Stručni rad

Razvoj kroničnih komplikacija u dijabetičara i potencijalni učinak antioksidansa u hrani

Professional article

Development of chronic complications in diabetics and potential role of food antioxidants

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SAŽETAK: *Dijabetes predstavlja najčešću endokrinološku bolest na svijetu. Samo dobra regulacija bolesti može usporiti razvoj kroničnih vaskularnih komplikacija. Oksidativni stres uzrokovan postprandijalnom hiperglikemijom značajan je patofiziološki čimbenik za nastanak kroničnih komplikacija dijabetesa. Glikemijski indeks hrane izravno utječe na postprandijalnu hiperglikemiju, time posredno na oksidativni stres odnosno upalu. U kontroli oksidativnog stresa uzrokovanog postprandijalnom hiperglikemijom potencijalnu ulogu imaju antioksidansi u hrani, što predstavlja zanimljivu i, u svakodnevnom radu, nedovoljno naglašenu terapeutsku mogućnost.*

KLJUČNE RIJEČI: *dijabetes, kronične vaskularne komplikacije, postprandijalna hiperglikemija, oksidativni stres, antioksidansi u hrani.*

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ABSTRACT: *Diabetes is the most common endocrynological disease in the world. Only the good disease control can slow down development of chronic vascular complications. Oxidative stress caused by postprandial hyperglycemia is a major patophysiological factor for chronic diabetic complications development. Dietary glycemic index directly affects on postprandial hyperglycemia, thus indirectly on oxidative stress and inflammation. Food antioxidants could have a potential role in control of oxidative stress caused by postprandial hyperglycemia, which represents an interesting terapeutic possibility in every day practice.*

KEYWORDS: *diabetes, chronic vascular complications, postprandial hyperglycemia, oxidative stress, food antioxidants.*

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Šećerna bolest ili diabetes mellitus predstavlja najčešću endokrinološku bolest u svijetu. To je istodobno i metabolička bolest višestruke etiologije, obilježena kroničnom hiperglikemijom i poremećajem mijene ugljikohidrata masti i bjelančevina koja se javlja kao posljedica poremećaja lučenja i/ili djelovanja inzulina.

Procjenjuje se da danas oko 150 milijuna ljudi diljem svijeta boluje od šećerne bolesti, a da će broj oboljelih do 2030. godine narasti na 370 milijuna. S obzirom na prevalenciju bolesti od 10%, razvidno je da se radi o pandemiji ove opasne bolesti. To je šesti najčešći uzrok smrti u Sjedinjenim Američkim Državama[1].

Postoji nekoliko tipova ove bolesti koji se razlikuju kako po nastanku, po načinu liječenja, kao i kliničkoj slici:

• Tip 1 (inzulin ovisni, "mladenački dijabetes, IDDM), koji nastaje radi apsolutnog manjka inzulina u organizmu;

• Tip 2 (inzulin neovisni), "starački dijabetes", NIDDM), koji nastaje radi relativnog manjka inzulina, odnosno njegove neučinkovitosti;

• Gestacijski dijabetes;

• Drugi posebni tipovi.

Najveći postotak oboljelih, više od 90% imaju dijabetes tipa 2, dijabetičari tipa 1 čine oko 8%, a ostatak su bolesnici s ostalim tipovima.

Ovakva distribucija oboljelih izravna je posljedica etiologije bolesti.

Smatra se da je tip 1 zapravo posljedica nedovoljno razjašnjenog autoimunog zbivanja koje za posljedicu ima prestanak lučenja inzulina iz beta stanica Langerhansovih otočića gušterače.

S druge strane tip 2 je posljedica genetske predispozicije, koja uz čimbenike rizika za bolest, odnosno čimbenika okoline (prehrana, debljina, nedostatak tjelesne aktivnosti) dovodi do otpornosti na inzulin, sve veće potrebe za inzulinom, posljedičnog relativnog nedostatka inzulina, koje na kraju dovodi do disfunkcije beta stanice, odnosno poremetnji mijene ugljikohidrata, masti i bjelančevina.

