Vitamin C u prevenciji i liječenju bolesti

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Vitamin C in disease prevention and therapy

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Sažetak

Vitamin C je esencijalan sastojak hrane uključen u mnoge biološke i biokemijske procese kao antioksidans. S obzirom da je oksidacijsko oštećenje povezano s nastankom različitih bolesti, vitamin C ima potencijalno preventivan, ali i terapijski učinak. Voće i povrće su preporučeni izvori vitamina C koji imaju preventivnu ulogu u razvoju malignih tumora i bolesti krvožilnog sustava, premda ne isključivo zbog vitamina C. Povrh toga, sintetski vitamin C uzet u količinama većim od preporučenog dnevnog unosa (RDA) djeluje povoljno na zarastanje rana, ublažavanje simptoma prehlade, ali i u prevenciji prehlade u osoba izloženih prekomjernom fizičkom stresu. Također, vitamin C je učinkovit u smanjivanju koncentracije fibrinogena povezanog s povećanim rizikom od nastanka bolesti krvožilnog sustava. Pozitivni učinci mogu se također ostvariti intravenskim unosom vitamina C kod bolesnika s šećernom bolesti i nekim oblicima malignih tumora. Međutim, pozitivni učinci vrlo često ovise o mnogim čimbenicima, kao što su doza, dob, zdravstvene navike i dr.

Ključne riječi: vitamin C, antioksidans, bolesti krvožilnog sustava, maligni tumori, prehlada, bolesti dišnog sustava, šećerna bolest, siva mrena.

Abstract

Vitamin C is an essential nutrient involved in many biological and biochemical processes as an antioxidant. As oxidative damage is implicated in the development of various diseases, vitamin C could have a preventive or even therapeutic effect. Fruits and vegetables are the recommended sources of vitamin C. Five servings of fruits and vegetables are protective against cancer and cardiovascular disease, however not because of vitamin C alone. On the other hand, oral vitamin C supplements in amounts higher than Recomended Daily Allowance (RDA) are beneficial in wound healing, reducing the duration of common cold symptoms, but also in prevention of common cold in heavily physically stressed persons. Furthermore, vitamin C is effective in decreasing serum fibrinogen, which is related to increased cardiovascular risk. Positive effects may be also achieved by intraarterial or intravenous administration of vitamin C in patients with diabetes mellitus and cancer. However, positive effects frequently depend on many factors, such are dose, age, health habits, etc.

Keywords: vitamin C, antioxidant, cardiovascular disease, cancer, common cold, respiratory diseases, diabetes mellitus, cataract.

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Uvod

L-askorbinska kiselina (vitamin C) je dio metabolizma glukoze koji kod ljudi ne postoji zbog nedostatka L-gulonolakton-oksidaze, tj. posljednjeg enzima u biosintetskom stvaranju tog vitamina koji se stoga nužno dobiva iz prehrambenih izvora (1). Vitamin C se nalazi u raznom voću, kao što su naranče, grejpfrut, jagode, maline, kivi, te povrću poput kupusa, rajčice i paprike (2). Taj je vitamin prvi izolirao Albert Szent-Gyorgyi 1928. godine, no zasluge za njegovu popularizaciju pripadaju Linusu Paulingu. Sedamdesetih je godina 20. stoljeća Pauling naznačio važnost vitamina C u sprječavanju ili ublažavanju prehlade te u potpornom liječenju karcinoma (3,4). Što se danas može reći o vitaminu C, posebice njegovoj ulozi u sprječavanju i liječenju bolesti?

Introduction

L-ascorbic acid (vitamin C) is part of glucose metabolism, which is not accessible to humans since they lack L-gulonolactone oxidase, the last enzyme in the biosynthetic pathway. Therefore, they must obtain it from dietary sources (1). Vitamin C could be found in many fruits such as oranges, grapefruit, strawberries, raspberries, kiwi fruit, and in vegetables such as cabbage, tomatoes, and bell peppers (2). Vitamin C was first isolated by Albert Szent-Gyorgyi in 1928 but the credit for its popularization goes to Linus Pauling. In the 1970s, Pauling implicated the importance of vitamin C in prevention or relief of the simple cold and in the supportive treatment of cancer (3,4). What can be said about vitamin C today, particularly regarding its role in disease prevention and therapy?

Preporuke vezane za prehranu

Referentni prehrambeni unosi (engl. *dietary reference intakes*, DRI) predstavljaju najnoviji skup prehrambenih preporuka koje je u SAD-u donio Odbor za prehranu Zavoda za medicinu, a koje se temelje na četiri kategorije: preporučenoj dnevnoj količini (eng. *recommended dietary allowance*, RDA) - prosječnoj količini dnevnog unosa hranjive tvari koja sprječava manjak u 98% populacije; procijenjenoj prosječnoj potrebi (engl. *estimated average requirement*, EAR) - vrijednosti unosa prehrambene tvari za koju se procjenjuje da zadovoljava potrebe 50% populacije; adekvatnom unosu (engl. *adequate intake*, AI) - vrijednosti koja je određena kao ciljna za individualan unos prehrambenih tvari za koje ne postoje RDA; te podnošljivoj gornjoj količini unosa (engl. *tolerable upper intake level*, UL) - najvišoj količini prehrambene tvari za koju je vjerojatno da ne predstavlja rizik nepovoljnih zdravstvenih učinaka u 98% populacije. AI se određuje umjesto RDA ukoliko ne postoji dovoljno znanstvenih podataka za izračun EAR, kao što je to slučaj u dojenčadi. Proces određivanja RDA ovisi o mogućnosti određivanja EAR (5). Kako bi se osigurala zaštita od antioksidansa, 75 mg/dan za žene te 90 mg/dan za muškarce određeni su kao RDA za vitamin C. 2000 mg/dan je određeno kao UL za odrasle osobe (6). Mnoge su studije, međutim, pokazale da bi unos vitamina C za optimalno smanjenje rizika kroničnih bolesti kao što su karcinom i kardiovaskularne bolesti trebao biti viši od najnovijih vrijednosti RDA (7,8). Preporučuje se pet obroka voća i povrća dnevno zbog toga što se čini da je vitamin C kao dodatak manje učinkovit u sprječavanju bolesti i bolesnih stanja (8).

Uloga vitamina C

Vitamin C je važan antioksidans koji sprječava oksidaciju drugih spojeva. Antioksidacijski učinak prehrambenih čimbenika *in vivo* može se procijeniti na temelju nekoliko pokazatelja, među kojima koncentracija vitamina C predstavlja vrlo osjetljiv pokazatelj oksidacijskog stresa (9). Vitamin C također obnavlja tokoferoksilni radikal vitamina E i time tom vitaminu omogućava da ponovno djeluje kao antioksidans (10). Vitamin C je specifičan donor elektrona za 8 enzima uključenih u biosintezu kolagena, karnitina i noradrenalina, amidaciju peptidnih hormona, te u metabolizam tirozina. Također ima neenzimske reduktivne funkcije u kemijskim reakcijama zbog svog redoksnog potencijala i intermedijera slobodnog radikala (5). Premda je topiv u vodi i lako se izlučuje iz tijela, vitamin C se nakuplja u mozgu, kori nadbubrežne žlijezde, jetri, slezeni, gušterači i bubrežnom tkivu (11). Nadbubrežna žlijezda je među organima s najvišom koncentracijom vitamina C radi biosinteze kateholamina i adrenalne steroidogeneze (12).

Metabolizam vitamina C

Ako se uzima oralno, vitamin C se dobro apsorbira u nižim dozama, no apsorpcija se smanjuje s povećanjem doze. Vi-

Dietary recommendations

The Dietary Reference Intakes (DRI) are the most recent set of dietary recommendations established by the Food and Nutrition Board of the Institute of Medicine, USA, which are based on the evaluation of four categories: Recommended Dietary Allowance (RDA) – the average dietary intake level of a nutrient that prevents a deficiency in 98% of a population, Estimated Average Requirement (EAR) – a nutrient intake value that is estimated to meet the needs of 50% of a population, Adequate Intake (AI) – a value set as a goal for individual intake for nutrients that do not have a RDA, and Tolerable Upper Intake Level (UL) – the highest level of a nutrient that is likely to pose no risk of adverse health effects to 98% of a population. The AI is set instead of an RDA if sufficient scientific evidence is not available to calculate an EAR, such as in infants. The process for setting the RDA depends on being able to set an EAR (5). To provide antioxidant protection, the RDA for adults for vitamin C is set at 75 mg/day for females and 90 mg/day for males. UL for adults is set at 2, 000 mg/day (6). However, many studies have shown that vitamin C intake for optimum reduction of chronic disease risk such as cancer and cardiovascular diseases should be higher than the newest RDA values (7,8). Five servings of fruits and vegetables daily are recomended, because vitamin C as a supplement seems to be less effective in the prevention of diseases and conditions (8).

The role of vitamin C

Vitamin C is an important antioxidant which prevents other compounds from being oxidized. Antioxidative effect of food factors *in vivo* can be evaluated on the basis of several indices, where vitamin C concentration represents a very sensitive index of oxidative stress (9). It also repairs the tocopheroxyl radical of vitamin E, thereby permitting vitamin E to function again as an antioxidant (10). Vitamin C is a specific electron donor for 8 enzymes involved in collagen, carnitine and noradrenaline biosynthesis, amidation of peptide hormones, and in tyrosine metabolism. It also has non-enzymatic reductive functions in chemical reactions, based on its redox potential and its free-radical intermediate (5). Although vitamin C is a water soluble vitamin which could be easily excreted from the body, brain, adrenal cortex, liver, spleen, pancreas and kidney tissues concentrate vitamin C (11). The adrenal gland is among the organs with the highest concentration of vitamin C in the body, where it is required both in catecholamine biosynthesis and adrenal steroidogenesis (12).

Vitamin C metabolism

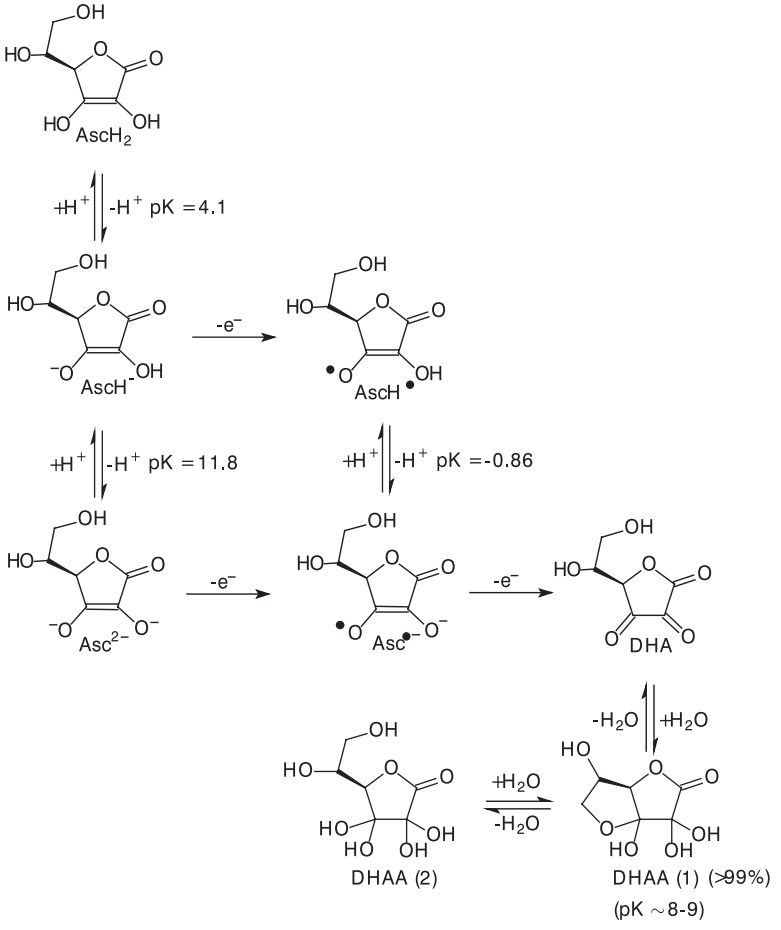
When given orally, vitamin C is well absorbed at lower doses, but absorption decreases as the dose increases. In the blood, vitamin C is not protein bound, so it is filtered and

tamin C nije vezan za proteine u krvi tako da se filtrira i reapsorbira u bubrezima. Najvjerojatnije nepromijenjen prolazi kroz glomerule i aktivnu tubularnu reapsorpciju koju provodi transportni protein za vitamin C, a koja je ovisna o koncentraciji. Kod zasićenja transportnog proteina vitamin C se dalje ne prenosi već se izlučuje kroz mokraću; u mokraći se pojavljuje u dozama iznad 100 mg/dan (11), dok se potpuna zasićenost plazme pojavljuje kod 1000 mg/dan (8).

Vitamin C se kroz stanične membrane najvjerojatnije prenosi dvama zasebnim mehanizmima. Askorbinska kiselina lako oksidira u dehidroaskorbinsku kiselinu (DHA) koju stanice, koristeći glutation, ubrzano preuzimaju i reduciraju u askorbinsku kiselinu (13). Kako se izvanstanično oksidiran askorbat unutar stanica reciklira, proces se naziva *recikliranje askorbata*. Specifične izoforme transportera glukoze, tj. GLUT1 i GLUT3, posreduju u prijenosu DHA

reabsorbed by kidneys. It probably passes unchanged through glomeruli and undergoes concentration-dependent active tubular reabsorption by a vitamin C transport protein. When the transport protein reaches saturation, remaining vitamin C is not transported, and it is excreted in urine. Vitamin C begins to appear in urine at doses above 100 mg/day (11), while complete plasma saturation occurs at 1,000 mg/day (8).

