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Utječe li uporaba vitamina C na razvoj vaskularnih komplikacija u pacijenata s dijabetesom?

Does the use of vitamin C affect the development of vascular complications in patients with diabetes?

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SAŽETAK: Vitamin C predstavlja esencijalni mikronutrijent s poznatim antioksidativnim efektom. Oksidativni stres je osnovni patofiziološki mehanizam oštećenja endotela. Podaci o pojavnosti dijabetesa i primjeni vitamina C su kontroverzni, a u regulaciji glikemije mogu se očekivati povoljni učinci nakon uzimanja vitamina C. S obzirom na antioksidativna svojstva vitamina C, povoljan učinak uzimanja može se očekivati i kod dijabetičara sa zatajivanjem srčane funkcije, kao i kod pacijenata s ishemijskim moždanim udarom. Niska razina C vitamina u plazmi kod dijabetičara tipa 1 uzrokuje smetnje u repolarizaciji klijetki. Primjena vitamina C nema povoljan učinak na perifernu cirkulaciju donjih udova, a ima povoljan na cirkulaciju u gornjim ekstremitetima. Vitamin C vjerojatno ima i povoljan učinak na usporavanje razvoja dijabetičke nefropatije i neuropatije, dok je učinak na razvoj retinopatije dvojben. Za razliku od dijastoličkog, sistolički arterijski tlak može biti dodatno snižen primjenom vitamina C. Obzirom na kontroverzne podatke za sada se ne preporuča rutinsko uzimanje vitamina C u preparatima koji su dodatak prehrani sa svrhom smanjenja kardiovaskularnih rizika. I dalje vrijedi preporuka o što većem uzimanju voća i povrća u svakodnevnoj prehrani.

KLJUČNE RIJEČI: vitamin C, dijabetes, arterijska hipertenzija, kardiovaskularne komplikacije.

SUMMARY: Vitamin C is an essential micronutrient with well-known antioxidant effect. Oxidative stress is the underlying pathological state of endothelial damage. Data on the incidence of diabetes and the use of vitamin C are controversial, while some beneficial effects can be expected in the regulation of blood glucose levels after taking vitamin C. Considering the antioxidant properties of vitamin C, a beneficial effect of taking vitamin C can be also expected in diabetic patients with heart failure and in patients with ischemic stroke. A low level of vitamin C in plasma in type 1 diabetic patients causes ventricular repolarization disturbances. The use of vitamin C does not have a beneficial effect on the peripheral circulation of the lower limbs, but it has a beneficial effect on the circulation in the upper limbs. Vitamin C probably has a beneficial effect on slowing down the development of diabetic nephropathy and neuropathy, while the impact on the development of retinopathy is uncertain. Unlike the diastolic pressure, systolic blood pressure can be further decreased by administering vitamin C. Considering the controversial data, for the time being we still do not advise regular intake of vitamin C in products that are dietary supplements for the purpose of reducing cardiovascular risks. The advice on eating as greater amounts of fruit and vegetables as possible in a daily diet still applies.

KEYWORDS: vitamin C, diabetes, hypertension, cardiovascular complications.

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Uvod

Vitamini su esencijalni organski mikronutrijenti potrebni u prehrani u vrlo malim količinama, no time njihov značaj u prehrani nije manje važan. Upravo je otkriće vitamina prije stotinjak godina obilježilo nutricionizam kao znanost.

Stoljećima je bilo poznato da su neke bolesti vezane uz prehranu, primjerice skorbut u mornara koji su se hranili isključivo suhim mesom, dvopekom, bez unosa svježeg voća i povrća mjesecima na dugim putovanjima.Također je već davno shvaćeno da se noćno sljepilo može liječiti konzumiranjem jetre, a beri-beri je povezivan s jednoličnom prehra-

Introduction

Vitamins are essential organic micronutrients needed in our diet in small amounts, but this does not mean that their importance in the diet is less important. It is the discovery of vitamins a hundred years ago that marked nutritionism as a science.

It has been known for centuries that some diseases are connected to nutrition, for example scurvy among sailors that were eating primarily dried meat, toast, without any intake of fresh fruit and vegetables for months on their long journeys. It was also found out a long time ago that a night blindness

nom temeljenom na poliranoj riži. No, važnost vitamina i tih esencijalnih tvari u prehrani nije se mogla "probiti" u medicinskim krugovima 19. stoljeća, jer su kao uzročnici bolesti "u modi" bile bakterije i bakterijski toksini.

Tek je otkriće Christiana Eijkmana o tvari iz neoljuštene riže koja je topiva u vodi i liječi beri-beri te otkriće Casimira Funka o važnosti tog amina za život ("vitamin") pomakla shvaćanje o nezamjenjivoj ulozi vitamina.[1]

Danas je poznato 13 vitamina te se prema topljivosti dijele na one topljive u mastima (D, E, K, A) i na topljive u vodi (vitamini B skupine i C vitamin). Vitamini pokazuju mnoge kemijske i funkcionalne sličnosti. Služe kao koenzimi u metabolizmu, odnosno imaju aktivnu ulogu u mnogobrojnim složenim biokemijskim reakcijama. Ove reakcije su bitne za intermedijarni metabolizam i osiguravaju iskorištenje glavnih nutrijenata.

Druga važna uloga vitamina je antioksidativna. Povećan rizik razvoja kroničnih komplikacija u dijabetičara posljedica je zajedničkog djelovanja rizičnih čimbenika (poput dislipidemije, hipertenzije, hiperglikemije, hiperinzulinemije), povećanog oksidativnog stresa sa stvaranjem završnih produkata glukozilacije, tromboza i fibrinolize te dovode do progresije ateroskleroze i pojave neželjenih kardiovaskularnih događaja.[2] Oksidativni stres, jedan od čimbenika rizika, neravnoteža je u redoks stanju organizma. Uzrokovan je ili prekomjernim uzimanjem oksidativnih tvari ili neadekvatnim unosom nutrijenata s antioksidativnim djelovanjem kao što su vitamini E i C, karotenoidi, polifenoli, kositar ili je posljedica smanjene raspoloživosti antioksidanata. Povećanje oksidativnog stresa u dijabetičara odvija se preko nekoliko metaboličkih puteva uključujući poliolski put, stvaranje krajnjih produkata glukozilacije,stvaranje malih LDL čestica.[2] Stoga oksidativni stres kroz proizvodnju slobodnih kisikovih radikala ima glavnu ulogu u patogenezi oštećenja krvožilja, posebice oštećenja endotela.[2,3]