Iako postoji nekoliko vrsta šećerne bolesti, postulati liječenja šećerne bolesti su za oba najčešća tipa isti: pravilna prehrana, tjelovježba, samokontrola, peroralni hipoglikemizantni lijekovi, inzulin. Pridržavanjem ovih pet postulata liječenja (svih!) u velikoj većini slučajeva može se postići dobra regulacija glikemije, a time odgoditi nastajanje kroničnih mikro- i makrovaskularnih komplikacija. Ove komplikacije zapravo predstavljaju glavnu tegobu bolesnicima i najveći trošak osiguravajućim društvima, a poznata je činjenica da je vrlo malo bolesnika s dijabetesom uspjelo obuzdati svoju bolest.

Tri kriterija dobre regulacije šećerne bolesti su zadovoljavajuća glikemija na tašte, zadovoljavajuća postprandijalna glikemija te zadovoljavajuća razina HbA1c, frakcije glikoliziranog hemoglobina. Ovi kriteriji dobre regulacije dijabetesa su posljedica dogovora krovnih svjetskih udruga za praćenje i liječenje šećerne bolesti nakon rezultata dugogodišnjih studija (UKPDS i DCCT). Rezultati DCCT studije koja prati dijabetičare tipa 1 upućuju da smanjenje frakcije glikoliziranog hemoglobina za svega 1% smanjuje ukupni rizik razvoja dijabetičkih komlipacija za 21%, smanjenje rizika od mikrovaskularnih komplikaci-

Diabetes or diabetes mellitus is the most common endocrynological disease in the world. It is also a metabolic disease of a multiple etiology, characterized by chronic hyperglycemia and impairment in carbohydrates, fat, and protein exchange, which appears as a consequence of insulin secretion and/or action.

Some 150 milion people around the world are estimated to suffer from diabetes and the number of people effected by diabetes will rise up to 370 milion by 2030. Considering the prevalence of the illness to the amount of 10%, it can be seen that we are experiencing the pandemics of this dangerous disease. It is the sixth common cause of death in the United States[1].

There are several types of this disease, which are different in their origin, as well as in its treatment and clinical picture:

• Type 1 (insulin dependent, "juvenile diabetes", IDDM), which appears due to an absolute insulin deficiency in the organism;

• Type 2 (insulin independent, "adult-onset diabetes", NIDDM), which appears due to a relative insulin deficiency, i.e. its inefficiency;

• Gestational diabetes;

• Other special types.

The greatest percentage of affected persons, over 90 %, are those having type 2 diabetes, while only around 8% have type 1 diabetes. The rest are patients with other diabetes types.

Such a distribution of the affected persons is the direct consequence of the illness etiology.

The type 1 diabetes is actually considered to be the insufficiently explained autoimmune occurrence which, as a consequence, has interrupted insulin secretion from pancreatic islets of Langerhans beta cells.

On the other hand, type 2 diabetes is a consequence of a genetic predisposition which, together with diabetes risk factors, i.e. environment factors (food, obesity, lack of physical activity) leads to insulin resistance, a larger need for insulin, having the consequence of relative insulin insufficiency, which finally results in beta cells dysfunctioning, i.e. in impairment in carbohydrates, fat and protein exchange.

Although there are several types of diabetes, the treatment postulates for both types of diabetes are the same: healthy eating habits, exercises, self-control, peroral hypoglycemic drugs, insulin. Following the above mentioned five postulates of diabetes (all of them!), the majority of cases can achieve a good regulation of the disease, i.e. postpone the occurrence of chronic micro- and macrovascular complications, which cause the main problem for patients and the highest costs to insurance companies. The main fact is that only a small number of diabetes patients have managed to stop the disease entirely.