Vitamin C is transported across cellular membranes most likely by two distinct mechanisms. Ascorbic acid is easily oxidized to the dehydroascorbic acid (DHA) which is rapidly taken up by cells and reduced to ascorbic acid, using glutathione for reduction (13). Because ascorbate oxidized extracellularly is recycled intracellularly, the process is called "ascorbate recycling". The specific glucose transporter isoforms, GLUT1 and GLUT3, mediate DHA transport because of its similarity to the molecule of glu-



Slika 1. Ravnoteža i redoks-vrste REDOX SPECIES u sustavu askorbinske - dehidroaskorbinske kiseline. AscH2 (askorbinska kiselina), AscH– (monoanion askorbata), Asc2– (dianion askorbata), AscH· (askorbil-radikal), Asc·– (radikal askorbata), DHA (dehidroaskorbat), DHAA(1) i DHAA(2) (hidrolizirani oblici dehidroaskorbata) (17).

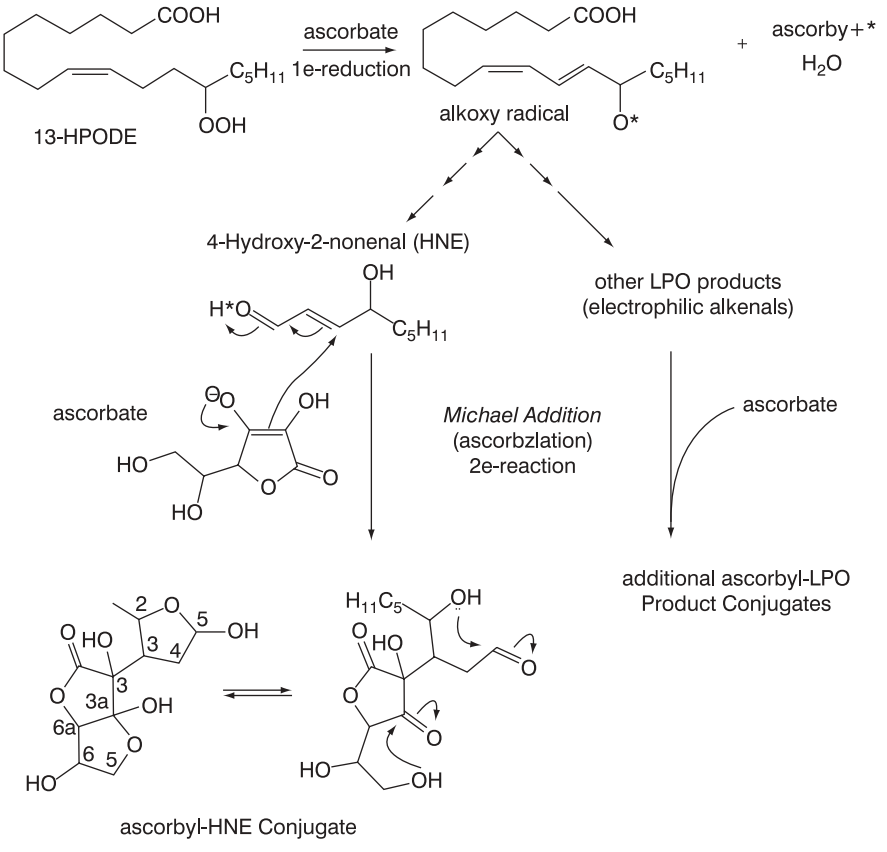
Figure 1. The equilibrium and redox species in the ascorbic acid-dehydroascorbic acid system. $AscH_2$ (ascorbic acid), $AscH^-$ (ascorbate monoanion), Asc^{2-} (ascorbate dianion), $AscH^{\cdot}$ (ascorbyl radical), $Asc^{\cdot-}$ (ascorbate radical), DHA (dehydroascorbate), DHAA(1) and DHAA(2) (dehydroascorbate hydrolyzed forms) (17).

zbog njene sličnosti s molekulom glukoze (14). GLUT1 je široko rasprostranjen u tkivima, a GLUT3 je ponajprije izražen u mozgu, posteljici, testisu i trombocitima. Askorbinska se kiselina, međutim, prenosi u stanicu i transporterima vitamina C, SVCT1 i SVCT2, ovisnima o natriju, od kojih se jedan ili oba nalaze u većini tkiva (15). Mutirani miševi s SVCT2 imaju izrazito smanjenu koncentraciju askorbinske kiseline u tkivu te umiru ubrzo nakon rođenja. Utjecaj manjka SVCT2 na tkivne kateholamine najizraženiji je u nadbubrežnoj žlijezdi gdje su i epinefrin i norepinefrin sniženi za 50% (16). Još uvijek je nejasno koji putovi, tj. da li SVCT1 i SVCT2 ili GLUT1 i GLUT3, prevladavaju *in vivo*.

Vitamin C ima različite oblike ovisno o pH-mediju i oksidacijskom stanju (Slika 1). U fiziološkim uvjetima 99,95% vitamina C je prisutno kao $AscH^-$, askorbatni monoanin ili samo "askorbat" (17).

cose (14). GLUT1 is widely tissue distributed, while GLUT3 is primarily expressed in brain, placenta, testis, and platelets. On the other hand, ascorbic acid is transported into the cell by sodium-dependent vitamin C transporters SVCT1 and SVCT2, one or both of which are found in most tissues (15). Mutant mice SVCT2 have severely reduced tissue levels of ascorbic acid and die soon after birth. The influence of the SVCT2 deficiency on tissue catecholamines is most prominent in the adrenals, where both epinephrine and norepinephrine are decreased over 50% (16). It still remains unclear which pathways, either SVCT1 and SVCT2 or GLUT1 and GLUT3, dominate *in vivo*.

Vitamin C has various forms, depending on pH media and its oxidation state (Figure 1). In physiological conditions, 99.95% of vitamin C is present as $AscH^-$, ascorbate monoanion or just "ascorbate" (17).

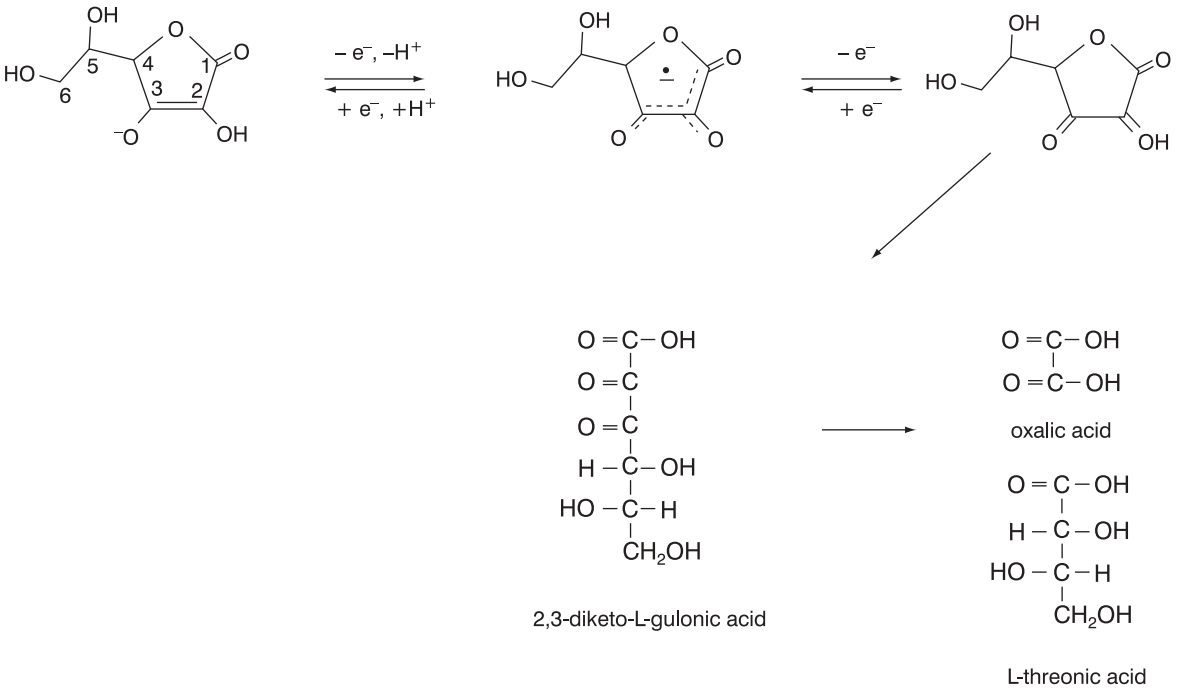


Slika 2. Vitamin C kao donor jednog elektrona te kao Michael-donor. Vitamin C može djelovati kao donor jednog elektrona HPODE i time potaknuti stvaranje alkoksi-radikala. Alkoksi-radikal je zatim podvrgnut raskidanju veze α,β-ugljik-ugljik, pri čemu se stvaraju HNE i ostali produkti LPO. Vitamin C može također funkcionirati kao *Michael*-donor i reagirati s HNE i drugim produktima LPO, stvarajući tako mnoštvo konjugata askorbila i produkata LPO (18).

Figure 2. Vitamin C as a one-electron donor and a Michael donor. Vitamin C may function as a one-electron donor to HPODE, thereby inducing formation of the alkoxy radical. The alkoxy radical then undergoes α,β-carbon-carbon bond cleavage, generating HNE as well as other LPO products. Vitamin C may also function as a Michael donor and react with HNE and other LPO products, giving a variety of ascorbyl-LPO product conjugates (18).

U međudjelovanju s reaktivnim radikalima ili lipidnim peroksidima askorbat otpušta jedan elektron, uz stvaranje znatno manje reaktivnoga askorbilnog radikala. Nedavno je dokazano da askorbat može posredovati u pretvorbi hidroperoksi-oktadekadienoičnih kiselina (HPODE) u genotoksičan 4-hidroksi-2-nonenal (HNE). Međutim, askorbat također stvara konjugat s HNE preko Michaelove reakcije, dvoelektronske reakcije u kojoj askorbinska kiselina ima ulogu nukleofila. Zbog toga vitamin C djeluje kao donor elektrona HPODE te uzrokuje stvaranje HNE, a zatim djeluje kao detoksikant prema HNE funkcionirajući kao Michaelova reakcija (Slika 2) (18).
S druge strane, askorbilni radikal je podvrgnut nerazmjernoj reakciji te obnavlja nešto askorbata i stvara DHA. DHA je nepostojana i na složen se način ubrzano razgrađuje uz konačni nastanak oksalne i L-treonske kiseline (Slika 3) (19).

Interacting with reactive radicals or lipid hydroperoxides, ascorbate releases one electron and a much less reactive ascorbyl radical is formed. Recently it has been shown that ascorbate can mediate the conversion of hydroperoxy octadecadienoic acids (HPODE) into genotoxic 4-hydroxy-2-nonenal (HNE). However, ascorbate also forms a conjugate with HNE by Michael addition, a two-electron reaction in which ascorbic acid plays the role of a nucleophile. Therefore, vitamin C acts as an electron donor to HPODE, causing HNE formation, and subsequently acts as a detoxifying agent against HNE by functioning as a Michael donor (Figure 2) (18).
On the other hand, ascorbyl radical undergoes a disproportional reaction, regenerating some ascorbate and producing DHA. DHA is unstable and degradates rapidly in a complex way, eventually producing oxalic and L-threonic acid (Figure 3) (19).



Slika 3. Razgradnja askorbata.

Figure 3. The degradation of ascorbate.

Vitamin C i slobodni radikali

Antioksidacijski mikronutrijenti, kao i antioksidacijski enzimi, su obrambeni sustavi u tijelu protiv slobodnih radikala i reaktivnih molekula. Nastanak visoko reaktivnih kisikovih metabolita jest karakteristika normalnoga staničnog metabolizma te je dio prirodnoga imunog sustava u tije-

Vitamin C and free radicals

Antioxidant micronutrients, as well as antioxidant enzymes, are the body's defense systems against free radicals and reactive molecules. The generation of highly reactive oxygen metabolites is a feature of normal cellular metabolism. It is a part of the body's natural immune

lu, mitohondrijskoga respiracijskog lanca, metabolizma arahidonske kiseline, ovulacije i fertilizacije. Iako se slobodni radikali neprekidno proizvode u ljudskome tijelu, njihovo se stvaranje može umnogostručiti u patološkim okolnostima (20). Halliwell je ukazao da bi terapija antioksidansima mogla imati zaštitne učinke ili pak pojačati oštećenje, ovisno o njenom mjestu u redoslijedu događaja (21). Uzimanje snažnog antioksidansa nakon što je oksidacijsko oštećenje već nastupilo moglo bi to oštećenje pojačati tako da što je antioksidans snažniji kao reducirajući agens, tim bi više problema mogao uzrokovati.

