Vitamin C Deficiency and Scurvy Are Not Only a Dietary Problem but Are Codetermined by the Haptoglobin Polymorphism

Ascorbic acid (vitamin C) is prone to oxidation in vivo. The human plasma protein haptoglobin (Hp) shows a genetic polymorphism with 3 major phenotypes (Hp 1-1, Hp 2-1, and Hp 2-2) that show important functional differences. Despite an adequate nutritional supply, in Hp 2-2 individuals (most common among Asian populations) vitamin C is markedly lower in concentration and particularly prone to oxidation in vivo. Therefore, susceptibility to subclinical and clinical vitamin C deficiency (scurvy) is partly genetically determined. The genetic advantage of the Hp1 allele as a vitamin C stabilizing factor helps to elucidate the direction and successes of long-distance sea crossing human migrations in history. Clinical trials demonstrated Hp phenotype–related effects of antioxidant treatment. Because vitamin C is a first line antioxidant, Hp polymorphism and its effects on vitamin C have major clinical consequences; a marked difference in genetic susceptibility toward atherosclerosis between Hp phenotypes is attributable to variation in LDL oxidation. The classical view of vitamin C and scurvy being a pure nutritional problem, correlation between vitamin C intake and vitamin C concentration is rather weak \( r = 0.42 \); only \(~17\%\) of the variance of the serum vitamin C concentration can be explained by vitamin C intake \( (2) \). Vitamin C status is determined not only by the dietary vitamin C content, but also by environmental and lifestyle factors \( (e.g.,\ smoking) \), biological factors \( (e.g.,\ inflammation,\ iron\ excess) \), and pathological conditions \( (e.g.,\ malabsorption,\ hemolysis) \). Clinical and in vitro studies have demonstrated that the genetic polymorphism of the abundant plasma protein haptoglobin (Hp) may play a role. Because of the presence of 2 codominant alleles \( (Hp1\ and\ Hp2) \), 3 major haptoglobin phenotypes are known in man: Hp 1-1, Hp 2-1, and Hp 2-2 \( (3) \). The stability of vitamin C in serum is lowest in Hp 2-2 individuals \( (4) \). This finding has major consequences in several medical problems and may offer explanations to intriguing historical questions. This report summarizes the evidence for the thesis that the Hp polymorphism is an important nonnutritional modifying factor in the pathogenesis of vitamin C deficiency and scurvy.

VITAMIN C METABOLISM AND HP POLYMORPHISM

The major biological function of Hp is binding and recycling of free hemoglobin (Hb) in plasma to prevent oxidative damage induced by heme iron after hemolysis \( (3) \). Hp phenotypes show important structural and functional differences. Hp 1-1 is an 86-kDa dimeric molecule, whereas Hp 2-1 and Hp 2-2 show polymeric forms \( (up\ to 900\ kDa)\). The capacity of Hp 2-2 to inhibit Hb-driven lipid oxidation and vitamin C depletion is inferior to that of Hp 1-1 \( (4) \). In vivo, the antioxidative capacity \( (ascorbic\ acid\ stability)\) is low in Hp 2-2 individuals because the ability of Hp 2-2 polymers to sieve into the extravascular compartment is restricted by their high molecular mass. Complexes of Hb and multimeric Hp 2-2 are endocytosed by the CD163 receptor on monocyte-macrophages \( (5) \). Parts of Hb-derived iron are delocalized and accumulate in inert, poorly accessible iron storage compartments \( (5,\ 6) \). Cytosolic ferritin content is twice as high in monocyte-macrophages from Hp 2-2 individuals compared with Hp 1-1 and 2-1 individuals \( (6) \). Vitamin C reduces \( \text{Fe}^{3+} \) to \( \text{Fe}^{2+} \) in the ferritin crystal core, a reaction in which ascorbic acid is oxidized. The released \( \text{Fe}^{2+} \) promotes the production of highly reactive hydroxyl radicals \( (\text{Fenton chemistry})\), which deplete vitamin C stores in Hp 2-2 individuals \( (4) \). Lower serum ascorbic acid concentrations have been observed in European and Chinese individuals with the Hp 2-2 phenotype \( (4,\ 7) \). The effect of Hp polymorphism on vitamin C concentration is of the same magnitude as the effect of nutritional intake \( (4) \).

