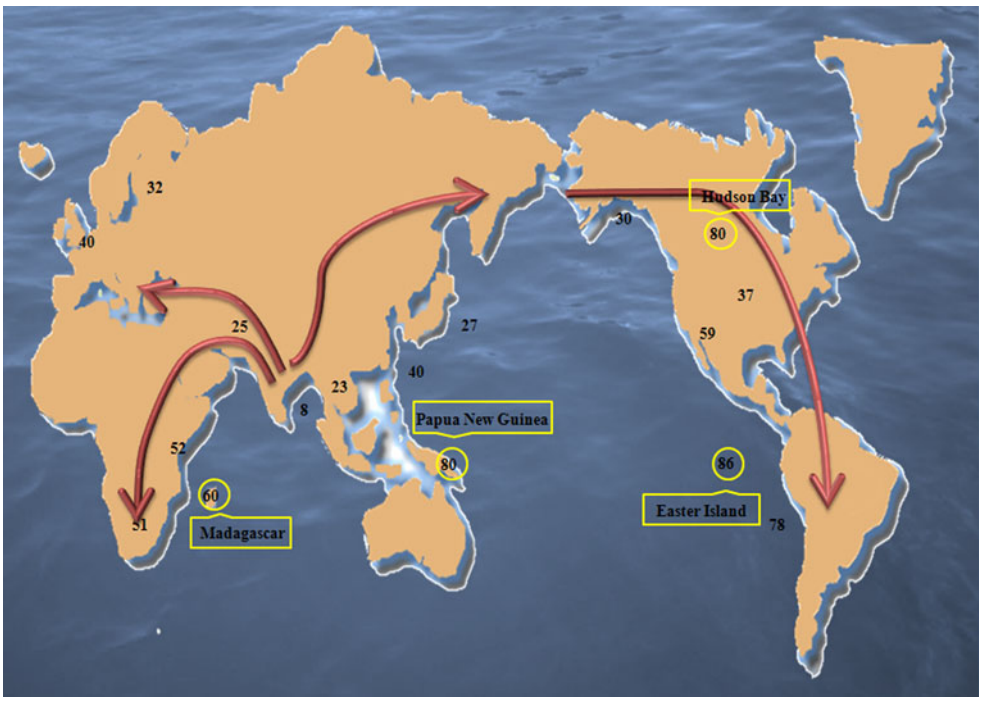

Fig. 1 Map of Hp1 allele frequency. The numbers represent the Hp1 allele frequency (as a percentage). The *arrows* represent the direction of human migration in pre-historical times. Four exceptions on the normal Hp allele distribution with extremely high Hp1 allele frequencies are found around the Hudson Bay, Easter Island, Madagascar, and Papua New Guinea [Frederik Hendrik Island (West Irian)]

Table 1 List of areas/populations with a high Hp 1 allele frequency and its relationship to the incidence of scurvy

	Hp 1 allele frequency	Comment
Easter Island (Rapa Nui)	0.86	Very remote place (Delanghe et al. 2007)
Hudson Bay (Inuit)	0.80	Extremely low vitamin C intake (10 mg/day) (Fediuk 2000)
Madagascar	0.60	Hp 1 allele frequency on the island exceeds the one of the founding populations (Buettner-Janusch et al. 1973; Cavalli-Sforza et al. 1994)
Papuna New Guinea (Awyu)	0.80	Scurvy unknown (Klein 1954; Hill et al. 1986)

results in iron-driven oxidative stress, which is reflected by lower serum vitamin C concentrations in Hp 2–2 subjects (Delanghe and Langlois 2002). No difference in renal threshold and urinary excretion of ascorbic acid is observed between Hp phenotypes (Langlois et al. 1997).

According to the guidelines of the Food and Nutrition Board, the RDA for vitamin C, which is the amount considered to maintain normal nutrition in the general population, is 90 mg/day for men and 75 mg/day for women. These data have been derived from a population, mainly consisting of Europeans and Afro-Americans. For smokers, the daily amount of vitamin C has to be increased with 35 mg/day (Food et al. 2000). However, based on the findings mentioned earlier, the influence of the Hp polymorphism on the vitamin C need should be taken into account. Research learns that the diet of the Inuit in the Hudson Bay (a region with a predominance of the Hp 1 allele) was mainly composed of animal sources, generally perceived as poor sources of vitamin C. It is assumed that the Inuit were able to obtain a minimum level of vitamin C (10 mg/day) from a diet of frozen/raw, fermented, and dried animal food, required to prevent scurvy (Fediuk 2000). As the stability of ascorbic acid is lower in Hp 2–2 individuals, the required daily intake of this nutrient is higher compared with the other Hp phenotypes (Cahill and El-Sohemy 2010; Delanghe et al. 2007; Langlois et al. 1997; Delanghe and Langlois 2002). Better tailored RDA guidelines for ascorbic acid taking into account the ethnical background could therefore contribute to a better nutritional health policy.

Conclusions

The classical view of vitamin C deficiency and scurvy being exclusively nutritional disorders needs to be tailored. Clinical and in vitro studies have demonstrated that the genetic polymorphism of the abundant plasma protein

haptoglobin (Hp) may play an important role. This finding has major consequences in a number of medical problems. It provides a new rationale to intriguing historical questions, e.g., it may give evidence for the thesis that Hp polymorphism is an important non-nutritional modifying factor in the pathogenesis of vitamin C deficiency and scurvy. These approaches may result in a better tailored treatment for diseases in which the redox state of the patient plays a role.

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