Zbog navedenoga nije iznenađujuća nedosljednost podataka koji se odnose na makromolekularnu oksidaciju i visok unos vitamina C. Oni ukazuju na zaštitnu ulogu u oksidaciji DNA (22,23), ali također na prooksidacijski kao i antioksidacijski učinak u zdravih pojedinaca (24). Drugi, pak, podatci ne ukazuju na učinak visokog unosa vitamina C bilo na oštećenje DNA ili zaštitu od toksičnosti uzrokovane vodikovim peroksidom (25), ili na djelotvornost u zaštiti od oštećenja kromosoma (26). S druge strane, manjak vitamina C i nekih drugih vitamina i minerala oštećuje DNA time što uzrokuje kidanje jednostrukih i dvostrukih lanaca te oksidacijske ozljede (27). Sposobnost vitamina C da ošteti DNA, lipide i proteine *in vitro* pripisuje se stvaranju reaktivnih metabolita kisika u prisutnosti tragova iona prijelaznih metala, kao što su radikal supeoksidnog aniona i vodikov peroksid (28):

$$AscH^- + O_2 \rightarrow AscH^{\cdot -} + O_2^{\cdot -}$$
$$AscH^- + O_2^{\cdot -} \rightarrow AscH^{\cdot -} + H_2O_2$$

ili čak hidroksilni radikal ($OH^\bullet$) (29):

$$Fe(III) + AscH^- \rightarrow Fe(II) + Asc^{\bullet -}$$
$$Fe(II) + H_2O_2 \rightarrow Fe(III) + OH^\bullet + OH^-$$

Hidroksilni radikal, koji je jedan od najsnažnijih poznatih slobodnih radikala, može pokrenuti peroksidaciju lipida, uzrokovati kidanje lanaca DNA i oksidirati gotovo bilo koju organsku molekulu (30,31). Liječenje štakora vitaminom C nakon kemijski potaknutog stvaranja $OH^\bullet$ suzbija nastanak tog radikala (32). U zdravih dobrovoljaca nadopune željeza i vitamina C pojačavaju oksidacijsko oštećenje DNA koje se kasnije normalizira moguće zbog prilagodbi u stanici kao što je porast koncentracija obnavljajućih enzima ili bolje pohranjivanje željeza u feritin (33). Međutim, vitamin C dalje ne pojačava oksidacijski stres potaknut visokim prehrambenim unosom željeza (34). Značajno je da se ioni željeza i bakra uglavnom odjeljuju u oblike koji ne mogu katalizirati stvaranje slobodnih radikala. Zbog toga je njihov oksidacijski učinak vrlo ograničen i, premda se još uvijek može dogoditi, vjerojatno je prikriven dominantnim antioksidacijskim učinkom vitamina C (20). U ljudskoj plazmi uzetoj *in vitro* vitamin C zaista djeluje u prisutnosti redoks-aktivnih željeza ili bakra i vodikovog peroksida kao antioksidans (35).

system, mitochondrial respiratory chain, arachidonic acid metabolism, ovulation and fertilization. Although free-radical species are continuously produced in the human body, their production can multiply during pathological circumstances (20). Halliwell suggested that the administration of antioxidants can have protective effects or worsen damage, depending on where one is in the sequence of events (21). Administration of a powerful antioxidant after oxidative damage has started could promote damage, and the more powerful the antioxidant is as a reducing agent, the more problems it might cause.

Therefore, it is not a surprise that data related to macromolecular oxidation and high vitamin C intake are inconsistent. They suggest a protective role in DNA oxidation (22,23), but also a pro-oxidant, as well as an antioxidant effect in healthy humans (24). Other data show no effect of high vitamin C intake on either DNA damage or protection against hydrogen peroxide-induced toxicity (25), or efficiency in protecting against chromosome damage (26). On the other hand, a deficiency of vitamin C and some other vitamins and minerals damage DNA by causing single- and double-strand breaks and oxidative lesions (27). Ability of vitamin C to damage DNA, lipids and proteins in vitro is attributed to the formation of reactive oxygen species in the presence of traces of transition metal ions, such as superoxide anion radical and hydrogen peroxide (28):

$$AscH^- + O_2 \rightarrow AscH^{\cdot -} + O_2^{\cdot -}$$
$$AscH^- + O_2^{\cdot -} \rightarrow AscH^{\cdot -} + H_2O_2$$

or even hydroxyl radical ($OH^\bullet$) (29):

$$Fe(III) + AscH^- \rightarrow Fe(II) + Asc^{\bullet -}$$
$$Fe(II) + H_2O_2 \rightarrow Fe(III) + OH^\bullet + OH^-$$

Hydroxyl radical, one of the most potent free radicals known, can initiate lipid peroxidation, cause DNA strand breaks and oxidize virtually any organic molecule (30,31). Treatment of rats with vitamin C, after chemically induced $OH^\bullet$ formation, suppresses the generation of the radical (32). In healthy volunteers, iron and vitamin C co-supplementation enhance oxidative DNA damage which is normalized afterwards, perhaps due to adaptations in the cell, such as increase in repair enzyme levels or better sequestration of iron into ferritin (33). However, vitamin C does not further increase the oxidative stress induced by high dietary iron (34). It is noteworthy that iron and copper ions are mainly sequestered in forms unable to catalyse free radical formation. Therefore, their oxidative effect is very limited. Although it still could happen, it is probably masked by the dominant antioxidative effect of vitamin C (20). Indeed, in human plasma taken *in vitro*, vitamin C acts in the presence of redox-active iron or copper and hydrogen peroxide as an antioxidant which pre-

roksida kao antioksidansa koji priječi peroksidaciju lipida i ne pospješuje oksidaciju proteina (35).

Pušenje i vitamin C

Za pušače je poznato da su izloženi mnogim oksidansima (36). Prosječne koncentracije vitamina C u plazmi pušača dvaput su niže nego u nepušača (37), zbog čega su potrebe za vitaminom C u pušača povećane. Prethodna terapija bilo s vitaminom C ili vitaminom E u potpunosti inhibira oštećenje DNA potaknuto ekstraktima iz dima cigarete (38). Nadalje, pušenje cigareta je povezano s endotelnom disfunkcijom uključujući oslabljenu, o endotelu ovisnu i protokom posredovanu dilataciju (39). Uobičajene kombinirane doze nadopune vitamina C i E poboljšavaju endotelnu funkciju u kroničnih pušača. Vitamin C također obnavlja brzinu koronarnog protoka oslabljenu zbog oksidacijskog stresa u pušača (40).

Vitamin C u sprječavanju i liječenju bolesti

Količine vitamina C koje pružaju sigurnu zaštitu od skorbuta još uvijek mogu biti preniske da bi osigurale učinkovitu zaštitu od drugih, najvjerojatnije antioksidacijskih reakcija u zaraženih osoba (41). RDA za vitamin C osigurava zdravstvene prednosti za ljude, dok više doze mogu imati i moguće terapijske učinke. Kliničke su studije pružile dokaze da cijeljenje rana u ispitanika bez manjka vitamina C može biti značajno ubrzano uz dnevne doze od 0,5 do 3 g (42). U kultiviranim ljudskim keratinocitima vitamin C djeluje kao modulator proliferacije i diferencijacije tako što izravno djeluje na keratinocit ili neizravno preko učinaka na fibroblaste (43). Vitamin C modulira rast i sazrijevanje hondrocita te ubrzava cijeljenje prijeloma kosti (44,45).
U literaturi se često spominje i sudjelovanje vitamina C u imunom obrambenom sustavu. Fagociti stvaraju slobodne radikale kao dio obrane tijela od infekcije, a odgovarajuće su količine neutralizirajućeg antioksidansa potrebne za sprječavanje oštećenja samih imunih stanica (46). Vitamin C potiče fagocitni odgovor mišjih peritonejskih makrofaga (47), kao i proliferacijski odgovor limfocita B i T te stvaranje interleukina-2 i interleukina-3 u svinja s nasljednim nedostatkom u sintezi vitamina C (48). Čini se da u ljudi kombinirana nadopuna vitamina C i E čak bolje jača imunološki sustav nego nadopuna svakog vitamina zasebno (49).
Smanjene razine vitamina C mogu se naći u različitim bolestima. Povezane su, primjerice, s šećernom bolesti (50), akutnim pankreatitisom (51), astmom (52) ili nestabilnim koronarnim sindromom (53). Studije koncentracija vitamina C u dozama koje uzimaju zdrave osobe pokazuju sigmoidan odnos između oralne doze i koncentracija vitamina C u plazmi i tkivu. Optimalno je doziranje stoga presudno za intervencijske studije u kojima se primjenjuje vitamin C (54).

vents lipid peroxidation and does not promote protein oxidation (35).

Cigarette smoking and vitamin C

Cigarette smokers are known to be exposed to a large number of oxidants (36). Mean levels of vitamin C in the plasma of smokers are twice lower when compared to nonsmokers (37), which increases the requirement for vitamin C in smokers. Pretreatment with either vitamin C or vitamin E completely inhibits the DNA damage induced by extracts from cigarette smoke (38). Furthermore, cigarette smoking is associated with endothelial dysfunction including impaired endothelium-dependent flow-mediated dilation (39). The combined usual dosage of vitamin C and E supplements improve the endothelial function in chronic smokers. Also, vitamin C restores impaired coronary flow velocity reserve against oxidative stress in smokers (40).

Vitamin C in disease prevention and therapy

The amounts of vitamin C which safely protect from scurvy may still be too low to provide an efficient rate for other, most likely antioxidant reactions in infected people (41). RDA for vitamin C has health benefit in humans, but higher doses may have the potential therapeutic effects. Clinical studies provide evidence that wound healing in subjects not deficient in vitamin C also can be significantly accelerated with daily dosages of 0.5 to 3 g (42). In cultured human keratinocytes vitamin C acts as a modulator of proliferation and differentiation, directly affecting the keratinocyte or indirectly through effects on fibroblasts (43). Vitamin C modulates the growth and maturation of chondrocytes, and accelerates bone fracture healing (44,45).
Vitamin C participation in immunological defense system has been frequently reported. Phagocytes produce free radicals as a part of the body's defense against infection, and adequate amounts of a neutralizing antioxidant are required to prevent damage to the immune cells themselves (46). Vitamin C stimulates the phagocytic response of murine peritoneal macrophages (47), as well as the proliferative response of B and T lymphocytes and interleukin-2 and interleukin-6 production in pigs with hereditary deficiency in vitamin C synthesis (48). In humans, combined supplementation with vitamins C and E seems to be even more immunopotentiating than supplementation with either vitamin alone (49).
Decreased blood levels of vitamin C can be found in various diseases. They are associated with, e.g., diabetes mellitus (50), acute pancreatitis (51), asthma (52) or an unstable coronary syndrome (53). Dose concentration studies of vitamin C in healthy people show a sigmoidal relationship between oral dose and plasma and tissue vitamin C concentrations. Therefore, optimal dosing is critical to intervention studies using vitamin C (54).

Prehlada

Uloga nadopune vitamina C u sprječavanju i liječenju prehlada ostaje prijeporna unatoč mnogim kontroliranim ispitivanjima. U studijama je ukazano da visoke doze vitamina C primijenjene ubrzo nakon nastupa prehlade nisu smanjile trajanje ili jačinu simptoma prehlade u zdravih odraslih osoba (55), no zato su uvelike umanjile simptome gripe i prehlade (56). Usporedna analiza 30 ispitivanja pokazala je skromnu korist skraćenog trajanja simptoma prehlade zahvaljujući visokom unosu vitamina C (57). Čini se da su preventivni učinci nadopune ograničeni uglavnom na ispitanike s niskim prehrambenim unosom vitamina C, no terapijski se učinci mogu pojaviti i u širim populacijskim skupinama (58). Profilaksa visokim dozama može biti osobito opravdana u osoba izloženih kratkim periodima težega tjelesnog vježbanja i/ili hladnoj okolini. Kada su tijekom ispitivanja ispitanici bili izloženi težim naporima, poput vojnih novaka, zabilježen je izraziti zaštitni učinak vitamina C na infekcije dišnog sustava (59). Nedavno je randomizirano, kontrolirano petogodišnje ispitivanje ukazalo na to da nadopuna vitamina C značajno smanjuje učestalost prehlade, no nema vidljivog učinka na trajanje ili jačinu prehlade (60).
Različiti uvjeti u studijama su najvjerojatnije objašnjenje zašto tako mnogo ispitivanja ima tako proturječne ishode. Simptomi prehlade variraju tijekom dana (61), podložnost prehladama također je povećana u pušača, dok je umjerena konzumacija alkohola povezana sa smanjenim rizikom u nepušača (62). S obzirom na odgovor na dozu, psihološki stres je također povezan s povećanim rizikom akutne zarazne respiracijske bolesti općenito (63). Čini se da je vitamin C od veće koristi za djecu nego odrasle u pogledu trajanja prehlade. Doza može također utjecati na veličinu te koristi tako da u prosjeku postoji veća korist od 2 g/dan nego 1 g/dan vitamina (64). Blagotvoran učinak vitamina C tijekom prehlade vjerojatno potječe od njegovih antioksidacijskih karakteristika. Kod infekcije se aktiviraju fagocitni leukociti i stvaraju oksidirajuće spojeve koji se oslobađaju iz stanica. Reakcijom s tim oksidantima vitamin C može umanjiti njihove upalne učinke (65).

Astma i opstrukcijska bolest pluća

Astma je ponajprije upalna bolest dišnih putova. Vitamin C ima ključnu ulogu u obrani pred napadajem oksidanata u dišnim putovima. Manjak tog vitamina u ispljuvku astmatičara može biti ili osnovni čimbenik u patofiziologiji astme ili odgovor na upalu astmatskih dišnih putova (65). U astmi izazvanoj vježbanjem, primjena nadopune vitamina C u dozi od 1 do 2 g/dan ima zaštitni učinak kod nekih bolesnika (66). Iako studije nadopune vitamina C ukazuju na kratkoročan zaštitni učinak na reaktivnost dišnih putova i funkciju pluća, zaštitni učinak vitamina C na razvoj kronične astme tek je potrebno ustanoviti.
Nekoliko je studija ukazalo na blagotvornu povezanost između unosa voća i povrća i plućne funkcije (67,68). Forsirani izdisajni volumen u 1 sekundi kod ispitanika s uno-

Common cold

The role of vitamin C supplement in the prevention and treatment of colds remains controversial despite many controlled trials. Studies have shown that high doses of vitamin C taken shortly after onset of a cold did not reduce the duration or severity of cold symptoms in healthy adults (55), but also highly decreased flu and cold symptoms (56). Comparative analysis of thirty trials has shown a modest benefit in reducing duration of cold symptoms from high vitamin C intake (57). The preventive effects of the supplementation seem to be limited mainly to subjects with low dietary vitamin C intake, but therapeutic effects may occur in wider population groups (58). High dose prophylaxis could be notably justified in persons exposed to brief periods of severe physical exercise and/or cold environments. When subjects were under heavy exertion during the trial, like military recruits, the vitamin C protective effect in respiratory infections was highly emphasized (59). Recently, a randomized, controlled 5-year trial suggested that vitamin C supplementation significantly reduces the frequency of the common cold but had no apparent effect on its duration or severity (60).
Most likely different study conditions provide explanation why so many trials give such contradictory outcomes. Cold symptoms vary diurnally (61), and susceptibility to colds is also increased in smokers, while moderate alcohol consumption is associated with decreased risk in nonsmokers (62). Psychological stress is also associated in a dose-response manner with an increased risk of acute infectious respiratory illness generally (63). It seems that vitamin C produces a greater benefit in cold duration for children than for adults. The dose may also affect the magnitude of the benefit, and there is on average greater benefit from 2 g/day compared to 1 g/day of the vitamin (64). The beneficial effect of vitamin C during a cold probably stems from its antioxidant properties. In an infection, phagocytic leukocytes become activated producing oxidizing compounds that are released from the cells. By reacting with these oxidants, vitamin C may decrease the inflammatory effects that they produce (65).