Anion superoksida, jedan od kisikovih slobodnih radikala, nastaje redukcijom molekularnog kisika. U to je uključeno nekoliko enzima kao npr. ksantin oksidaza NADH/NADPH oksidaza, lipooksigenaza. Anioni superoksida se reduciraju do hidrogen peroksida ili spontano ili enzimatski. Nusproizvod oksidativnog metabolizma je stvaranje spojeva koji uzrokuju daljnje oksidativne reakcije,naročito u organskim dijelovima stanice, odnosno u staničnim membranama i nukleinskim kiselinama. Za zaštitu od tih reaktivnih kisikovih spojeva tijelo koristi sofisticirani sustav ograničavanja njihove aktivnosti putem složenih molekula, kao što su vitamini A, C, E ili enzimskih sustava koji uklanjaju proizvode oksidacije (superoksid dismutaza ili glutation peroksidaza).[2]

Uloga vitamina C u metabolizmu

Vitamin C (askorbinska kiselina) sudjeluje u redoks procesima. Stvaraju ga biljke i većina životinja sintezom iz glukoze i galaktoze pomoću enzima 1-gulonolakton oksidaze koji nedostaje u viših primata i čovjeka. Te vrste uzimaju askorbinsku kiselinu hranom iz koje se više od 80% apsorbira u crijevima. Transportira se plazmom i ulazi u stanicu preko sustava nosača za glukozu te preko posebnog sustava aktivnog transporta. Sustav koji koristi nosače za glukozu stimuliran je inzulinom i inhibiran glukozom, stoga dijabetičari imaju visoku razinu askorbata u plazmi i nisku razinu u stanicama, što dovodi do povećanog oksidativnog stresa u stanicama dijabetičara.[4] Nakon ulaza u stanicu dehidroaskorbinska kiselina se reducira do askorbata. Vitamin C se *in vivo* oksidira tvoreći slobodan radikal monodehidroaskorbinsku

can be cured by liver consumption, and Beriberi is connected with a monotonous diet based on converted or paraboiled rice. However, the importance of vitamins and the above mentioned essential substances could not find its way through the medical circles in 19th century, since the disease causes that were "fashionable" included bacteria and bacterial toxins.

It was not until the discovery of Christian Eijkman about the matter from unpeeled rice that can be melted in water and cures Beriberi, and the discovery of Casimir Funk about the importance of this vitamin for a life ("vitamin") that changed the understanding of indispensible role of vitamins.[1]

There are currently 13 vitamins and they are divided into fat-soluble (D, E, K, A) and water-soluble (vitamins belonging to group B and vitamin C) according to their solubility. Vitamins show many chemical and functional similarities. They serve as coenzymes in the metabolism, that is, they have an active role in numerous complex biochemical reactions. These reactions are important for the intermediary metabolism and they ensure main nutrients usage.

The other important role of vitamins is the antioxidative one. Increased risk of chronic complications development in diabetics is the consequence of a mutual action of risk factors such as dyslipidemia, hypertension, hyperglycemia, hyperinsulinemia, increased oxidative stress with creation of final products of glycosylation, thrombosis and fibrosis, which lead to progression of atherosclerosis and occurrence of undesired cardiovascular events.[2] Oxidative stress, one of the risk factors, is an imbalance in the redox organism state. It is caused by either abuse of oxidative substances or by inadequate intake of nutrients with antioxidative effect such as vitamins E and C, carotenoids, polyphenols, pewter, or it is the consequence of a reduced antioxidants availability. Oxidative stress increase in diabetics takes place through several metabolic pathways, including the polyol pathway, creation of final products of glycosylation, creation of small LDL particles.[2] Therefore, oxidative stress, through its production of free oxygen radicals has the major role in pathogenesis of blood vessels damage, especially blood vessel endothelium damage.[2,3]

A superoxide anion, one of the oxygen free radicals, originates from the reduction of molecular oxygen. This includes several enzymes, such as xanthine oxidase, NADH/NADPH oxidase, lypoxigenase. Superoxide anions are reduced to hydrogen peroxide either spontaneously or enzymatically. The oxidative metabolism by-product is the creation of compounds that cause further oxidative reactions, especially in organic parts of the cell, that is, in the cell membranes and nucleic acids. For protection from those reactive oxygen compounds, the body uses a sophisticated system of limiting their activities through complex molecules, such as vitamins A, C, E or enzyme system that remove oxidation processes (superoxide dismutase or gluthathione peroxidase).[2]

The role of the vitamin C in the metabolism

Vitamin C or ascorbic acid takes part in redox processes. It is created by plants and majority of animals by glucose and galactose synthesis with the help of the enzyme L- gulonolactone oxidase, which is insufficient in higher primates and humans. These species take ascorbic acid by food from which over 80 % of taken ascorbic acid by food is absorbed in the bowels. It is transported through the plasma and it enters the cell through the system of carriers for glucose and through a special system of an active transport. The system

kiselinu. Ovaj međuprodukt može nadalje biti oksidiran do dehidroaskorbinske kiseline. Posljedično oksidirani produkt je podložan ireverzibilnoj hidrolizi do 2,3 di-keto-1-gulonske kiseline koja može biti dekarboksilirana do ugljičnog dioksida i nekoliko spojeva s pet atoma ugljika (ksiloza, ksilonska kiselina). Dehidroaskorbinska kiselina može biti oksidirana do oksalne kiseline ili nekoliko spojeva sa 4 ugljikova atoma, npr. treoninske kiseline.[4] S obzirom da se askorbinska kiselina lako oksidira do dehidroaskorbinske kiseline sudjeluje u mnogim redoks reakcijama uključujući stvaranje kolagena i karnitina. Tijekom stvaranja ova dva produkta vitamin C služi kao reducirajuća tvar za željezo omogućujući time funkciju enzima hidroksilacije.

Vitamin C sudjeluje i u hidroksilaciji nekih steroida koji se stvaraju u nadbubrežnoj žlijezdi.