Fig. 1 summarizes the Hp-related effects on vitamin C metabolism.

GEOGRAPHICAL DISTRIBUTION OF HP PHENOTYPES

The human Hp2 allele originated in South Asia as a result of partial duplication by unequal crossing-over between Hp1 alleles \( (3) \). South-East Asian populations show the highest frequencies of the Hp2 allele and the lowest of the wild-type Hp1 allele \( \sim0.25)\). Humans are currently in a state of transient gene equilibrium, in which the Hp2 allele has been generally favored during evolution. Among Western European populations, Hp1 and Hp2 allele frequencies are \(~0.40\) and 0.60, respectively. Indigenous Latin American populations are characterized by

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very high (0.58–0.78) Hp1 allele frequencies (3). Amerind populations showing very high Hp1 allele frequencies
amazingly proved their ability to cross the ocean on simple rafts without any advanced shipbuilding knowl-
edge or technology (8). The advantage of Hp1-1 as a genetic factor favoring survival in long-distance sea voy-
ages 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 Hp1 allele frequency (0.86) known (2). Undoubt-
edly, early immigrants of Easter Island were subjected to
challenging vitamin C depletion (scurvy) during the long
voyage on the Pacific Ocean. Similarly, Madagascar has a
mixed population of African and proto-Indonesian origin.
The Hp1 allele frequency of the island’s population is
remarkably higher than those of the constituting founding
populations (9), a finding that pleads the case for genetic
selection based on Hp phenotype during the migration.

HISTORICAL FINDINGS
Early literature on scurvy relied mainly on Western
sources, and thus the traditional view of scurvy was
narrowed to a health problem of European seagoing
nations. However, a detailed review of non-Western his-
torical sources revealed that scurvy was a major health
issue in East and South-East Asians as well (10), a finding
that can be reconciled with the fact that South-East Asian
populations show very high Hp 2 allele frequencies (e.g.,
Chinese and Japanese: ~0.75) and that the Hp 2 allele is
associated with a higher in vivo vitamin C instability.

Despite the advanced development and technology in
navigation, shipbuilding, cartography, and even the use
of empirical antiscorbutic preventive dietary measures in
China during the Ming era (1368–1644) (10), the Chinese
seagoing expeditions led by Admiral Zheng He (1371–
1433) suffered from extremely heavy casualties and were
finally discontinued (10). Clinical cases of scurvy oc-
curred frequently among the Chinese garrisons operating
beyond the Great Wall (10). Fig. 2 shows an 18th century
Chinese description of scurvy (11).

In the mid-19th century, scurvy was extremely com-
mon among Chinese migrant workers crossing the Pacific
to California (10). In addition, Japanese sailors were
particularly susceptible to scurvy during drifting acci-
dents in the Pacific. In early modern Japan (19th century),
there is a description of the Tsugaru soldiers with up to
72% mortality from scurvy (12). Among castaways, mor-
tality rates as high as 50% and 78% have been reported in
19th century records (13).

For Europeans, relative losses by scurvy were lower
than for Asians. The French expedition of Cartier in 1536
counted 25 victims (a rate of ~30%) (1). For the Dutch
East Indies Company, typical crew losses for a 1-way trip
between Europe and the Indonesian archipelago in the
17th century were ~20%. The Dutch expedition to
Novaya Zemlya in 1596 counted only 2 scurvy victims
among 17 crew members. In the Crimean War (1854–
1856), the French Navy counted ~30% of scurvy cases (1).
In Perth general prison in Scotland, during 1845–1846
scurvy occurred at a rate of 50 of 330 inmates. In 1819, 160
scurvy victims were counted of 800 soldiers in the US
Army outpost at Fort Atkinson (Nebraska) (1). In 1864,
during the US Civil War, Andersonville prison counted
3000 scurvy deaths among 30 000 prisoners (1). Despite
the fact that conditions are not completely comparable,
these data are striking because they were recorded in
relative homogeneous populations sharing a uniform
diet. The relative number of victims roughly corresponds

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**Fig. 1.** The effects of haptoglobin polymorphism on vitamin C metabolism.