Asthma and obstructive pulmonary disease

Asthma is primarily an inflammatory disease of the airways. Vitamin C plays an essential role in defending against oxidant attack in the airways. Its deficiency in the sputum of asthmatics may be either an underlying factor in the pathophysiology of asthma or a response to asthmatic airway inflammation (65). In exercise-induced asthma, the use of vitamin C supplementation at a dosage of 1 to 2 g per day has a protective effect in some patients (66). Although studies of vitamin C supplementation suggest a short-term protective effect on airway responsiveness and pulmonary function, a protective effect of vitamin C on the development of chronic asthma remains to be established.

som voća jednom tjedno ili više bio je oko 80-100 mL viši nego u ispitanika s unosom voća manjim od jednom tjedno. Povećanje unosa vitamina C od 100 mg dnevno također je povezano s približnim povećanjem od 10-50 mL forsiranog izdisajnog volumena u 1 sekundi (69).

Kardiovaskularna bolest

Prehrambeni unos od 100 mg/dan vitamina C povezan je sa smanjenom pojavnošću ili smrtnošću od srčanih bolesti, moždanog udara ili karcinoma (7). U starijih se osoba čini da je vitamin C povezan s kasnijim rizikom smrti od moždanog udara, ali ne i od koronarne bolesti (70). Moždani udar, koronarna bolest te bolest perifernog krvožilja imaju mnogo zajedničkih čimbenika rizika, no neki su od njih važniji za pojedino kardiovaskularno oboljenje od drugih. Visoka koncentracija fibrinogena u plazmi također može biti važna u svim tim stanjima (71). Povišene koncentracije fibrinogena biološki su uvjerljiv mehanizam kojim bi akutna ili kronična infekcija mogla povećati kardiovaskularni rizik. Vitamin C u dozi od 2 g/dan povećava fibrinolitičku aktivnost i smanjuje adhezijski indeks trombocita i kolesterol u serumu (72). Čest unos voća i povrća koji su bogati vitaminom C također povećava aktivnost fibrinolitičkog sustava sniženjem aktivnosti inhibitora aktivatora plazminogena (73). Varijacije vezane za godišnja doba kako u dišnim infekcijama tako i kardiovaskularnoj bolesti pripisuju se sniženom vitaminu C te porastu koncentracija fibrinogena u serumu tijekom zime (74).

Ukupan kolesterol, LDL kolesterol i HDL kolesterol su među glavnim čimbenicima rizika za kardiovaskularnu bolest (75). Nekoliko je studija izvijestilo o negativnoj korelaciji između vitamina C u serumu i ukupnog kolesterola (76,77), te pozitivnoj korelaciji između serumskog vitamina C i HDL (78), barem među ženama (79), iako ne sve studije (80). Čini se da je vitamin C uključen u metabolizam kolesterola na nekoliko načina: smanjuje aktivnost 3-hidroksi-3-metilglutaril-koenzima A reduktaze i sinteze kolesterola (81,82). Vitamin C također aktivira kolesterol-7α-hidroksilazu u štakora te katabolizam kolesterola u žučne kiseline (83).

Unos antioksidacijskih tvari prehranom može zaštititi od koronarne bolesti jer se za oksidaciju lipoproteina pretpostavlja da pospješuje aterosklerozu (84,85). Pretpostavka je da oksidirani LDL ima aterogeni potencijal zbog peroksidacije lipida (86). Askorbat potpuno štiti lipide u plazmi od mjerljivoga peroksidacijskog oštećenja izazvanog vodenim peroksilnim radikalima i on je, zapravo, jedini antioksidans u plazmi koji to može učiniti (87). Vitamin C štiti od oksidacije LDL posredovane neutrofilima najvjerojatnije zbog čišćenja izvanstaničnih oksidansa. On također priječi prooksidantske učinke urata kod oksidacije LDL-a (88). Nadalje, vitamin C bi mogao pomoći u sprječavanju ateroskleroze jačanjem stijenki arterija jer sudjeluje u sintezi kolagena, kao i sprječavanjem neželjene adhezije leukocita na oštećene arterije (89).

Several studies showed a beneficial association between fruit and vegetable intake and lung function (67,68). The forced expiratory volume in 1 second in subjects with the intake of fruits once per week or more was about 80–100 mL higher than in subjects with the intake less than once per week. A 100 mg increase in vitamin C intake per day is also associated with an approximately 10–50 mL increase in forced expiratory volume in 1 second (69).

Cardiovascular disease

Dietary intake of 100 mg/day of vitamin C is associated with reduced incidence of, or mortality from heart diseases, stroke and cancer (7). In elderly people, vitamin C seems to be related to subsequent risk of death from stroke, but not from coronary heart disease (70). Stroke, coronary heart disease, and peripheral vascular disease have many risk factors in common, yet some factors are more important for one cardiovascular disease than another. A high plasma fibrinogen concentration may be equally important in all these conditions (71). Increased concentrations of fibrinogen provide a biologically persuasive mechanism by which acute or chronic infection could increase cardiovascular risk. Vitamin C in 2 g/day dose increases fibrinolytic activity and decreases the platelet adhesive index and serum cholesterol (72). Frequent intake of fruit and vegetables, food rich in vitamin C, also increases activity of the fibrinolytic system by lowering plasminogen activator inhibitor activity (73). Seasonal variations in both respiratory infection and cardiovascular disease are attributed to decrease in vitamin C and increase in fibrinogen serum levels during the winter (74).

Total cholesterol, low-density-lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL) are among the major risk factors for cardiovascular disease (75). Several studies reported negative correlation between serum vitamin C and total cholesterol (76,77), and positive correlations between serum vitamin C and HDL (78), at least among women (79), but not all studies (80). It seems that vitamin C is involved in cholesterol metabolism in several ways. It reduces 3-hydroxy-3-methylglutaryl coenzyme A reductase activity and cholesterol synthesis (81,82). It also activates cholesterol-7α-hydroxylase in rats, and the catabolism of cholesterol to bile acids (83).

Intake of antioxidant nutrients may protect against coronary heart disease, because oxidation of lipoproteins is hypothesized to promote atherosclerosis (84,85). It is presumed that oxidized LDL has an atherogenic potential due to lipid peroxidation (86). Ascorbate completely protects plasma lipids against detectable peroxidative damage induced by aqueous peroxyl radicals and it is the only plasma antioxidant that can do so (87). Vitamin C protects against neutrophil-mediated LDL oxidation, most likely due to the scavenging of extracellular oxidants. It also prevents pro-oxidant effects of urate in LDL oxidation (88). Further, vitamin C could help prevent atherosclerosis by

Kao snažan antioksidans, vitamin C ispravlja endotelnu disfunkciju nastalu zbog pojačanog oksidacijskog stresa time što priječi hiperoksičnu vazokonstrikciju (90). On također poboljšava lipidima izazvano oštećenje vazodilatacije ovisne o endotelu (91). Eksperimentalne studije esencijalne hipertenzije ukazuju na to da pojačano stvaranje reaktivnih metabolita kisika može imati ulogu u etiologiji tog poremećaja (92). One također pokazuju da su povišene koncentracije vitamina C u serumu dosljedno i značajno povezane s nižim sistoličkim i dijastoličkim krvnim tlakom u sredovječnim i starijim populacijama (93,94). Ukazano je da je 500 mg vitamina C dnevno korisno za nadzor krvnog tlaka u bolesnika s hipertenzijom (95). Međutim, u dvostruko slijepoj, randomiziranoj križnoj studiji uz kontrolu placebom krvni tlak nije bio snižen nakon nadopune 500 mg vitamina C dnevno tijekom 3 mjeseca, premda su dnevne razine ambulantnoga sistoličkoga krvnog tlaka bile neznatno snižene (96).
Ne postoje konačni dokazi o zaštitnom učinku nadopune vitamina C na kardiovaskularni rizik, premda podatci ukazuju na njegov blagotvoran učinak. S druge strane, prehrana bogata voćem i povrćem ima visok zaštitni utjecaj na aterosklerozu i koronarnu bolest (97,98).

Neurodegenerativni poremećaji

Oksidacijski stres može imati izraženu ulogu u neurodegenerativnim bolestima. Alzheimerova bolest je najčešći uzrok demencije povezane sa starenjem. Čini se da nadopuna antioksidanasa može odgoditi razvoj Alzheimerove bolesti. Kombinacija nadopuna vitamina E i vitamina C povezana je sa sniženom prevalencijom i pojavnošću Alzheimerove bolesti (99). Vitamin C i melatonin imaju blagotvoran utjecaj na koncentracije lipidnih peroksida i aktivnost antioksidacijskih enzima u modelu Alzheimerove bolesti, ukazujući time na njihovu moguću uporabu u liječenju neurodegenerativnih bolesti (100). Vitamin C također pruža zaštitu od oštećenja pamćenja izazvanog skopolaminom i dijazepamom u miševa. Osnovni mehanizam toga za pamćenje obnavljajućeg djelovanja mogao bi se također pripisati antioksidacijskom svojstvu tog vitamina C (101).

Karcinom

Antioksidacijske i općenite imunostimulacijske karakteristike vitamina C mogle bi biti korisne za oboljele od karcinoma, uključujući i regresiju tumora te inhibiciju tumorskog rasta. Epidemiološke studije pokazuju da vitamin C ima zaštitni učinak osobito kod zloćudnih tumora koji ne ovise o hormonima (102). Eksperimentalne studije *in vivo* i *in vitro* dale su, međutim, proturječne rezultate ukazujući na to da su učinci vitamina C ovisni o dozi, a možda i vremenu, uz različite učinke ovisno o vrsti i proučavanom organu ili vrsti karcinogene stanice (103).
Sedamdesetih godina 20. stoljeća Pauling i Cameron primijenili su vitamin C u gramskim količinama u liječenju

strengthening the artery walls through its participation in the synthesis of collagen, and by preventing the undesirable adhesion of white blood cells to damaged arteries (89).
As a powerful antioxidant, vitamin C reverses endothelial dysfunction due to increased oxidative stress, preventing hyperoxic vasoconstriction (90). It also improves lipid-induced impairment of endothelium-dependent vasodilation (91). Experimental studies of essential hypertension suggest that increased production of reactive oxygen species may play a role in the etiology (92). They also show that higher serum levels of vitamin C are consistently and significantly related to lower systolic and diastolic blood pressure among middle-aged or elderly populations (93,94). It has been suggested that 500 mg of vitamin C daily is useful for blood pressure control in patients with hypertension (95). However, in a double-blind, randomized, placebo-controlled crossover study clinic blood pressure was not reduced after supplementation with 500 mg vitamin C per day for 3 months, although daytime levels of ambulatory systolic blood pressure were slightly reduced (96).
No conclusive evidence is available on the protective effect of vitamin C supplementation on cardiovascular risk, although they implicate a beneficial effect. On the other hand, a diet rich in fruits and vegetables is highly protective against atherosclerosis and coronary heart disease (97,98).

Neurodegenerative disorders

Oxidative stress may play a pronounced role in neurodegenerative diseases. Alzheimer's disease is the most common cause of dementia associated with aging. It seems that supplementation with antioxidants may delay the development of Alzheimer's disease. Combination of vitamin E and vitamin C supplements is associated with reduced prevalence and incidence of Alzheimer's disease (99). Vitamin C and melatonin have beneficial effect on lipid peroxide levels and the activity of antioxidant enzymes in a model of Alzheimer's disease, suggesting their possible use in the treatment of neurodegenerative diseases (100). Vitamin C also provides protection against scopolamine- and diazepam-induced impairment of memory in mice. The underlying mechanism of memory-restorative action could also be attributed to its antioxidant property (101).

Cancer

Antioxidant and general immunostimulant properties of vitamin C could be beneficial to cancer patients, including tumor regression, and the inhibition of tumor growth. Epidemiological studies show that vitamin C has a protective effect against, in particular, non-hormone-dependent malignancies (102). Experimental *in vivo* and *in vitro* studies, however, yielded more controversial results, suggesting that the effects of vitamin C are dose- and perhaps time-dependent with different effects, depending on the species and organ studied or cancer cell type (103).

bolesnika u uznapredovaloj fazi karcinoma. Njihovi su rezultati pokazali poboljšanje općeg stanja ispitanika. Većina se bolesnika subjektivno osjećala mnogo bolje, sa smanjenim napadajima bolova te uz produljeno trajanje životnog vijeka (4). Premda je pokusno ispitivanje provedeno u Japanu dalo slične rezultate (104), znanstveni rad iz ugledne Klinike Mayo nije ukazao na nikakav učinak vitamina C u liječenju karcinoma (105). Tijekom kasnijih su godina, međutim, istraživači otkrili moguću ulogu vitamina C u sprječavanju karcinoma. Konzumacija namirnica bogatih vitaminom C povezana je ne samo sa smanjenim rizikom kardiovaskularne bolesti već i s mnogim vrstama karcinoma, a moguće i neurodegenerativnih bolesti. Ipak, opseg u kojem vitamin C doprinosi tim učincima još uvijek nije jasan (106). Vjerojatnije je da je smanjenje rizika za karcinom postignuto izmjenama u prehrani nego nadopunom vitamina (107). Prehrana koja uključuje 200 mg ili više vitamina C dnevno kroz 5 obroka voća i povrća povezana je s nižim rizikom za karcinom, osobito karcinom usne šupljine, jednjaka, želuca, debelog crijeva i pluća. Iako nekoliko različitih čimbenika u voću i povrću vjerojatno djeluje zajedno, epidemiološki i biokemijski podatci upućuju na važnu ulogu vitamina C (108).