Svojstvo da lako gubi elektrone čini vitamin C potentnim antioksidansom. Reagira s potencijalno opasnim slobodnim radikalima kisika, kao što su superoksid ili hidroksi radikali. Vitamin C je nephodan za oksidaciju fenilalanina i tirozina, konverziju folata u tetrahidrofolnu kiselinu, konverziju triptofana u 5 hidroksitriptofan i zatim u neurotransmiter serotonin te za stvaranje noradrenalina iz dopamina. Isto tako reducira feri u fero oblik željeza potičući time apsorpciju željeza u crijevima. Uloga vitamina C u imunologiji svodi se na ulogu u integritetu mukoze kao barijere infekciji, aktivnosti leukocita te stvaranju interferona.[4]

Unos vitamina C i pojavnost dijabetesa

Epidemiološke studije ukazuju da povećan unos voća i povrća može smanjiti rizik od pojavnosti dijabetesa. Razina vitamina C u plazmi uzima se kao dobar biomarker učestalosti uzimanja voća i povrća.

Studija provedena kroz 12 godina u Velikoj Britaniji ukazuje na jaku inverznu povezanost između razine vitamina C u plazmi i rizika pojavnosti dijabetesa.[5]

Međutim, u nešto starijoj kohortnoj studiji rađenoj tijekom 23 godine u Finskoj i objavljenoj 2004. godine nije pronađena veza između rizika nastanka dijabetesa tipa 2 i količine unesenoga vitamina C.[6] Jednako tako niti studija provedena na ženama s povećanim rizikom za kardiovaskularnu bolest ne pokazuje utjecaj vitamina C na smanjenje učestalosti pojavnosti dijabetesa tipa 2.[7]

S druge strane, postoje naznake da je količina uzetog vitamina C obrnuto proporcionalna s pojavnošću gestacijskog dijabetesa. U studiji *Zhang i sur*, trudnice s koncentracijom C vitamina u plazmi <55,9 μmmol/L mogu očekivati 3,1x viši rizik za razvoj gestacijskog dijabetesa u usporedbi s onima koje su imale koncentraciju C vitamina u plazmi ≥74,6 μmol/L. Žene koje su uzimale <70 mg vitamina C dnevno imaju 1,8x viši rizik obolijevanja od gestacijskog dijabetesa.[8]

Studija *Shim i sur* provedena u Koreji 2010. godine na 2048 odraslih ispitanika u dobi iznad 30 godina zaključuje da dijabetičari imaju nižu razinu C vitamina od kontrolne skupine. Naročito nisku razinu C vitamina imaju dijabetičari koji su pušači, stoga je zaključeno da pušenje i dijabetes zajednički imaju negativan utjecaj na razinu C vitamina u serumu.[9]

Podaci o povezanosti učestalosti dijabetesa tipa 2 i unosa vitamina C su kontroverzni, ali nisu zanemarivi kao moguća javnozdravstvena poruka o potrebi konzumiranja većih količina namirnica bogatih vitaminom C.

that uses carriers for glucose is stimulated by insulin and inhibited by glucose, and therefore the diabetics have a high level of ascorbates in the plasma and a low level in cells, which leads to increased oxidative stress in the diabetics' cells.[4] After entering into the cell, dehydroascorbic acid is reduced to acorbates. Vitamin C is oxidised in vivo creating a free radical, monohydroascorbic acid. This intermediary product can be oxidised further up to dehydroascrobic acid. Consequentially oxidised product is pervious to irreversible hydrolysis up to 2,3 diketogulonic acid, which can be decarboxylated into carbon dioxide and several compounds with 5 atoms of carbon (xylose, xylonic acid). Dehydroascorbic acid can be oxidised into oxsalic acid or several compounds with 4 carbon atoms, for example threonine acid.[4] Since ascorbic acid easily oxidises into dehydroascorbic acid, it takes part in many redox reactions, including colagene and carnitine creation. During the creation of these two products, vitamin C serves as a reduced substance for iron, thus enabling the enzyme hydroxylation function.

Vitamin C also takes part in hydroxylation of some steroids that are created in the adrenal gland.

Characteristics of losing electrons easily makes vitamin C a potent antioxidant. It reacts with potentially dangerous free radicals of oxygen, such as superoxide or hydroxyl radicals. Vitamin C is essential for oxidation of phenylanine and thyrosine, folates conversion into tetrahydrofolic acid, tryptophan conversion into 5-hydroxytryptophan and then into neurotransmitter serotonin, as well as for noradrenalin creation from dopamine. It also reduces ferri into ferro form of iron, thus inducing iron absorption in bowels. The role of vitamin C in immunology comes down to the role in the mucosa integrity as an infection barrier, leucocytes activity and interferons creation.[4]

Vitamin C intake and diabetes occurrence

Epidemiological studies suggest that the increased intake of fruit and vegetables can reduce the risk of diabetes occurrence. The level of vitamin C in plasma is taken as a good biomarker of prevalence in fruit and vegetables intake.

The study conducted throughout 12 years in the United Kingdom suggests a strong reverse connection between vitamin C in plasma and the risk of diabetes occurrence.[5]

However, in a slightly older cohort study conducted throughout 23 years in Finland and published in 2004, there was no connection found between the risk of diabetes type 2 occurrence and the quantity of vitamin C intake.[6] Also, the study conducted among women with a higher risk of cardiovascular diseases does not show the influence of vitamin C on a decrease in diabetes type 2 incidence.[7]

On the other hand, there are some indicators that the quantity of taken vitamin C is inversely proportional to the gestational diabetes incidence. In the study conducted by *Zhang et al*, pregnant women with the concentration of vitamin C in plasma of <55.9 μmmol/L can expect 3.1 times higher risk of gestational diabetes development in comparison with pregnant women that had vitamin C concentration in plasma ≥74.6 μmmol/L. Women that took <70 mg of vitamin C a day have 1.8 times higher risk of having gestational diabetes.[8]

The study by *Shim et al* conducted in Korea in 2010 among 2048 adult participants within the age over 30 concludes that patients suffering from diabetes can still have a lower level of vitamin C than the controlled group. Especially low level of vitamin C is found among smokers suffering from