In individuals carrying the Hp 2-2 type, ascorbic acid is more prone to oxidation
at different levels. (a) Free Hb, continuously released from erythrocytes, is
recycled by the formation of Hb-Hp complexes, which are transported to the liver,
a pathway contributing to normal iron turnover. Hp 2-2 polymers are less efficient
inhibitors of Hb-driven oxidative stress, leading to ascorbic acid depletion. (b)
complexes of Hb and multimeric Hp 2-2 are selectively taken up by the CD163
receptor on monocyte-macrophages, leading to accumulation of heme-derived
iron as intracellular ferritin. Vitamin C reduces Fe^{3+} to Fe^{2+} in the ferritin crystal
core, a reaction in which ascorbic acid is oxidized, and the released Fe^{2+}
promotes the production of reactive hydroxyl radicals (Fenton reaction), which
can further deplete vitamin C in Hp 2-2 individuals. AA, Ascorbic acid; AA•,
ascorbate radical; Hb, hemoglobin; Hp, haptoglobin; RBC, erythrocytes.
with the relative frequency of the Hp 2-2 phenotype among populations of European ancestry (3).

The effect of the Hp polymorphism on vitamin C metabolism offers a plausible explanation as to how, during the course of human history, some populations characterized by a high Hp1 allele frequency have been able to migrate successfully over long distances and some genetically privileged nations (in terms of vitamin C stability) could advance to colonizing empires with a global presence. Apart from cultural, technological, and political variables, genetic and biochemical influences such as Hp polymorphism may have played a major role in human mass migration, in which some populations may have been more favored than others.

CLINICAL FINDINGS

The effect of Hp phenotypes on in vivo vitamin C stability may have important consequences in a variety of clinical conditions related to oxidative stress, particularly atherosclerosis. Circulating concentrations of oxidized LDL, which play a key role in atherogenesis, are higher in male Hp 2-2 individuals (14). The beneficial effect of oral antioxidant supplementation (containing supraphysiological doses of ascorbic acid and other antioxidants) on LDL oxidation was more pronounced among Hp 1-1 individuals (15). The differences in iron status and susceptibility to LDL oxidation among Hp 2-2 individuals helps to explain why communities from the Indian subcontinent (with high Hp 2 allele frequency) develop more atherosclerosis when exposed to a modern western lifestyle. The Hp 2-2 phenotype is overrepresented in whites suffering from cardiovascular disease (3). Discrete biochemical signs of subclinical vitamin C deficiency have been observed in peripheral arterial disease patients with pronounced inflammation, despite a largely sufficient nutritional supply of vitamin C (16). Clinicians should be aware that patients presenting with an Hp 2-2 phenotype (in whites typically ~35% of the population, in South- and East-Asians, ≥50%) genetically are more prone to develop subclinical scurvy in the case of inflammation-associated oxidative stress conditions.

CONCLUSIONS

The classical view of vitamin C deficiency and scurvy being exclusively nutritional disorders (postulated by Szent-Györgyi more than 70 years ago) needs to be updated. Despite the promising predictions from in vitro studies, overall results of clinical trials with supraphysiological supplements of vitamin C and other antioxidants have not been very convincing (17), possibly because of genetic variation within the investigated study populations. Stratifying patient outcome according to Hp phenotype in such studies could potentially give a more differentiated picture. These approaches may result in disease treatments better tailored to diseases in which the redox state of the patient plays a role.

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