Nadopuna antioksidanasa povezana je sa smanjenim postotkom stanica s kromosomskim aberacijama te s blagotvornim utjecajem u pušača (109). Čini se da je u visokim koncentracijama vitamin C toksičan za karcinogene stanice *in vitro* (110,111). Takve se koncentracije mogu postići u plazmi jedino intravenskom terapijom; stoga bi negativni rezultati zaštite od karcinoma mogli potjecati od primjene oralnog, a ne intravenskog vitamina C (11). Vršna koncentracija u plazmi od 1 000 µmol/L može se postići nakon intravenskog davanja 1,25 g vitamina C, dok se oralnim dozama ne može prijeći 100 µmol/L zbog ograničavajućeg mehanizma apsorpcije (112). Ovisno o dozi i brzini infuzije, najnoviji podatci pokazuju da intravenski postignute vršne koncentracije u plazmi mogu doseći 14 000 µmol/L, dok koncentracije iznad 2 000 µmol/L mogu biti prisutne nekoliko sati (113). U koncentracijama koje se mogu postići isključivo intravenskom primjenom vitamin C može djelovati kao pro-lijek za stvaranje vodikovog peroksida i time uzrokovati smrt nekoliko ispitivanih vrsta karcinogenih stanica, no ne i normalnih stanica (114). Za prehranu s visokim udjelom voća i povrća, a time i vitamina C, utvrđeno je da je povezana s nižim rizikom karcinoma usne šupljine, jednjaka, želuca, debelog crijeva i pluća (115). Stvaranje nitrozamina, koje je povezano s karcinomom želuca, može se smanjiti primjenom vitamina C (116). Vitamin C također izaziva apoptozu različitih vrsta karcinogenih stanica djelujući kao prooksidans te povećavajući razine unutarstaničnih reaktivnih radikala kisika (117,118). S druge strane, u nižim koncentracijama vitamin C očituje svojstvo antioksidansa sprječavajući spontanu apoptozu ili apoptozu izazvanu stresom ili antitumorskim

In the 1970s, Pauling and Cameron used vitamin C in gram quantities in the treatment of patients with advanced stage of cancer. Their results showed improvement of general condition of tested subjects. Most of the patients subjectively felt much better, with reduced pain seizures, and prolonged lifetime (4). Although an experiment performed in Japan yielded similar results (104), a report from the eminent Mayo Clinic showed no effect of vitamin C in cancer treatment (105). However, in the following years researchers revealed a possible role of vitamin C in the cancer prevention. Consumption of foods rich in vitamin C is associated not only with decreased risk of cardiovascular disease, but also of many types of cancer and possibly neurodegenerative diseases. However, the extent to which vitamin C contributes to these effects is still uncertain (106). Reduction in cancer risk is more likely to be achieved through dietary modification, rather than through vitamin supplementation (107). Diets with 200 mg or more of vitamin C per day, obtained from five servings of fruits and vegetables, are associated with lower cancer risk, especially for cancers of the oral cavity, esophagus, stomach, colon and lung. Although several different factors in fruits and vegetables probably act jointly, the epidemiological and biochemical evidence indicates an important role for vitamin C (108).

Supplementation with antioxidants is associated with a decrease in the percentage of cells with chromosome aberrations, and with beneficial effect in smokers (109). Vitamin C at high concentrations seems to be toxic to cancer cells *in vitro* (110,111). These concentrations can be achieved in plasma only by intravenous administration. Therefore, negative cancer protective results might originate from the use of oral rather than intravenous vitamin C (11). Following the administration of 1.25 g intravenously, a peak plasma level of 1,000 µmol/L could be reached, although 100 µmol/L could not be exceeded by oral dosing due to limiting absorptive mechanism (112). Most recent data show that, depending on the dose and infusion rate, peak plasma concentrations obtained intravenously can reach 14,000 µmol/L, and concentrations above 2,000 µmol/L may persist for several hours (113). Vitamin C, in concentrations which can be achieved only by intravenous administration, may act as a pro-drug for the formation of hydrogen peroxide, causing death of several studied cancer cell types but no normal cells (114). Diets high in fruit and vegetables, and hence high in vitamin C, have been found to be associated with lower risk for cancers of the oral cavity, esophagus, stomach, colon, and lung (115). Formation of nitrosamines, which is associated with gastric cancer, can be decreased by administration of vitamin C (116). Vitamin C also induces the apoptosis of various cancer cell types by acting as a pro-oxidant and increasing intracellular reactive oxygen species levels (117,118). On the other hand, at lower concentrations

agensom (116). Nadalje, vitamin C može izazvati prolazni zastoj staničnog ciklusa. Vitamin C inhibira sintezu DNA u stanicama HeLa (adenokarcinoma ljudskog cerviksa), odgađajući ulazak p53-deficijentnih sinkroniziranih HeLa i karcinogenih stanica T98G (multiformnih stanica ljudskog glioblastoma) u mitozu (119). Esteri askorbinske kiseline privukli su znatan interes kao antikarcinogeni spojevi zbog njihove lipofilne naravi koja im omogućuje prijelaz kroz stanične membrane i krvno-moždanu branu. Askorbilni stearat inhibira proliferaciju stanica interferirajući sa staničnim ciklusom te izaziva apoptozu modulacijom izražaja receptora inzulinu sličnog čimbenika rasta u T98G te stanica karcinoma gušterače (120,121).

Trenutni dokazi upućuju na to da sam vitamin C ne mora biti dovoljno učinkovit u liječenju najaktivnijih karcinoma. Vitamin C, međutim, poboljšava kvalitetu života i produljuje životni vijek oboljelih od karcinoma, što predstavlja dovoljne razloge da ga se uzme u obzir kao nadopunu u terapiji karcinoma (122).

Šećerna bolest

Šećerna bolest je još jedna bolest koja je povezana s povećanim stvaranjem reaktivnih radikala kisika te smanjenom obranom od antioksidanasa. Te pojave dovode do oksidacijskog stresa koji je djelomice odgovoran za komplikacije u šećernoj bolesti (123). Status vitamina C ovisi o međudjelovanju unosa prehranom, koncentracijama inzulina u plazmi, te glikemiji. Inzulin promiče aktivni stanični unos vitamina C, dok hiperglikemija inhibira bubrežnu reapsorpciju vitamina C. Oksidacijski stres je uobičajeni patogenetski čimbenik dijabetičke nefropatije. Kako se DHA i glukoza natječu za transportere glukoze, hiperglikemija rezultira otpuštanjem vitamina C iz tubularnih epitelnih stanica i sniženim antioksidacijskim kapacitetom (124). Hiperglikemija i oksidacijski stres su odgovorni za endotelnu disfunkciju u dijabetičkih bolesnika. Intraarterijska infuzija vitamina C poboljšava vazodilataciju ovisnu o endotelu u bolesnika bilo s tipom 1 ili tipom 2 šećerne bolesti (125,126). S druge strane, visoka oralna doza vitamina C ne može iznova nadopuniti razine vitamina C i poboljšati endotelnu disfunkciju (127). Niske unutarstanične koncentracije vitamina C u osoba s hiperglikemijom i s niskim razinama vitamina C u plazmi mogu biti odgovorne za povišene razine oštećenja DNA u takvih bolesnika. Stoga bi nedovoljno kontrolirani dijabetički ispitanici mogli imati koristi od povećanog unosa vitamina C kroz prehranu (128).

Katarakta

Vitamin C koji je nađen u visokim koncentracijama u leći oka može biti značajan za sprječavanje sive mrene (katarakte) u starijoj populaciji (129). Premda se oksidacijsko oštećenje u leći može spriječiti vitaminom C, ukazano je ujedno i na prooksidacijski učinak tog vitamina kroz stva-

vitamin C displays antioxidant property, preventing spontaneous and stress- or antitumor agent-induced apoptosis (116). Furthermore, vitamin C can induce transient cell cycle arrest. Vitamin C inhibits DNA synthesis in HeLa (human cervix adenocarcinoma) cells, delaying the entry of p53-deficient synchronized HeLa and T98G (human glioblastoma multiform) cancer cells into mitosis (119). Fatty acid esters of ascorbic acid have attracted considerable interest as anticancer compounds due to their lipophilic nature which enables their crossing through cell membranes and blood-brain barrier. Ascorbyl stearate inhibits cell proliferation by interfering with cell cycle and induces apoptosis by modulation of insulin-like growth factor 1-receptor expression in T98G and pancreatic cancer cells (120,121).

Current evidence suggests that vitamin C alone may not be effective enough in the treatment of most active cancers. However, vitamin C improves the quality of life and extends longevity in cancer patients, which are the reasons why it should be considered as a supplement in cancer therapy (122).

Diabetes mellitus

Diabetes mellitus is another disease associated with an increased production of reactive oxygen species and a reduction in antioxidant defenses. This leads to oxidative stress, which is partially responsible for diabetic complications (123). Vitamin C status depends on the interactions of dietary intake, plasma insulin concentrations and glycemia. Insulin promotes the active cellular uptake of vitamin C, whereas hyperglycemia inhibits renal vitamin C reabsorption. Oxidative stress is a common pathogenetic factor of diabetic nephropathy. Since DHA and glucose compete for glucose transporters, hyperglycemia discharges vitamin C from tubular epithelial cells, resulting in decreased antioxidant capacity (124). Hyperglycemia and oxidative stress are responsible for endothelial dysfunction in diabetic patients. Intraarterial infusion of vitamin C improves endothelium-dependent vasodilation in patients with either type 1 or type 2 diabetes (125,126). On the other hand, oral high dose of vitamin C could not replenish vitamin C levels and improve endothelial dysfunction (127). Low intracellular levels of vitamin C in individuals with both hyperglycemia and low plasma levels of vitamin C may be responsible for the increased levels of DNA damage in such patients. Thus, poorly controlled diabetic subjects might benefit from increased dietary vitamin C (128).

Cataract

Vitamin C, found in high concentrations in the lens, may be of importance for the prevention of cataract in older population (129). Although oxidative damage in the lens can be prevented by vitamin C, a pro-oxidant effect of vitamin C through hydrogen peroxide generation has also been suggested. On the other hand, vitamin C could play

ranje vodikovog peroksida. S druge strane, vitamin C bi mogao imati ulogu u glikaciji proteina koja je zapažena u stvaranju katarakte (130,131). Ozračenje *in vitro* starih ljudskih leća s UVA u prisutnosti vitamina C uzrokuje znatno razaranje kromofora u vidljivom i UV području, što je moguće povezati s glikacijskim produktima proteina u fibroznim stanicama leća (132). Premda većina epidemioloških podataka ukazuje na činjenicu da je razborito konzumirati hranu s visokim udjelom vitamina C, vitamina E te karotenoida kao osiguranja protiv razvoja katarakte (133), za sada još nije moguće zaključiti da antioksidansi iz prehrane imaju ulogu u sprječavanju te bolesti.

Nepovoljni učinci te upozorenja

Nadopune vitamina C općenito se dobro podnose. Visoke doze, međutim, mogu uzrokovati nadraženost želuca, mučninu, povraćanje, pospanost, glavobolje ili osip. Nepovoljne se reakcije rijetko, ako ikada, zapažaju ako se nadopuna uzima prema utvrđenim smjernicama. Treba naglasiti da vrijednosti UL, čija je svrha zaštita najosjetljivijih pojedinaca u općoj populaciji, nisu namijenjene za najosjetljivije osobe u osjetljivim subpopulacijama (134). Općenito je potreban oprez kod visokog unosa nadopune, kao i vitamina C, kod takvih osoba. Tako, primjerice, jednostruka doza vitamina C od 6 g izaziva hemolizu u bolesnika s nedostatkom glukoza-6-fosfat-dehidrogenaze.

Vitamin C je prepoznat kao pojačivač crijevne apsorpcije anorganskog željeza iz hrane time što ga reducira ili priječi njegovu kelaciju fitatima ili drugim ligandima iz hrane (136). Nije, međutim, vjerojatno da vitamin C izaziva pretjeranu apsorpciju željeza u zdravih osoba (137). Premda postoji određena zabrinutost da osobe koje boluju od hemokromatoze (sklonost preopterećenju željezom) mogu biti osjetljive na visoke doze vitamina C, čini se da je vitamin C potpuno siguran čak i u dnevnim količinama od 10 g ili više (138,139).

Prijeporan je doprinos askorbata stvaranju oksalata kod bubrežnih kamenaca. Kako je oksalat katabolički produkt vitamina C, određena se zabrinutost pojavila u vezi s izlučivanjem oksalata. S obzirom da su gastrointestinalna apsorpcija kao i bubrežna tubularna reapsorpcija vitamina C procesi koji su karakterizirani zasićenjem, a metabolička pretvorba u oksalat je također ograničena, vitamin C ne bi trebao povećati rizik kalcijevog oksalata u bubrežnim kamencima (140). Stoga u zdravih osoba nije utvrđena povezanost između visokog unosa vitamina C i povišenog izlučivanja oksalata mokraćom (141) ili rizika za stvaranje kamenca (142). Neki su, međutim, nalazi ukazali da količina manja od 1 g dnevno predstavlja siguran unos vitamina C (8). U nekih osoba metabolička konverzija askorbata u oksalat može prouzročiti relativnu hiperoksaluriju, kao i kristaluriju koja se očituje kao hematurija (143). Pojačano izlučivanje oksalata mokraćom nakon intravenske primjene vitamina C u osjetljivih pojedinaca stvara predispozicija

a role in protein glycation, which is observed in cataract formation (130,131). *In vitro* irradiation of aged human lenses with UVA in the presence of vitamin C causes extensive destruction of their chromophores in the UV and visible region, which could be related to glycation products of proteins in lens fiber cells (132). Although most epidemiological evidence suggests that it is prudent to consume diets high in vitamin C, vitamin E and carotenoids as insurance against the development of cataract (133), it is not yet possible to conclude that antioxidant nutrients have a role in prevention of cataract.