Vitamin C i regulacija glikemije

Tri su kriterija dobre regulacije dijabetesa: zadovoljavajuća glikemija na tašte, zadovoljavajuća postprandijalna glikemija te zadovoljavajuća razina Hba1c (frakcije glikoliziranog hemoglobina).[10] Godine 2008. kriteriji dobre regulacije postaju još stroži te se do nedavno smatralo da je dijabetes dobro reguliran ako zadovoljava ove kriterije: glikemija na tašte <5,5mmol, postprandijalna glikemija <7,8 mmol te Hba1c <6,5%.[9] U travnju 2012. izdane su nove smjernice preporučene od krovnih svjetskih strukovnih udruga *American Diabetes Association* (ADA) i *European Association for the Study of Diabetes* (EASD) za liječenje dijabetesa tipa 2 koje više ne navode jedinstvene stroge kriterije "glukotrijade" (glikemija na tašte, postprandijalna glikemija i Hba1c) za zadovoljavajuću kontrolu bolesti, već u prvi plan stavljaju individualni pristup svakom pacijentu. Tako su primjerice zadovoljavajući kriteriji kontrole bolesti za mlađeg dijabetičara, s kraćim "dijabetičkim stažom" i s manje kroničnih komplikacija stroži nego za starijeg dijabetičara koji dulje vrijeme ima uz razvijene kronične komplikacije. U obzir se mora uzeti i četvrti kriterij dobre regulacije, a to je stabilnost razine glikemije.[11]

Postoji svega nekoliko članaka o utjecaju vitamina C na regulaciju dijabetesa. Studija *Ganesh i sur* iz 2011. je ispitivala utjecaj vitamina C na glikemiju natašte, postprandijalnu glikemiju i razinu Hba1c nakon primjene 2 x 500mg askorbinske kiseline kroz 12 tjedana u dijabetičara tipa 2. U studiju je bilo uključeno 70 pacijenata. Inicijalno je pronađena niža razina vitamina C. Nakon primjene lijeka razina vitamina C, glikemija natašte, postprandijalna glikemija i razina Hba1c su pokazale značajno poboljšanje.[12] Tek nešto starija studija *Afkhami-Ardekani i sur* iz 2007. godine uključila je 84 pacijenta s dijabetesom tipa 2 koji su primali 500mg ili 1gr askorbinske kiseline kroz 6 tjedana. Zabilježeno je značajno smanjenje glikemije natašte, Hba1c, kao i triglicerida u grupi pacijenata na 1 gr. vitamina C.[13]

Postoje dokazi da dodatak vitamina C inzulinskoj terapiji također donosi dobrobit. Studija *Evansa i sur* iz 2003. kod 20 dijabetičara s tipom 2 koji su liječeni lispro inzulinom uz dodatak vitamina C 1 gr/dan pokazala je da inzulin popravlja postprandijalni lipidni metabolizam, što ima povoljan utjecaj na funkciju endotela, a vitamin C smanjujući oksidativni stres dodatno poboljšava endotelnu funkciju.[14]

Vitamin C i makrovaskularne komplikacije dijabetesa

Makrovaskularni poremećaji dobro su poznate kronične komplikacije dijabetesa. Uključuju kardiovaskularne, cerebrovaskularne i komplikacije na perifernim krvnim žilama. Dugi niz godina je poznato da je šećerna bolest povezana s povećanim rizikom zatajivanja srca. Smatra se da se to djelomično može objasniti stresom endoplazmatskog retikuluma i apoptozom stanice. Bjelančevina disulfid izomeraza (engl. *protein disulfide isomerase*, PDI) sprječava stresnu apoptozu miocita. U srcima pacijenata oboljelih od dijabetesa nakon ishemije postoji povećana razina PDI s paradoksnim sniženjem aktivne forme iste bjelančevine, što objašnjava smanjenu zaštitnu ulogu ove bjelančevine. Dehidroaskorbat popravlja učinak PDI i smanjuje postinfarktno remodeliranje srca.[15] Endotelna disfunkcija, zadebljanje intime i promjene u repolarizaciji klijetki pridonose povećanom kardiovaskularnom morbiditetu u pacijenata oboljelih od dijabetesa tipa 1.[16]

diabetes, so it is concluded that smoking and diabetes combined have a negative influence on vitamin C level in serum.[9]

The data on connection of diabetes type 2 prevalence and vitamin C intake are obviously controversial, but they are not less important as a possible public health suggestion on the need of dietary ingredients consumption which are rich in vitamin C.

Vitamin C and glycaemia regulation

There are three criteria for a good regulation of diabetes; satisfactory glycaemia on an empty stomach, satisfactory postprandial glycaemia and satisfactory level of Hba1c (fractions of glycosylated hemoglobin).[10] In 2008, the criteria of a good regulation became even stricter, so not so long ago people thought that diabetes was well regulated if it satisfied the following criteria; fasting glycaemia <5.5mmol, postprandial glycaemia <7.8mmol and Hba1c <6.5%.[9] In April, 2012 new guidelines were published, recommended by professional institutions for diabetes type 2 treatment such as ADA and EASD, which do not mention unique strict criteria of "glucotriade" (fasting glycaemia, postprandial glycaemia and Hba1c) for satisfactory control of the disease, but they put the individual approach to each patient in the foreground. This way, for example, the satisfactory criteria of the disease control for a younger diabetic, with a shorter "diabetic's period" and with fewer chronic complications, are much stricter than for an older diabetic patient, who has had diabetes for a longer period of time followed by developed chronic complications. We must also take into account the fourth criterion of good regulation, which is the glycaemia level stability.[11]

There are only a few professional articles on vitamin C influence on diabetes regulation. The study of *Ganesh et al* from the year 2011 explored the influence of vitamin C on fasting glycaemia, postprandial glycaemia and the level of Hba1c after supplementation of 2x500 mg of ascorbic acid throughout 12 weeks among patients with diabetes type 2. The study included 70 patients. Initially, a lower level of vitamin C was found. After administering the medicine, the level of vitamin C, fasting glycaemia, postprandial glycaemia and the level of Hba1c showed a considerable improvement.[12] An earlier study by *Afkhami-Ardekani et al* conducted in 2007 included 84 patients with type 2 diabetes who were administered either 500mg or 1gram of ascorbic acid throughout 6 weeks. A considerable decrease was noted in glycaemia on an empty stomach, Hba1c, as well as in triglycerides and Hba1c within the group of patients who were administered 1 gram of vitamin C.[13]

There is some evidence that vitamin C supplement to the insulin therapy is also beneficial for the patients. The study by *Evans et al* study conducted in 2003 on twenty patients suffering from diabetes type 2, who were treated by Insulin Lispro with vitamin C addition/supplement in the amount of 1 gram per day, showed that insulin repairs postprandial lipid metabolism, which has a beneficial influence on the endothelium function, while vitamin C additionally improves endothelium function by decreasing oxidative stress.[14]