Three criteria of good diabetes control are: satisfactory glycemia on an empty stomach, satisfactory postprandial glycemia and a satisfactory level of HbA1c, a fractions of glycolized haemoglobin. These criteria of good diabetes regulation are the consequence of an agreement among the top world associations for monitoring and treatment of diabetes after many years of its studying (UKPDS and DCCT). The results of the DCCT study that monitors people with Type 1 diabetes indicates that decreasing the glycolized haemoglobin fraction by only 1% decreases the total risk development of diabetes complications by 21%, while the decrease of the risk in microvascular complications is 37%, and the risk of myocardial infarction is lower

ja je 37%, a rizik infarkta miokarda je manji 14%[2]. Studija UKPDS koja prati dijabetičare tipa 2 također zahtjeva sve strože kriterije dobre reguliranosti bolesti. Tako su preporuke dobre regulacije 2003. godine bile glikemija natašte niža od 7,2 mmol/L, postprandijalna glikemija do 10 mmol/L, a HbA1c niži od 7%[3]. Godine 2008. kriteriji dobre regulacije postaju još stroži te se danas smatra da je dijabetes dobro reguliran ako zadovoljava sljedeće kriterije: glikemija natašte niža od 5,5, postprandijalna glikemija niža od 7,8 mmol/L te HbA1 niži od 6,5%. Razlozi za pooštrenje kriterija dobre regulacije leže u patofiziologiji razvoja kroničnih komplikacija dijabetesa.

Patofiziologija razvoja kroničnih komplikacija šećerne bolesti

Povišen rizik razvoja kroničnih komplikacija u dijabetičara je posljedica zajedničkog djelovanja čimbenika rizika poput dislipidemije, arterijske hipertenzije, hiperglikemije, hiperinzulinemije. Povećani oksidativni stres sa stvaranjem završnih produkata glukozilacije, tromboza i fibrinoliza dovode do progresije ateroskleroze i pojave neželjenih kardiovaskularnih događaja[4].

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 pak posljedica smanjene raspoloživosti antioksidanata. Povećanje oksidativnog stresa odvija se preko nekoliko metaboličkih putova uključujući poliolski put, stvaranje krajnjih produkata glukozilacije, stvaranje malih LDL čestica. Stoga oksidativni stres kroz proizvodnju slobodnih kisikovih radikala ima glavnu ulogu u patogenezi oštećenja krvožilja, posebice oštećenju endotela krvožilja[4]. Anion superoksida, jednog od kisikovih slobodnih radikala, nastaje redukcijom molekularnog kisika. U to je uključeno nekoliko enzima npr. ksantin oksidaza, NADH/NADPH oksidaza, lipooksigenaza. Anioni superoksida se reduciraju do hidrogen peroksida ili spontano ili enzimatski. Reakcije u koje su uključeni željezo i bakar stvaraju visoko toksične hidroksi radikale. Hiperglikemija inducira stvaranje aniona superoksida mitohondrijskim lancem transporta elektrona. Prekomjerna produkcija aniona superoksida je povezana s povećanom produkcijom NO što dovodi do stvaranja peroksinitrita, vrlo jakog oksidanta, odgovornog za oštećenja DNA[4].

Nastajanje završnih produkata glukozilacije je posljedica neenzimatskog glukoziliranja lipida i bjelančevina. Glukozilacijom bjelančevina stvaraju se se labave kovalentne veze između glukoze i amino skupine bjelančevine i lipida (Shiffove baze) što u daljnjoj reakciji tvori ketoamin (Amadori produkt). Nastaje kumulativno oksidativno oštećenje bjelančevina krvnih žila (bazalne membrane) koje dovodi do mikrovaskularnih dijabetičkih komplikacija. Završni produkti glikozilacije lipida, nastaju okidacijom postraničnih lanaca nezasićenih masnih kiselina, pridonose stresu reagirajući s amino skupinama, mahom ostacima lizina. Daljnja glukooksidacija lipoproteina je vjerojatno odgovorna za razvoj makrovaskularnih komplikacija u dijabetičara[5].

than 14%[2]. The UKPDS study that monitors people with Type 2 diabetes also requires more strict criteria for good diabetes regulation. The recommendations for good diabetes regulations in 2003 were glycemia on an empty stomach lower than 7.2 mmol/L, postprandial glycemia up to 10 mmol/L, and HbA1c lower than 7%[3]. In 2008 the criteria of good regulation became even more strict and we consider diabetes well regulated today if it satisfies the following criteria: glycemia on an empty stomach lower than 5.5 mmol/L, postprandial glycemia lower than 7.8 mmol/L, and HbA1c lower than 6.5%. The reasons for making the criteria for good regulation stricter lie in pathophysiology of diabetes chronic complications development.