Adverse effects and cautions

Vitamin C supplements are generally well tolerated. However, high doses may cause stomach irritation, nausea, vomiting, drowsiness, headaches or rash[2]. Adverse reactions are rarely, if ever, seen when the nutrient is consumed according to established guidelines. It should be emphasized that UL values, which are designed to protect the most sensitive individuals in the general population, are not intended to apply to the most sensitive persons in sensitive subpopulations (134). There should be a caution with a high supplement intake generally, as well as vitamin C, in these individuals. Thus, single 6 g dose of vitamin C induces hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency (135).

Vitamin C has been recognized as the enhancer of the intestinal absorption of dietary inorganic iron, either by reducing it or preventing its chelation by phytates or other food ligands (136). However, it seems unlikely that vitamin C induces iron overabsorption in healthy people (137). Although there has been some concern that people suffering from hemochromatosis (a tendency to iron overload) may be sensitive to high dosages of vitamin C, it seems that vitamin C is entirely safe, even in daily quantities of 10 g or more (138,139).

The contribution of ascorbate to oxalate kidney stone formation is controversial. Since oxalate is a vitamin C catabolitic product, certain concern has been raised for oxalate excretion. Since gastrointestinal absorption as well as renal tubular reabsorption of vitamin C are saturable processes and the metabolic transformation to oxalate is limited as well, vitamin C should not increase the risk of calcium oxalate kidney stones (140). Thus, an association between high vitamin C intake and increased urinary oxalate excretion (141) or the risk of stone formation (142) has not been found in healthy adults. However, some findings suggested safe vitamin C intake to be less than 1 g daily (8). In some individuals, metabolic conversion of ascorbate to oxalate can cause relative hyperoxaluria and crystalluria, the latter manifesting as hematuria (143). Increased urinary oxalate excretion by intravenous vitamin C administration predisposes susceptible individuals to nephrolithiasis (144). The ingestion of high vitamin C

ju za nefrolitijazu (144). Ingestija visokih doza vitamina C trebala bi biti kontraindicirana u slučajevima bubrežne insuficijencije, hemodijaliziranih bolesnika, te osoba s oksalatnim kamencima (145).
Podatci o učinku vitamina C na izlučivanje urata također su proturječni. U nekoliko je studija utvrđeno povišeno izlučivanje urata nakon duljega visokog unosa vitamina C prehranom (5,146), no ne u svima (147,148). Mogući uzroci proturječnih rezultata su nedostatak postojanog stanja vitamina C, razlike u plazmatskim koncentracijama, ili trajanje primjene vitamina C. Međutim, u svim je studijama hiperurikozurija bila odsutna kod doza vitamina C nižih od 1 g/dan.
Visok unos vitamina C prehranom također može utjecati na određene laboratorijske dijagnostičke pretrage tako što stvara lažno pozitivne rezultate pretraga glukoze u mokraći, razina proteina u cerebrospinalnoj tekućini i mokraći, kao i lažno negativnih rezultata u pretragama bilirubina u mokraći. Vitamin C također smanjuje vrijednosti bilirubina, kolesterola, kreatinina i triglicerida u serumu (145).
Neki su, pak, štetni učinci pogrešno pripisani vitaminu C, uključujući hipoglikemiju, ponovljeni skorbut, neplodnost, mutagenezu, te razaranje vitamina B_{12} (8).

Interakcije s lijekovima

Čini se da su interakcije između lijekova i visokih doza vitamina C vrlo rijetke. U nekoliko se proturječnih studija navodi učinak vitamina C na sniženi antikoagulacijski odgovor na varfarin ili dikumarol (149). Visoke doze vitamina C također mogu sniziti stabilne koncentracije u plazmi indinavira koji je inhibitor proteaze indiciran za liječenje virusa ljudske imunodeficijencije tipa 1 (150). S druge strane, vitamin C može poboljšati apsorpciju levodope u starijih bolesnika s Parkinsonovom bolešću i slabom bioraspoloživošću levodope (151). Visok unos vitamina C također može interferirati s drugim lijekovima, što je tek potrebno utvrditi. Osim toga, dijareja koju uzrokuju visoke oralne doze vitamina C općenito može smanjiti crijevnu apsorpciju.

Zaključci

Vitamin C daje pozitivne rezultate kod liječenja mnogih zdravstvenih stanja, a djeluje ponajprije kao antioksidans (Tablica 1). Na temelju novijih dokaza opravdano je promicati prehranu bogatu vitaminom C radi sprječavanja kardiovaskularne bolesti i karcinoma. Nadopune vitamina C su blagotvorne u cijeljenju rana te smanjuju pojavnost prehlade ponajprije u osoba izloženih težem fizičkom stresu. Također je učinkovit u sprječavanju peroksidacije lipida u plazmi te snižavanju vrijednosti fibrinogena i kolesterola u serumu kao rizičnih čimbenika za kardiovaskularnu bolest. Međutim, neki se povoljni učinci mogu postidoses should be contraindicated in cases of renal insufficiency, hemodialysed patients, and oxalate stoneformers (145).
Data concerning the effect of vitamin C on urate excretion are also contradictory. Several studies have found elevated urate excretion after prolonged high dietary vitamin C intake (5,146), but not all (147,148). The conflicting findings may be due to lack of steady-state for vitamin C, differences in plasma concentrations, or duration of vitamin C administration. However, in all reports hyperuricosuria was absent at vitamin C doses less than 1 g/day.
High dietary vitamin C intake can also affect certain laboratory diagnostic tests, producing false positive readings in urine glucose tests, protein levels in cerebrospinal fluid and urine, as well as false negative readings in urine bilirubin tests. It also decreases serum bilirubin, cholesterol, creatinine, and triglyceride values (145).
Some harmful effects have been mistakenly attributed to vitamin C, including hypoglycemia, rebound scurvy, infertility, mutagenesis, and destruction of vitamin B_{12} (8).

Interaction with drugs

Drug interactions with vitamin C high doses seem to be very rare. There are some conflicting reports about the effect of vitamin C on decreased anticoagulation response to warfarin or dicoumarol (149). High doses of vitamin C also can reduce steady-state plasma concentrations of indinavir, a protease inhibitor indicated for treatment of the human immunodeficiency virus type 1 (150). On the other hand, vitamin C can improve levodopa absorption in elderly patients with Parkinson disease and with poor levodopa bioavailability (151). High vitamin C intake could also interfere with other drugs, which remains to be established. In addition, diarrhea caused by large oral vitamin C doses can reduce the intestinal absorption generally.

Conclusions

Vitamin C achieves positive results in numerous health conditions, acting primarily as an antioxidant (Table 1). On the basis of current evidence, it is justified to promote diets rich in vitamin C for the prevention against cardiovascular disease and cancer. Vitamin C supplements are beneficial in wound healing, reducing the incidence of common cold primarily in heavily physically stressed persons. It is also effective in preventing plasma lipid peroxidation, and decreasing serum fibrinogen and cholesterol values as risk factors for cardiovascular disease. Howeverer, some positive effects could be achieved only by intraarterial or intravenous administration of vitamin C, such as in patients with diabetes melitus and some types of cancer. The evidence from observational studies also suggests a role of vitamin C in asthma and obstructive pulmonary disease, although causality of the association has not been

ći isključivo intraarterijskom ili intravenskom terapijom vitaminom C, primjerice u bolesnika sa šećernom bolešću i nekim vrstama karcinoma. Dokazi iz opservacijskih studija također ukazuju na ulogu vitamina C u astmi i opstrukcijskoj bolesti pluća, iako uzročnost te veze nije potvrđena. Unatoč proturječnim izvješćima, prevladavajuće mišljenje na temelju opširne literature jest da nepovoljni učinci na zdravlje nisu u zdravih osoba izazvani ingestijom visokih doza vitamina C. Oprez je, međutim, potreban kod osoba s nekim specifičnim metaboličkim poremećajima.

confirmed. Despite contradictory reports, the consensus from extensive literature is that adverse health effects are not induced in healthy persons by ingesting high doses of vitamin C. However, there should be a caution in persons with some specific metabolic disorders.

Tablica 1. Učinci vitamina C u raznim zdravstvenim stanjima

Table 1. The effect of vitamin C in various health conditions

Health condition	Type of research	Effect of vitamin C
Cigarette smoking	Controlled clinical trial; single oral dose (2 g)	Restores impaired coronary flow velocity reserve (40)
Wound healing	Controlled clinical trials; oral supplementation (0.5-3 g)	Accelerated wound healing (42)
Common cold	Double blind, controlled trials; oral supplementation in various doses	Under heavy exertion the protective effect in respiratory infections was highly emphasized (59)
	Double-blind, randomized controlled trial; oral supplementation (0.5 g/day)	Reduces the frequency of the common cold with no effect on its duration or severity (60)
Asthma	Double-blind, controlled trial; single oral dose (2 g)	Protective effect on airway hyperreactivity in some patients with exercise-induced asthma (66)
Cardiovascular disease	Controled clinical trial; oral supplementation (2 g/day)	Increased fibrinolytic activity in patients with coronary artery disease (72)
	Observational study within elderly population	Negative correlation between serum vitamin C and total cholesterol (75)
	Double-blind, randomized, controlled, 2-way cross over trial; intraarterial administration (24 mg/min for 110 min)	Improves lipid-induced impairment of endothelium-dependent vasodilation (88)
	In vitro study; various concentrations added to human plasma	Completely protects human plasma from lipid peroxidation (90)
Neurodegenerative disorders	Cross-sectional and prospective study; vitamin C and vitamin E supplementation	Reduced prevalence and incidence of Alzheimer disease in elderly population (99)
	Mouse behavioral models; intraperitoneal injection (60 and 120 mg)	Memory-restorative action, particularly in aged mice (101)
Cancer	*In vitro* study; dose concentration studies and pharmacokinetic modeling	Toxicity to various cancer cells (111)
	In vitro human lymphoma cell study	Action as a pro-drug to deliver hydrogen peroxide to tissues (114)
	Case-control prospective study	Inverse association of gastric cancer risk with high levels of plasma vitamin C (116)
	In vitro B16 murine melanoma cell study	Induces the apoptosis in melanoma cells (118)
Diabetes mellitus	Controlled trial; intraarterial infusion (< 1 g)	Improves endothelium-dependent vasodilation (125)
Cataract	Probability survey of Americans	Importance for the prevention of cataract among older Americans (129)

Budući pravci

Podatci u ovom preglednom članku pružaju solidnu osnovu za daljnje istraživanje, odnosno za kako klinička, tako i eksperimentalna ispitivanja. Oralnom se nadopunom vitamina C ne mogu osigurati tako visoke koncentracije u plazmi kao parenteralnom terapijom. Stoga je potrebno provesti daljnja istraživanja vitamina C, posebice kao agensa u liječenju karcinoma, kao i kliničku studiju sigurnosti i djelotvornosti intravenske terapije vitaminom C kako bi se potvrdila preko tri desetljeća stara zamisao Linusa Paulinga.

Future directions

The evidence in this review provides a substantial basis for further research, both clinical and experimental trials. Oral supplementation of vitamin C cannot yield plasma concentrations as high as parenteral administration. Therefore, further research into vitamin C, particularly as a treatment agent for cancer, as well as clinical study of safety and efficacy of intravenous administration of vitamin C, should be performed to confirm over three decades old Linus Pauling's idea.

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Literatura / References

1. *Smirnoff N. L-*ascorbic acid *biosynthesis. Vitam Horm 2001;61:241-66.*
2. *Kaegi E. Unconventional therapies for cancer: Vitamins A, C and E. Can Med Assoc J 1998;158(11):1483-8.*
3. Pauling *L. Ascorbic acid and the common cold. Am J Clin Nutr 1971;24(11):1294-9.*
4. *Cameron E, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: reevaluation of prolongation of survival times in terminal human cancer. Proc Natl Acad Sci U S A 1978;75(9):4538-42.*
5. Levine *M, Conry-Cantilena C, Wang Y, Welch RW, Washko PW, Dhariwal KR, et al. Vitamin C pharmacokinetics in healthy volunteers: Evidence for a recommended dietary allowance. Proc Natl Acad Sci USA 1996; 93(8):3704-9.*
6. *Food and Nutrition Board, Institute of Medicine, US National Academy of Science. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. National Academy Press, Washington; 2000, pp 95-185.*
7. *Carr AC, Frei B. Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. Am J Clin Nutr 1999;69(6):1086-107.*
8. *Levine M, Rumsey SC, Daruwala RC, Park JB, Wang Y. Criteria and recommendations for vitamin C intake. JAMA 1999;281(15):1415-23.*
9. *Kojo S. Vitamin C: basic metabolism and its function as an index of oxidative stress. Curr Med Chem 2004;11(8):1041-64.*
10. *Buettner GR. The pecking order of free radicals, antioxidants: lipid peroxidation, alpha-tocopherol, and ascorbate. Arch Biochem Biophys 1993;300(2):535-43.*
11. *Padayatty SJ, Levine M. New insights into the physiology and pharmacology of vitamin C. Canad Med Assoc J 2001;164(3):353-5.*
12. *Patak P, Willenberg HS, Bornstein SR. Vitamin C is an important cofactor for both adrenal cortex and adrenal medulla. Endocr Res 2004;30(4):871-5.*
13. *Rumsey SC, Levine M. Absorption, transport, and disposition of ascorbic acid in humans. J Nutr Biochem 1998;9:116-30.*
14. *Rumsey SC, Kwon O, Xu GW, Burant CF, Simpson I, Levine M. Glucose transporter isoforms GLUT1 and GLUT3 transport dehydroascorbic acid. J Biol Chem 1997;272:18982-9.*
15. *Tsukaguchi H, Tokui T, Mackenzie B, Berger UV, Chen XZ, Wang Y, et al. A family of mammalian Na+-dependent L-ascorbic acid transporters. Nature 1999;399:70-5.*
16. *Bornstein SR, Yoshida-Hiroi M, Sotiriou S, Levine M, Hartwig HG, Nussbaum RL, et al. Impaired adrenal catecholamine system function in mice with deficiency of the ascorbic acid transporter (SVCT2). FASEB J 2003;17(13):1928-30.*
17. *Bors W, Buettner GR. The vitamin C radical and its reactions. In: Vitamin C in Health and Disease. Packer L, Fuchs J, eds. New York: Marcel Dekker; 1997; 75-94.*
18. *Sowell J, Frei B, Stevens JF. Vitamin C conjugates of genotoxic lipid peroxidation products: structural characterization and detection in human plasma. Proc Natl Acad Sci U S A 2004;101(52):17964-9.*
19. *Halliwell B, Gutteridge JMC. Ascorbic acid. In: Free radicals in biology and medicine. 3rd ed. Oxford Press, Oxford; 1999;200-8.*
20. *Ahmad IM, Aykin-Burns N, Sim JE, Walsh SA, Higashikubo R, Buettner GR, et al. Mitochondrial O2*- and H2O2 mediate glucose deprivation-induced stress in human cancer cells. J Biol Chem 2005;280(6):4254-63.*
21. *Halliwell B. The antioxidant paradox. Lancet 2000;355(9210):1179-80.*
22. *Bijur GN, Briggs B, Hitchcock CL, Williams MV. Ascorbic acid-dehydroascorbate induces cell cycle arrest at G2/M DNA damage checkpoint during oxidative stress. Environ Mol Mutagen 1999;33(2):144-52.*
23. Lenton *KJ, Therriault H, Fulop T, Payette H, Wagner JR. Glutathione and ascorbate are negatively correlated with oxidative* DNA *damage in human lymphocytes. Carcinogenesis 1999;20(4):607-13.*
24. *Podmore ID, Griffiths HR, Herbert KE, Mistry N, Mistry P, Lunec J. Vitamin C exhibits pro-oxidant properties. Nature 1998;392:559-66.*