Vitamin C and macrovascular complications of diabetes

Macrovascular complications are well known chronic complications of diabetes. They include cardiovascular and cerebrovascular, as well as complications on peripheral blood vessels. It has been known for a long period of time that diabetes is connected to a higher risk of heart failure. It can partly be explained by endoplasmatic reticulum stress and cell apoptosis. Protein Disulfide Isomerise (PDI) stops stres-

Studija *Odemarsky i sur* iz 2009. proučavala je debljinu intime karotida, mikrovaskularnu funkciju u koži i duljinu QT(c) intervala u 59 pacijenata s dijabetesom tipa 1 utvrdila je da su niže koncentracije C vitamina u ovih bolesnika povezane sa smetnjama u mikrocirkulaciji, perifernim arterijama i repolarizaciji klijetki.[16] MIVIT studija provedena 2006. godine kod 800 pacijenata, među kojima su bila 222 s dijabetesom, pokazala je značajan pad mortaliteta u pacijenta koji su dobivali vitamine C i E (antioksidante) u ranoj fazi bolesti. Ovog dodatnog povoljnog učinka nije bilo u pacijenata koji nisu dijabetes.[17]

Iako većina literature navodi povoljan učinak davanja vitamina C na smanjenje oksidativnog stresa, čini se da davanje visokih doza vitamina C kao dodatka prehrani možda ima i negativan učinak. Studija *Lee i sur* iz 2004. god. proučavala je povezanost uzimanja vitamina C s mortalitetom u postmenopauzalnih žena s dijabetesom tijekom 15 godina. Zaključak je da su visoke doze vitamina C iz dodataka prehrani povezane s višim rizikom od kardiovaskularne smrtnosti u postmenopauzalnih žena oboljelih od dijabetesa. Vitamin C iz hrane nije pokazao ovaj učinak. Negativan učinak vitamina C može se objasniti prooksidantnim učinkom vitamina C u određenim okolnostima in vitro.[18]

Hiperglikemija u pacijenata s moždanim udarom povezana je s lošijim neurološkim ishodom.[19] Kompromitacija endotelne funkcije moždanih krvnih žila, kao i narušavanje krvno moždane barijere, pridonose ovakvoj nepovoljnoj prognozi. U studiji *Alen i sur* na kulturi ljudskih moždanih endotelnih stanica (engl. *human brain microvascular endothelial cell*, HBMEC) i ljudskih astrocita koji su simulirali krvno moždanu barijeru, dokazano je da nakon 5 dana od simuliranog moždanog udara s hiperglikemijom nastaje značajno narušavanje krvno moždane barijere koje se može normalizirati regulacijom glikemije i dodavanjem antioksidanasa, uključujući vitamin C.[19]

Čini se da se i učestalost moždanog udara osim s dijabetesom, može povezati s prehrambenim navikama i kvalitetom prehrane. Prehrana s visokim totalnim antioksidativnim kapacitetom (engl. *total antioxidant capacity*, TAC) povezana je sa smanjenim rizikom moždanog udara. Talijanska studija *Del Rio i sur* iz 2011. God. proučavala je povezanost prehrane s visokim TAC i rizika od ishemijskog i hemoragijskog moždanog udara kod 41.620 pacijenata koji ranije nisu imali moždani ili srčani udar. Prehrana s visokim TAC bila je povezana sa smanjenim rizikom od svih tipova moždanog udara, a zanimljivo je da podaci iz iste studije ukazuju da je vitamin C jasno povezan sa smanjenjem rizika od ishemijskog, ali ne i hemoragijskog moždanog udara.[20] Studija *Lim i sur* iz 2011. god. kod 146 pacijenata s moždanim infarktom proučavala je kvalitetu prehrane i prehrambene navike. Uočeno je da pacijenti s moždanim infarktom češće preskaču obroke, neredovito se hrane i vole slaniju i začinjeniju hranu. Nutritivna gustoća (vitamin C, vitamin B_1, vitamin B_2, folat i kalcij) uzimani su u manjoj količini u odnosu na pacijente koji nisu imali moždani udar. Učestalost uzimanja voća i mliječnih proizvoda također je bila lošija u skupinii s moždanim udarom. U zaključku, pacijenti sa cerebrovaskularnim incidentom imali su nekvalitetniju prehranu.[21]

Učinak vitamina C na mozak posredovan je transporterima za C vitamin ovisnima o natriju (engl. *sodium-dependent ascorbat transporter*, SVCT1 i SVCT2). Ovi transporteri su ključni za održavanje intracelularne koncentracije vitamina C u gotovo svim tipovima stanica. SVCT2 transporteri su naraširenji u mozgu i neuroendokrinim tkivima. To su hidrofobne bjelančevine stanične membrane koje koncentriraju

sed myocyte apoptosis. The hearts of diabetes patients after ischemia contain an increased level of PDI with a paradox decrease of an active form of the same protein, which explains the decreased protective role of this protein. Dehydroascorbate repairs the effect of PDI and decreases post-heart attack remodelling of the heart.15 Endothelium dysfunction, intimal thickening and changes in repolarisation of ventricle contribute to the increased cardiovascular morbidity in patients suffering from diabetes type 1.[16]

The study by *Odemarsky et al* conducted in 2009, which explored the thickness of carotid intima-media, microvascular function in skin and the length of QT(c) interval in 59 patients with diabetes type 1, established that lower concentrations of vitamin C in those patients are connected to complications in microcirculation, peripheral arteries and ventricle repolarisation.16 MIVIT study conducted in 2006 among 800 patients, where 222 patients had diabetes, showed a considerable drop in mortality in patients who were given vitamins C and E (antioxidants) in the early stage of the disease. This additional beneficial effect was not present among patients who did not suffer from diabetes.[17]

Although a large amount of literature mentions a beneficial effect of administering vitamin C on the decrease in oxidative stress, it seems that administering high dosages of vitamin C as a dietary supplement can also have a negative effect. The study by *Lee et al* conducted in 2004 explored the connection of taking vitamin C with the mortality in postmenopausal women suffering from diabetes throughout 15 years. The conclusion is that high dosages of vitamin C from the dietary supplements are connected with a higher risk of cardiovascular death in postmenopausal women suffering from diabetes. Vitamin C from the diet did not show this effect. The negative effect of vitamin C can be explained by pro-oxidant effect of vitamin C in certain in vitro circumstances.[18]