25. Crott JW, Fenech M. Effect of vitamin C supplementation on chromosome damage, apoptosis, necrosis ex vivo. Carcinogenesis 1999;20(6):1035-41.
26. Antunes LM, Takahashi C. Effects of high doses of vitamins C and E against doxorubicin-induced chromosomal damage in Wistar rat bone marrow cells. Mutat Res 1998;419(1-3):137-43.
27. Ames BN. DNA damage from micronutrient deficiencies is likely to be a major cause of cancer. Mutat Res 2001;475(1-2):7-20.
28. Scarpa M, Stevanato R, Vigilino P, Rigo A. Superoxide ion as active intermediate in the auto oxidation of ascorbate by molecular oxygen. Effect of superoxide dismutase. J Biol Chem 1983;258(11):6695-7.
29. Halliwell B, Gutteridge JMC. Role of free radicals and catalytic metal ions in human disease: an overview. Methods Enzymol 1990;186:1-85.
30. Burkitt MJ, Duncan J. Effects of trans-resveratrol on copper-dependent hydroxyl-radical formation and DNA damage: evidence for hydroxyl-radical scavenging and a novel, glutathione-sparing mechanism of action. Arch Biochem Biophys 2000;381(2):253-63.
31. McCord M. The evolution of free radicals and oxidative stress. Am J Med 2000;108(8):652-9.
32. Shankaran M, Yamamoto BK, Gudelsky GA. Ascorbic acid prevents 3,4-methylenedioxymethamphetamine (MDMA)-induced hydroxyl radical formation and the behavioral and neurochemical consequences of the depletion of brain 5-HT. Synapse 2001;40(1):55-64.
33. Rehman A, Collis CS, Yang M, Kelly M, Diplock A T, Halliwell B, Rice-Evans E. The effects of iron and vitamin C co-supplementation on oxidative damage to DNA in healthy volunteers. Biochem Biophys Res Commun 1998;246:293-8.
34. Premkumar K, Bowlus CL. Ascorbic acid does not increase the oxidative stress induced by dietary iron in C3H mice. J Nutr 2004;134(2):435-8.
35. Suh J, Zhu BZ, Frei B. Ascorbate does not act as a pro-oxidant towards lipids and proteins in human plasma exposed to redox-active transition metal ions and hydrogen peroxide. Free Radic Biol Med 2003;34(10):1306-14.
36. Church DF, Pryor WA. Free-radical chemistry of cigarette smoke and its toxicological implications. Environ Health Perspect 1985;64:111-26.
37. Gackowski D, Kowalewski J, Siomek A, Olinski R. Oxidative DNA damage and antioxidant vitamin level: comparison among lung cancer patients, healthy smokers and nonsmokers. Int J Cancer 2005;114(1):153-6.
38. Chen HW, Chien ML, Chaung YH, Lii CK, Wang TS. Extracts from cigarette smoke induce DNA damage and cell adhesion molecule expression through different pathways. Chem Biol Interact 2004;150(3):233-41.
39. Takase B, Etsuda H, Matsushima Y, Ayaori M, Kusano H, Hamabe A, et al. Effect of chronic oral supplementation with vitamins on the endothelial function in chronic smokers. Angiology 2004;55(6):653-60.
40. Teramoto K, Daimon M, Hasegawa R, Toyoda T, Sekine T, Kawata T, Yoshida K, Komuro I. Acute effect of oral vitamin C on coronary circulation in young healthy smokers. Am Heart J 2004;148(2):300-5.
41. Hemila H. Vitamin C and the common cold. Brit J Nutr 1992;67:3-16.
42. Ringsdorf WM Jr, Cheraskin E. Vitamin C and human wound healing. Oral Surg Oral Med Oral Pathol 1982;53(3):231-6.
43. Wha Kim S, Lee IW, Cho HJ, Cho KH, Han Kim K, Chung JH, et al. Fibroblasts and ascorbate regulate epidermalization in reconstructed human epidermis. J Dermatol Sci 2002;30(3):215-23.
44. Freyria AM, Ronziere MC, Roche S, Rousseau CF and Herbage D. Regulation of growth, protein synthesis, and maturation of fetal bovine epiphyseal chondrocytes grown in high-density culture in the presence of ascorbic acid, retinoic acid, and dihydrocytochalasin. B J Cell Biochem 1999;76:84–98.
45. Sarisozen B, Durak K, Dincer G, Bilgen OF. The effects of vitamins E and C on fracture healing in rats. J Int Med Res 2002;30(3):309-13.
46. Hughes DA. Effects of dietary antioxidants on the immune function of middle-aged adults. Proc Nutr Soc 1999;58:79-84.
47. Del Rio M, Ruedas G, Medina S, Victor VM, De La Fuente M. Improvement by several antioxidants of macrophage function in vitro. Life Sci 1998;63:871-81.
48. Schwager J, Schuize J. Modulation of interleukin production by ascorbic acid. Vet Immunol Immunopathol 1998;64:45-57.
49. Jeng KC, Yang CS, Siu WY, Tsai YS, Liao WJ, Kuo JS. Supplementation with vitamins C and E enhances cytokine production by peripheral blood mononuclear cells in healthy adults. Am J Clin Nutr 1996;64:960-5.
50. Will JC, Byers T. Does diabetes mellitus increase the requirement for vitamin C? Nutr Rev 1996;54(7):193-202.
51. Bonham MJ, Abu-Zidan FM, Simovic MO, Sluis KB, Wilkinson A, Winterbourn CC, et al. Early ascorbic acid depletion is related to the severity of acute pancreatitis. Brit J Surg 1999;86(10):1296-1301.
52. Vural H, Uzun K. Serum and red blood cell antioxidant status in patients with bronchial asthma. Can Respir J 2000;7(6):476-80.
53. Vita JA, Keaney JF Jr, Raby KE, Morrow JD, Freedman JE, Lynch S, et al. Low plasma ascorbic acid independently predicts the presence of an unstable coronary syndrome. J Am Coll Cardiol 1998;31(5):980-6.
54. Padayatty SJ, Katz A, Wang Y, Eck P, Kwon O, Lee JH, et al. Vitamin C as an antioxidant: evaluation of its role in disease prevention. J Am Coll Nutr 2003;22(1):18-35.
55. Audera C, Patulny RV, Sander BH, Douglas RM. Mega-dose vitamin C in treatment of the common cold: a randomised controlled trial. Med J Aust 2001;175(7):359-62.
56. Gorton HC, Jarvis K. The effectiveness of vitamin C in preventing and relieving the symptoms of virus-induced respiratory infections. J Manipulative Physiol Ther 1999;22(8):530-33.
57. Douglas RM, Chalker EB, Treacy B. Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev 2004;(2): CD000980.
58. Hemila H, Douglas RM. Vitamin C and acute respiratory infections. Int J Tuberc Lung Dis 1999;3(9):756-61.
59. Hemila H. Vitamin C supplementation and respiratory infections: a systematic review. Mil Med 2004;169(11):920-5.
60. Sasazuki S, Sasaki S, Tsubono Y, Okubo S, Hayashi M, Tsugane S. Effect of vitamin C on common cold: randomized controlled trial. Eur J Clin Nutr 2006;60(1):9-17.
61. Smith A, Tyrrell D, Coyle K, Higgins P, Willman J. Diurnal variation in the symptoms of colds and influenza. Chronobiol Int 1988;5(4):411-6.
62. Cohen HA, Neuman I, Nahum H. Blocking effect of vitamin C in exercise-induced asthma. Arch Pediatr Adolesc Med 1997;151(4):367-70.
63. Cohen S, Tyrrell Da, Smith AP. Psychological stress and susceptibility to the common cold. N Engl J Med 1991;325(9): 606-12.
64. Hemila H. Vitamin C supplementation and common cold symptoms: factors affecting the magnitude of the benefit. Med Hypotheses 1999;52(2):171-8.
65. Kongerud J, Crissman K, Hatch G, Alexis N. Ascorbic acid is decreased in induced sputum of mild asthmatics. Inhal Toxicol 2003;15(2):101-9.
66. Cohen HA, Neuman I, Nahum H. Blocking effect of vitamin C in exercise-induced asthma. Arch Pediatr Adolesc Med 1997;151(4):367-70.
67. Butland BK, Fehily AM, Elwood PC. Diet, lung function, and lung function decline in a cohort of 2512 middle aged men. Thorax 2000;55:102-8.
68. Hu G, Zhang X, Chen J, Peto R, Campbell TC, Cassano PA. Dietary vitamin C intake and lung function in rural China. Am J Epidemiol 1998;148:594-9.
69. Smit HA, Grievink L, Tabak C. Dietary influences on chronic obstructive lung disease and asthma: a review of the epidemiological evidence. Proc Nutr Soc 1999;58(2):309-19.
70. Gale CR, Martyn CN, Winter PD, Cooper C. Vitamin C and risk of death from stroke and coronary heart disease in cohort of elderly people. BMJ 1995;310:1563-6.
71. Bulpitt CJ. Vitamin C and vascular disease. BMJ 1995;310:1548-9.
72. Bordia AK. The effect of vitamin C on blood lipids, fibrinolytic activity, platelet adhesiveness in patients with coronary artery disease. Atherosclerosis 1980;35(2):181-7.
73. Nilsson TK, Sundell IB, Hellsten G, Hallmans G. Reduced plasminogen activator inhibitor activity in high consumers of fruits, vegetables and root vegetables. J Intern Med 1990;227(4):267-71.
74. Khaw KT, Woodhouse P. Interrelation of vitamin C, infection, haemostatic factors, and cardiovascular disease. BMJ 1995;310(6994):1559-63.
75. Sullivan DR. Screening for cardiovascular disease with cholesterol. Clin Chim Acta 2002;315(1-2):49-60.