Hyperglycaemia in patients having a stroke is connected with a worse neurologic outcome.[19] Compromising of endothelial function of brain blood vessels, as well as damaging the brain blood barrier contribute to such a negative prognosis. The study conducted by *Alen et al* on a culture of human brain microvascular endothelial cell (HBMEC) and on human astrocytes, which simulated the blood brain barrier, showed that after 5 days from the simulated stroke with hyperglycemia, a considerable damaging of blood brain barrier occurs, which can be normalized by glycemia regulation and by adding antioxidants, including vitamin C.[19]

It seems that the stroke frequency can apart from diabetes be connected to dietary habits and food quality. The diet with a high total antioxidant capacity (TAC) is connected with a decreased risk of stroke. An Italian study conducted by *Del Rio et al* in 2011 explored the connection of the diet with the high TAC and the risk of an ischemic and a hemorrhagic stroke in 41 620 patients, who did not have a stroke or a heart attack previously. The diet with the high TAC was connected with the decreased risk of all stroke types. It is interesting to note that the data from the same study suggest that vitamin C is clearly connected to the decrease of risk of the ischemic stroke, but not from the hemorrhagic one.[20] The study by *Lim et al* conducted in 2011 on 146 patients with a stroke explored the diet quality and dietary habits. It was noticed that the patients with a stroke skip their meals more often, they eat irregularly and like salty and spiced food. Nutritive density, including vitamin C, vitamin B_1, vitamin B_2, folate and calcium, were taken in a lower quantity in relation to the patients who did not have a stroke. Fruit and diary product consumption frequency also was worse in the group with the stroke. To conclude, the patients with cerebrovascular incidence had an inappropriate diet.[21]

askorbate intracelularno pomoću natrijskog gradijenta stvorenog Na/K pumpom.[22]

Na životinjskim modelima je pokazano da vitamin C u slučaju moždanog udara ima zaštitnu ulogu u moždanom tkivu. Imunohistokemijski je dokazano povećanje SVCT2 transportera u endotelu moždanih kapilara u subakutnoj fazi 2. do 5. dana nakon moždanog udara.[23]

Ishemija te zatim reperfuzija uzrokuju tkivno oštećenje i disfunkciju epitela krvožilja i na udovima. Poznato je da u tome ključnu ulogu ima oksidativni stres.

Narušena funkcija endotela može se popraviti intraarterijskim davanjem C vitamina kako nakon inducirane ishemije podlaktice u zdravih pojedinaca, tako i u pojedinaca koji već imaju razvijenu perifernu arterijsku bolest.[24] Nedvojbeni korisni učinak vitamina C na endotel krvnih žila ne pokazuje tako jasan korisni učinak u slučaju periferne ishemije na donjim udovima. Studija iz 2007. godine koja je proučavala 366 pacijenata sa stupnjem I i II periferne vaskularne bolesti dokumentirane angiografijom i ultrazvučno bilo je podijeljeno u četiri skupine. Prva skupina je dobivala acetilsalicilnu kiselinu100 mg na dan, druga je dobivala oralno antioksidanse (vitamin C i E, beta karoten), treća skupina je dobivala i acetilsalicilnu kiselinu i antioksidanse, a četvrta nije dobivala nikakvu terapiju. Podaci upućuju na povoljan utjecaj aspirina, ali ne i spomenutih vitamina na smanjenje incidencije vaskularnih događaja.[25]

Vitamin C i mikrovaskularne komplikacije dijabetesa

Mikrovaskularne komplikacije dijabetesa su uzrokovane promjenama na malim krvnim žilama ciljnih organa uzrokujući sindrome dijabetičke polineuropatije, retinopatije i nefropatije. I u patogenezi dijabetičke nefropatije oksidativni stres ima važnu ulogu.[26] Studija iz 2009. god. proučavala je varijable oksidativnog stresa (razinu superoksid dismutase, glutation peroksidaze, vitamina C, razinu serummalondialdehida i završnih produkata glikolizacije bjelančevina) u u 40 zdravih ljudi, 40 osoba oboljelih od šećerne bolesti tipa 2 te 37 osoba s dijabetesom i dijabetičkom nefropatijom. Razine superoksid dizmutaze, glutation peroksidaze i vitamina C su u osoba oboljelih od dijabetesa, a naročito u dijabetičara s već izraženom nefropatijom, bile snižene. Obrnuto, razina serumskog malondialdehida, završnih produkata oksidacije bjelančevina bile su najviše u dijabetičara s prisutnom dijabetičkom nefropatijom.[26]

Stoga zanimljivo zvuči hipoteza da dodatak antioksidanasa (vitamina C, E, N-acetilcisteina) može smanjiti upalu u bubrezima uzrokovanu dijabetesom. U radu *Park i sur* iz 2011. god. eksperimentalne životinje s dijabetesom izazvanom aloksonom dobivale su jedan ili više antioksidanasa. Nakon dva mjeseca životinje su žrtvovane i određene su urea i kreatinin kao parametri bubrežne funkcije. Pokazano je da primjena antioksidansa smanjuje koncentraciju ureje i kreatinina, a također se poboljšala regulacija glikemije i regulirala ekspresija bakar-cink superoksid dismutaze.[27] Ovi nalazi upućuju da je zatajivanje bubega kod dijabetesa povezano s upalnim odgovorom, a da primjena antioksidansa može polučiti povoljan učinak na razvoj dijabetičke nefropatije.[27] U radu *Lee i sur* na eksperimentalnim životinjama je dokazano da je skupina životinja s dijabetesom koja je primala i vitamin C imala manje apoptoze u stanicama epitela proksimalnih tubula bubrega, nižu razinu albuminurije, proteinurije, manje glomerularne i tubulointersticijalne skleroze,

The vitamin C effect on a brain is mediated by sodium-dependent ascorbat transporter, SVCT1 and SVCT2). These transporters are crucial for maintaining intracellular concentration of vitamin C in almost all cell types. SVCT2 transporters are the most spread in the brain and neuroendocrine tissues. Those are hydrophobic proteins of the cell membrane that concentrate ascorbates intracellularly by a sodium-potassium gradient established by Na/K pump.[22]

Animal samples showed that vitamin C, in case of a stroke, has a protective role in the cerebral tissue. Immunohistochemically, and increase in SVCT2 transporter in the endothelium of brain capillary has been proved in a sub-acute phase of the 2nd to 5th day after the stroke.[23]

Ishemia and reperfusion cause tissue damage and blood vessels epithelium dysfunction on the limbs. It is known that oxidative stress has a crucial role in this.