76. Cerna O, Ginter E. Blood lipids and vitamin-C status. Lancet 1978; 1(8072):1055–6.
77. Greco AM, LaRocca L. Correlation between chronic hypovitaminosis C in old age and plasma levels of cholesterol and triglycerides. Int J Vit Nutr Res 1982;23:129-36.
78. Itoh R, Yamada K, Oka J, Echizen H, Suyama Y, Murakami K. Serum ascorbic acid and HDL cholesterol in a healthy elderly Japanese population. Int J Vitam Nutr Res 1990;60(4):360-5.
79. Simon JA, Hudes ES. Relation of serum ascorbic acid to serum lipids and lipoproteins in US adults. J Am Coll Nutr 1998;17(3):250-5.
80. Jacques PF, Sulsky SI, Perrone GE, Jenner J, Schaefer EJ. Effect of vitamin C supplementation on lipoprotein cholesterol, apolipoprotein, and triglyceride concentrations. Ann Epidemiol 1995;5(1):52-9.
81. Harwood HJ Jr, Greene YJ, Stacpoole PW. Inhibition of human leukocyte 3-hydroxy-3-methylglutaryl coenzyme A reductase activity by ascorbic acid. An effect mediated by the free radical monodehydroascorbate. J Biol Chem 1986;261(16): 7127-35.
82. Greene YJ, Harwood HJ Jr, Stacpoole PW. Ascorbic acid regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity and cholesterol synthesis in guinea pig liver. Bioch Biophys Acta 1985; 834(1):134-8.
83. Santillo M, Santangelo F, Belfiore A, Mastursi M, Mondola P. Effect of ascorbic acid administration on B and E apoproteins in rats fed a cholesterol enriched diet. Horm Metab Res 1993;25(3):156-9.
84. Knekt P, Reunanen A, Jarvinen R, Seppanen R, Heliovaara M, Aromaa A. Antioxidant vitamin intake and coronary mortality in a longitudinal population study. Am J Epidemiol 1994; 139(12): 1180-9.
85. Stringer MD, Gorog PG, Freeman A, Kakkar VV. Lipid peroxides and atherosclerosis. BMJ 1989;298:281-4.
86. Diaz MN, Frei B, Vita JA, Keaney JF. Antioxidants and atherosclerotic heart disease. N Engl J Med 1997;337:408-16.
87. Frei B, England L, Ames BN. Ascorbate is an outstanding antioxidant in human blood plasma. Proc Natl Acad Sci U S A 1989;86(16):6377-81.
88. Abuja PM. Ascorbate prevents prooxidant effects of urate in oxidation of human low density lipoprotein. FEBS Lett 1999;446(2-3):305-8.
89. Lehr HA, Frei B, Olofsson AM, Carew TE, Arfors KE. Protection from oxidized LDL-induced leukocyte adhesion to microvascular and macrovascular endothelium in vivo by vitamin C but not by vitamin E. Circulation 1995;91(5):1525-32.
90. Mak S, Egri Z, Tanna G, Colman R, Newton GE. Vitamin C prevents hyperoxia-mediated vasoconstriction and impairment of endothelium-dependent vasodilation. Am J Physiol Heart Circ Physiol 2002;282(6): H2414-21.
91. Bayerle-Eder M, Pleiner J, Mittermayer F, Schaller G, Roden M, Waldhausl W, et al. Effect of systemic vitamin C on free fatty acid-induced lipid peroxidation. Diabetes Metab 2004;30(5):433-9.
92. Nakazono K, Watanabe N, Matsuno K, Sasaki J, Sato T, Inoue M. Does superoxide underlie the pathogenesis of hypertension? Proc Natl Acad Sci USA 1991;88:10045-8.
93. Moran JP, Cohen L, Greene JM, Xu G, Feldman EB, Hames CG, et al. Plasma ascorbic acid concentrations relate inversely to blood pressure in human subjects. Am J Clin Nutr 1993;57:213-7.
94. Bates CJ, Walmsley CM, Prentice A, Finch S. Does vitamin C reduce blood pressure? Results of a large study of people aged 65 or older. J Hyperten 1998;16(7):925-32.
95. Duffy SJ, Gokce N, Holbrook M, Huang A, Frei B, Keaney JF Jr, et al. Treatment of hypertension with ascorbic acid. Lancet 1999;354(9195):2048-9.
96. Chen J, He J, Hamm L, Batuman V, Whelton PK. Serum antioxidant vitamins and blood pressure in the United States population. Hypertension 2002;40(6):810-6.
97. Kritchevsky SB, Shimakawa T, Tell GS, Dennis B, Carpenter M, Eckfeldt JH, et al. Dietary antioxidants and carotid artery wall thickness. The ARIC Study. Atherosclerosis risk in communities study. Circulation 1995;92:2142 –50.
98. Joshipura KJ, Hu FB, Manson JE, Stampfer MJ, Rimm EB, Speizer FE, et al. The effect of fruit and vegetable intake on risk for coronary heart disease. Ann Intern Med 2001;134:1106-14.
99. Zandi PP, Anthony JC, Khachaturian AS, Stone SV, Gustafson D, Tschanz JT, et al. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. Arch Neurol 2004;61(1):82-8.
100. Montilla-Lopez P, Munoz-Agueda MC, Feijoo Lopez M, Munoz-Castaneda JR, Bujalance-Arenas I, et al. Comparison of melatonin versus vitamin C on oxidative stress and antioxidant enzyme activity in Alzheimer's disease induced by okadaic acid in neuroblastoma cells. Eur J Pharmacol 2002;451(3):237-43.
101. Parle M, Dhingra D. Ascorbic acid: a promising memory-enhancer in mice. J Pharmacol Sci 2003;93(2):129-35.
102. Chan SW, Reade PC. The role of ascorbic acid in oral cancer and carcinogenesis. Oral Dis 1998;4(2):120-9.
103. Lupulescu A. The role of vitamins A, beta-carotene, E and C in cancer cell biology. Int J Vitam Nutr Res 1994;64(1):3-14.
104. Murata A, Morishige F, Yamaguchi H. Prolongation of survival times of terminal cancer patients by administration of large doses of ascorbate. Int J Vitam Nutr Res 1982;23:103-13.
105. Moertel CG, Fleming TR, Creagan ET, Rubin J, O'connell MJ, Ames MM. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy. A randomized double-blind comparison. N Engl J Med 1985;312(3):137-44.
106. Halliwell B. Vitamin C and genomic stability. Mutat Res 2001;475(1-2):29-35.
107. Moorman PG, Ricciuti MF, Millikan RC, Newman B. Vitamin supplement use and breast cancer in a North Carolina population. Public Health Nutr 2001;4(3):821-7.
108. Block G. Epidemiologic evidence regarding vitamin C and cancer. Am J Clin Nutr 1991;54(6):S1310-4.
109. Dusinska M, Kazimirova A, Barancokova M, Beno M, Smolkova B, Horska A, et al. Nutritional supplementation with antioxidants decreases chromosomal damage in humans. Mutagenesis 2003;18(4):371-6.
110. Koh WS, Lee SJ, Lee H, Park C, Park MH, Kim WS, et al. Differential effects and transport kinetics of ascorbate derivatives in leukemic cell lines. Anticancer Res 1998;18:2487-93.
111. Padayatty SJ, Sun H, Wang Y, Riordan HD, Hewitt SM, Katz A, et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. Ann Intern Med 2004;140(7):533-7.
112. Graumlich JF, Ludden TM, Conry-Cantilena C, Cantilena LR Jr, Wang Y, Levine M. Pharmacokinetic model of ascorbic acid in healthy male volunteers during depletion and repletion. Pharm Res 1997;14:1133-9.
113. Padayatty SJ, Riordan HD, Hewitt SM, Katz A, Hoffer LJ, Levine M. Intravenously administered vitamin C as cancer therapy: three cases. CMAJ 2006;174(7):937-42.
114. Chen Q, Espey MG, Krishna MC, Mitchell JB, Corpe CP, Buettner GR, et al. Pharmacologic ascorbic acid concentrations selectively kill cancer cells: Action as a pro-drug to deliver hydrogen peroxide to tissues. Proc Natl Acad Sci U S A 2005;102(38):13604-9.
115. Byers T, Guerrero N. Epidemiologic evidence for vitamin C and vitamin E in cancer prevention. Am J Clin Nutr 1995;62:1385S -92S.
116. Jenab M, Riboli E, Ferrari P, Sabate J, Slimani N, Norat T, et al. Plasma and dietary vitamin C levels and risk of gastric cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). Carcinogenesis 2006 Jun 14; Epub ahead of print.
117. Sakagami H, Satoh K, Hakeda Y, Kumegawa M. Apoptosis-inducing activity of vitamin C and vitamin K. Cell Mol Biol 2000;46:129-143.
118. Kang JS, Cho D, Kim YI, Hahm E, Yang Y, Kim D, et al. L-ascorbic acid (vitamin C) induces the apoptosis of B16 murine melanoma cells via a caspase-8-independent pathway. Cancer Immunol Immunother 2003;52(11):693-698.
119. Thomas CG, Vezyraki PE, Kalfakakou VP, Evangelou AM. Vitamin C transiently arrests cancer cell cycle progression in S phase and G(2)/M boundary by modulating the kinetics of activation and the subcellular localization of Cdc25C phosphatase. J Cell Physiol 2005;205(2):310-8.
120. Naidu KA, Tang JL, Naidu KA, Prockop LD, Nicosia SV, Coppola D. Antiproliferative and apoptotic effect of ascorbyl stearate in human glioblastoma multiforme cell: Modulation of insulin-like growth factor-I receptor (IGF-IR) expression. J Neurooncol 2001;54(1):15-22.

121. Naidu AK, Karl RC, Naidu KA, Coppola D. The antiproliferative and pro-apoptotic effect of Ascorbyl Stearate in Human pancreatic cancer cells: Association with decreased expression of insulin-like growth factor receptor-1. Digest Dis Sci 2003;48(1):230-7.
122. Naidu AK. Vitamin C in human health and disease is still a mystery? An overview. Nutr J 2003;2(1):7.
123. Bonnefont-Rousselot D. The role of antioxidant micronutrients in the prevention of diabetic complications. Treat Endocrinol 2004;3(1):41-52.
124. Chen L, Jia RH, Qiu CJ, Ding G. Hyperglycemia inhibits the uptake of dehydroascorbate in tubular epithelial cell. Am J Nephrol 2005;25(5):459-65.
125. Timimi FK, Ting HH, Haley EA, Roddy MA, Ganz P, Creager MA. Vitamin C improves endothelium-dependent vasodilation in patients with insulin-dependent diabetes mellitus. J Am Coll Cardiol 1998;31(3):552-7.
126. Ting HH, Timimi FK, Boles KS, Creager SJ, Ganz P, Creager MA. Vitamin C improves endothelium-dependent vasodilation in patients with non-insulin-dependent diabetes mellitus. J Clin Invest 1996;97(1):22-8.
127. Chen H, Karne RJ, Hall G, Campia U, Panza JA, Cannon RO 3rd, Wang Y, Katz A, Levine M, Quon MJ. High dose oral vitamin C partially replenishes vitamin C levels in patients with type 2 diabetes and low vitamin C levels but does not improve endothelial dysfunction or insulin resistance. Am J Physiol Heart Circ Physiol 2006;290(1):H137-45.
128. Choi SW, Benzie IF, Lam CS, Chat SW, Lam J, Yiu CH, et al. Inter-relationships between DNA damage, ascorbic acid and glycaemic control in Type 2 diabetes mellitus. Diabet Med 2005;22(10):1347-53.
129. Simon JA, Hudes ES. Serum ascorbic acid and other correlates of self-reported cataract among older Americans. J Clin Epidemiol 1999;52(12):1207-11.
130. Van der Pols JC. A possible role for vitamin C in age-related cataract. Proc Nutr Soc 1999;58(2):295-301.
131. Cheng R, Lin B, Lee KW, Ortwerth BJ. Similarity of the yellow chromophores isolated from human cataracts with those from ascorbic acid-modified calf lens proteins: evidence for ascorbic acid glycation during cataract formation. Biochim Biophys Acta 2001;1537(1):14-26.
132. Argirov OK, Lin B, Ortwerth BJ. 2-ammonio-6-(3-oxidopyridinium-1-yl)hexanoate (OP-lysine) is a newly identified advanced glycation end product in cataractous and aged human lenses. J Biol Chem 2004;279(8):6487-95.
133. Jacques PF. The potential preventive effects of vitamins for cataract and age-related macular degeneration. Int J Vitam Nutr Res 1999;69(3):198-205.
134. Hathcock JN, Azzi A, Blumberg J, Bray T, Dickinson A, Frei B, et al. Vitamins E and C are safe across a broad range of intakes. Am J Clin Nutr 2005;81(4):736-45.
135. Rees DC, Kelsey H, Richards JD. Acute haemolysis induced by high dose ascorbic acid in glucose-6-phosphate dehydrogenase deficiency. BMJ 1993;306:841-2.
136. Hallberg L. Iron and vitamins. Bibl Nutr Dieta 1995;52:20-9.
137. Cook JD, Watson SS, Simpson KM, Lipschitz DA, Skikne BS. The effect of high ascorbic acid supplementation on body iron stores. Blood 1984;64:721-6.
138. Diplock AT. Antioxidant nutrients and disease prevention: An overview. Am J Clin Nutr 1991;53(1):S189- 93.
139. Meyers DG, Maloley PA, Weeks D. Safety of antioxidant vitamins. Arch Intern Med 1996;156:925-35.
140. Gerster H. No contribution of ascorbic acid to renal calcium oxalate stones. Ann Nutr Metab 1997;41(5):269-82.
141. Wandzilak TR, D'Andre SD, Davis PA, Williams HE. Effect of high dose vitamin C on urinary oxalate levels. J Urol 1994;151(4):834-37.
142. Curhan GC, Willett WC, Rimm EB, Stampfer MJ. A prospective study of the intake of vitamins C, B6, and the risk of kidney stones in men. J Urol 1996;155:1847-51.
143. Auer BL, Auer D, Rodgers AL. Relative hyperoxaluria, crystalluria and haematuria after megadose ingestion of vitamin C. Eur J Clin Invest 1998;28(9):695-700.
144. Pena de la Vega L, Lieske JC, Milliner D, Gonyea J, Kelly DG. Urinary oxalate excretion increases in home parenteral nutrition patients on a higher intravenous ascorbic acid dose. J Parenter Enteral Nutr 2004;28(6):435-8.
145. Rivers JM. Safety of high-level vitamin C ingestion. Int J Vitam Nutr Res 1989;30:95-102.
146. Stein HB, Hasan A, Fox IH. Ascorbic acid-induced uricosuria. Ann Intern Med 1976;84:385-8.
147. Schmidt KH, Hagmaier V, Hornig DH, Vuilleumier JP, Rutishauser G. Urinary oxalate excretion after large intakes of ascorbic acid in man. Am J Clin Nutr 1981;34(3):305-11.
148. Mitch WE, Johnson MW, Kirshenbaum JM, Lopez RE. Effect of large oral doses of ascorbic acid on uric acid excretion by normal subjects. Clin Pharmacol Ther 1981;29:318-21.
149. Wynne H, Khan T, Avery P, Wood P, Ward A, Kamali F. Dietary related plasma vitamin C concentration has no effect on anticoagulation response to warfarin. Thromb Res 2005 Aug 30; Epub ahead of print.
150. Slain D, Amsden JR, Khakoo RA, Fisher MA, Lalka D, Hobbs GR. Effect of high-dose vitamin C on the steady-state pharmacokinetics of the protease inhibitor indinavir in healthy volunteers. Pharmacotherapy 2005;25(2):165-70.
151. Nagayama H, Hamamoto M, Ueda M, Nito C, Yamaguchi H, Katayama Y. The effect of ascorbic acid on the pharmacokinetics of levodopa in elderly patients with Parkinson disease. Clin Neuropharmacol 2004;27(6):270-3.