Endothelial function damage can be repaired by intra-arterial administration of vitamin C, both after the induced forearm ischemia in healthy individuals and in individuals who already have a developed peripheral arterial disease.[24] Undoubted beneficial effect of vitamin C on the endothelium of blood vessels does not show such a clear beneficial effect in case of peripheral ischemia on lower limbs. In a study conducted in 2007, which explored 366 patients suffering from I and II grade of peripheral artery disease documented by angiography and ultrasound, the patients were divided into four groups. The first group received 100mg aspirin/day, the second one received antioxidants orally (vitamins C and E, beta-carotene), the third group received both aspirin and antioxidants, while the fourth one did not receive any kind of therapy. Data suggest a positive influence of aspirin, but not the mentioned vitamins on a decrease in incidence of vascular events.[25]

Vitamin C and microvascular complications of diabetes

Microvascular complications of diabetes are caused by changes in small blood vessels target organs, thus causing syndromes of diabetes polyneuropathy, retinopathy and nephropathy. Oxidative stress has also an important role in the pathogenesis of diabetic nephropathy.[26] A study conducted in 2009 explored oxidative stress parameters (superoxide dismutase level, glutathione peroxsidase, vitamin C, serum malondialdehyde level and protein glycolisation of end products) in 40 healthy persons, 40 patients with diabetes type 2 and 37 patients with diabetes and diabetic nephropathy. The levels of superoxide dismutase, glutathione peroxsidase and vitamin C were decreased for patients with diabetes, especially among diabetic patients with already diagnosed nephropathy. On the other hand, the level of serum malondialdehyde and protein oxidation end-products were highest in the group of diabetic patients with diabetic nephropathy.[26]

Therefore, the hypothesis that antioxidants additives (vitamins C, E, N-acetylcysteine) can decrease inflammation in kidneys caused by diabetes sounds interesting. The 2011 article by *Park et al* deals with experimental animals suffering from diabetes induced by aloxsone received one or more antioxidants. After two months, the animals were sacrificed and urea and creatinine were determined as parameters for kidney function. It was shown that antioxidant administration reduces urea and creatinine concentration, whereas the glycaemia regulation was improved and the copper-zinc expression of superoxide dismutase was regulated.[27] These results suggest that kidney failure in diabetes is connected

u odnosu na skupinu koje nisu dobivale C vitamin.[28] Ovime je dokazano da blokiranje patofizioloških procesa oksidativnog stresa vitaminom C postaje koristan dodatak liječenju i albuminurije i renalne skleroze u dijabetičkoj nefropatiji te da možda usporava propadanje bubrežne funkcije radi smanjivanja apoptoze epitelnih stanica proksimalnog tubula.[28]

Dijabetička retinopatija predstavlja vodeći uzrok sljepoće u dijabetičara. Jedan od najznačajnijih patogenetskih događaja u nastanku te kronične komplikacije je propadanje pericita.[29] Pregledni članak *Lee i sur* iz 2010. god. obradio je 766 studija koje su se bavile mikronutrijentima i dijabetičkom retinopatijom. Za vitamin C pronađena je inverzna povezanost između razine u plazmi i retinopatije u hospitalnim studijama, a u populacijskim studijama takva povezanost nije pronađena.[30] Dvojbu u učinkovitost vitamina C na dijabetičku retinopatiju pobuđuje i pregledni rad *Lopes de Jesus i sur* koji su proučavali 240 publikacija i zaključili da nije provedeno ispitivanje koje bi adekvatno ispitalo utjecaj vitamina C superoksid dismutaze na dijabetičku retinopatiju, na takav način da to ima značajan utjecaj na na progresiju ovog stanja te da uporaba vitamina C i superoksid dismutaze u ovom slučaju ostaje dvojbena.[31]

Za nastanak dijabetičke neuropatije postoji nekoliko teorija. One uključuju metabolizam masnih kiselina, poremetnju krvnog optoka u živcima, završne produkte neenzimatske glikozilacije, oksidativni stres, aktivaciju poliolskog puta.[32] Aldoza reduktaza višak glukoze pretvara u sorbitol koji je odgovoran za edem i oštećenje živca. Koncentracija sorbitola može biti smanjena uzimanjem askorbinske kiseline koja inhibira aldoza reduktazu.[32] U radu *Farvid i sur* koji su 2011. proveli dvostruko slijepo kliničko ispitivanje kod 75 dijabetičara tipa 2 i koji su dobivali antioksidanse, uključujući i vitamin C u dozi 200 mg na dan neuropatski simptomi temeljeni na MNSI upitniku pokazuju poboljšanje. Zanimljivo je da su različite grupe pacijenata dobivale različitu kombinaciju antiksidanasa i da među njima nije bilo statistički značajne razlike.[33]

Dijabetička neuropatija može zahvatiti različite živce, stoga i klinička slika može imati razne oblike, primjerice oštećenje slušnog živca ili mijenteričkog pleksusa. Čini se da postoji povezanost između gubitka sluha i dijabetesa, što se može objasniti mikroangiopatijom, neuropatijom i encefalopatijom.[34] Dijabetičari tipa 2 imaju značajno više razine oksidativnih produkata bjelančevina, enzimatsku antioksidativnu aktivnost (glutation peroksidazu, superoksid dismutazu) u odnosu na kontrolnu skupinu, a oni s oštećenjem sluha imaju značajno nižu razinu oksida nitrata u odnosu na dijabetičare s normalnim sluhom. Također, postoji negativna korelacija između razine vitamina C i E i oštećenja sluha.[34] Primjena vitamina C eksperimentalnim životinjama u količini 1 gr/L također može pružiti umjerenu neuroprotekciju.[32]

Vitamin C i arterijska hipertenzija

Jedan od najvećih čimbenika rizika za kardiovaskularne bolesti je arterijska hipertenzija. Ova bolest odgovorna je za trećinu smrti uzrokovanih kardiovaskularnim bolestima.[35] U radu *Phyo i sur* kod 20.000 ispitanika iz 2011. god. dokazano je da je koncentracija vitamina C u plazmi u korelaciji s uzimanjem svježeg voća i povrća. Također postoji izravna linearna povezanost koncentracije vitamina C u plazmi i sistoličkog arterijskog tlaka (AT).[35] Još nekoliko studija ukazalo je na povoljan učinak dodatka vitamina C prehrani na vrijednost sistoličkog AT.[36] U radu *Carly i sur* navodi se studija

with inflammation response, and that antioxidants intake can result in a positive effect for the development of diabetic nephropathy.[27] The article by *Lee et al* deals with experimental animals that showed that the group of animas suffering from diabetes, which were also administered vitamin C, had less apoptosis in the epithelial cells of kidney proximal tubule, lower level albuminuria, proteinuria, less glomerular and tubulointerstitial sclerosis compared to the group of animals that were not administered any vitamin C.[28] This showed that blocking patophysiological processes of oxidative stress by vitamin C becomes a useful addition to the treatment of both albuminurial and renal sclerosis in diabetic nephropathy and that it may slow down the failure of kidney function due to the decrease of apoptosis in the epithelial cells of kidney proximal tubule.[28]

Diabetic retinopathy is the leading cause of blindness among diabetics. One of the most significant pathogenetic incidences in occurrence of this chronic complication of diabetes is pericytes loss.[29] A review article written by *Lee et al* in 2010 dealt with 766 studies, which explored micronutrients and diabetic retinopathy. It was discovered that vitamin C had a reverse connection between the level of vitamin C in plasma and retinopathy in hospital studies, while in population studies such a connection was not found.[30] The controverse regarding vitamin C efficacy on diabetic retinopathy was also aroused in the review article by *Lopes de Jesus et al*, that studied 240 publications and concluded that no research had been conducted that would appropriately examine the influence of vitamin C superoxide dismutase on diabetic retinopathy in order to prove that it has a significant influence on progression of this condition, so the administration of vitamin C and superoxide dismutase in this case remains doubtful.[31]

There are a few theories about diabetic neuropathy occurrence. They include fat acids metabolism, complications in blood flow in nerves, end products of nonezymic glycosylation, oxidative stress, activation of polyol pathway.[32] Aldose reductose transforms excess glucose into sorbitol, which is responsible for edema and nerves damage. Sorbitol concentration can be reduced by taking ascorbic acid that inhibits aldose reductose.[32] In the article by Farvid et al, who conducted a double blind clinical research on 75 patients suffering from diabetes type 2 in 2011, and who were given antioxidants, including vitamin C in the amount of 200 mg/day, the neuropathic symptoms, which were based on the MNSI questionnaire, showed improvements. It is interesting to note that various groups of patients were given different antioxidants combination and there were no significant differences in their statistics data.[33]

Diabetic neuropathy can affect various nerves, so the clinical features can have different forms, such as auditory nerve or myenteric plexus damage. It seems that there is a connection between the loss of hearing and diabetes, which can be explained by microangiopathy, neuropathy and encephalopathy.[34] The patients who suffer from diabetes type 2 have considerably higher levels of oxidative proteins, enzymatic antioxidant activity (glutathione peroxidase, superoxide dismutase) in comparison with the control group, while diabetics type 2 with hearing damage have considerably lower level of oxide nitrate in comparison with the diabetics with normal hearing. There is also a negative correlation between the level of vitamins C and E and hearing damage.[34] Giving vitamin C to experimental animals in the amount of 1 g/L can also provide a moderate neuroprotection.[32]

Vitamin C and hypertension

Hypertension is one of the most important risk factors for cardiovascular diseases. This disease is responsible for a

u kojoj su ispitanici dobivali dozu zasićenja vitaminom C od 2 grama, koju je slijedila dnevna doza od 500 mg kroz mjesec dana, registriran je pad sistoličkog AT od 13 mmHg. Zanimljivo je da dodatak vitamina C, čini se, nema utjecaja na vrijednost dijastoličkog AT.[36] Utjecaj koncentracije C vitamina u plazmi na sistolički AT izraženiji je u nepušača i bivših pušača. I u ovom slučaju djelovanje vitamina C je posljedica njegovih antioksidativnih i vazodilatacijskih svojstava.[35]

Zaključak

Hiperglikemija i posljedični oksidativni stress te arterijska hipertenzija predstavljaju značajne čimbenike za nastanak kardiovaskularnih i mikrovaskularnih kroničnih komplikacija dijabetesa. Uzimanje vitamina C, kao snažnog oksidansa, vjerojatno ima povoljan učinak na smanjenje oksidativnog stresa, a možda i na regulaciju same glikemije, iako su podaci o tome kontroverzni. U ovom trenutku, pacijente treba poticati na uzimanje svježeg voća i povrća, a trenutno dostupni podaci[37] ne preporučaju rutinsko i redovito uzimanje dodataka prehrani u svrhu smanjenja kardiovaskularnog rizika.

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third of deaths caused by cardiovascular diseases.[35] The article by *Phyo et al* conducted on 20,000 subjects in 2011 has proved that the concentration of vitamin C in plasma correlates with taking fresh fruit and vegetables. There is also a direct linear correlation between the concentration of vitamin C in plasma and systolic blood pressure (BP).[35] A few additional studies have showed a beneficial effect of vitamin C dietary supplement on systolic BP.[36] The article by *Carly et al* mentions the study where the subjects were given a 2 gram of vitamin C saturation dose, followed by a daily dose of 500mg, throughout one month's period, recording decreased systolic BP of 13 mmHg. It is interesting to note that the vitamin C supplement does not seem to have any impact on the value of diastolic BP.[36] The effect of concentration of vitamin C in plasma on a systolic BP is more pronounced in non-smokers and former smokers. Even in this case, the effect of vitamin C is the result of its antioxidant and vasodilatation properties.[35]

Conclusion

Hyperglycaemia, resulting oxidative stress and hypertension are some important factors for occurrence of cardiovascular and microvascular chronic diabetes complications. Taking vitamin C as a strong oxidant probably has a beneficial effect on oxidative stress decrease, even maybe on regulation of glycaemia itself, although the data on the above information are controversial. At the moment, patients should be encouraged to eat fresh fruit and vegetables, while the currently available data[37] do not advise routine and regular taking dietary supplements for the purpose of reducing cardiovascular risk.

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