Pathophysiology of diabetes chronic complications development

A higher risk of cardiovascular events in people with diabetes is a consequence of risk factors, such as dyslipidemia, hypertension, hyperglycemia, hyperinsulinemia. Increased oxidative stress with creation of end products of glucolisation, thrombosis and fibrinolysis leads to progression of atherosclerosis and occurrence of cardiovascular events[4].

Oxidative stress, one of the risk factors, is an imbalance in redox organism state. It is caused by excessive consumption of oxidative substances or inadequate nutritive substance intake with antioxidant action such as vitamins E and C, charotenoides, polyphenols, selenium, or it is a consequence of decreased availability of antioxidants. The increase of oxidative stress happens through several metabolic paths, including the poliol path, creation of glucolisation end products, creation of small LDL particles. Therefore oxidative stress, by producing reactive oxygen species plays a pivotal role in the pathogenesis of vascular failure, especially vascular endothelial dysfunction[4]. Superoxide anion, one of the oxygen free radicals, is created by molecular oxygen reduction. This includes a few enzymes such as xanthine oxidase, NADH/NADPH oxidase, lipoxygenase. Superoxide anions are reduced to hydrogen peroxide either spontaneously or enzymatically. Reactions which include iron and copper create highly toxic hydroxy radicals. Hyperglycemia induces creation of superoxide anion by a mitochondrial electron transport chain. An excessive anion superoxide production is connected with an increased production of NO, which leads to creation of peroxynitrite, a very strong oxidant responsible for DNA damaging[4].

The creation of glucolisation end products is the consequence of nonenzymatic glucolisation of lipids and proteins. Proteins glucolisation causes the creation of a weak covalent bond between glucose and the amino group of proteins and lipids (Shiff's base), which, in further reaction, form ketoamine (Amadori product). The above causes a cumulative oxidative damage of blood vessels proteins (basal membrane), which leads to microrvascular diabetic complications. Lipids glycosylation end products are the result of oxidation of non-saturated fatty acid side chains and contribute to stress in reaction with amino groups, mainly lysine residues. Further lipoprotein gluco-oxidation is probably responsible for macro-vascular complications development in diabetics[5].

Utjecaj glikemijskog indeksa hrane na oksidativni stres

Glikemijski indeks hrane predstavlja sposobnost određenog obroka (50 grama ugljikohidrata) da povisi razinu glukoze u krvi u usporedbi s referentnom hranom (50 grama glukoze ili bijelog kruha). Smatra se da hrana ima niski glikemijski indeks ako je niži od 55, umjereni od 55 do 70, a visoki više od 70.

Oksidativni stres potaknut uzimanjem hrane s visokim glikemijskim indeksom je prvi događaj u metaboličkoj kaskadi povišenog rizika za kardivaskularni događaj. Interventne studije ukazuju da hrana s visokim glikemijskim indeksom, u usporedbi s hranom niskog glikemijskog indeksa, uzrokuju inzulinsku rezistenciju, povišene vrijednosti triglicerida, sniženje vrijednosti LDL, povišenje CRP i povišenje plasminogen aktivator inhibitor-1[6].

Studija Botera i suradnika[6], iz 2009. godine, imala je za cilj proučiti učinak hrane s različitim glikemijskim indeksom na antioksidativni kapacitet, oksidativni stres i čimbenike rizika za kardiovaskularne bolesti i dijabetes kod pretilih zdravih osoba. Mjerene su totalni antioksidativni kapacitet, (totalni antioksidativni kapacitet i kapacitet apsorpcije kisikovih radikala, ORAC) oksidativni stres (mokraćni F 2 alfa isoprostan), funkcija endotela, proizvodnja NO, osjetljivost na inzulin, funkcija beta stanica, lipidogram, PAI-1, fibrinogen i CRP. Nakon gladovanja totalni antioksidativni kapacitet je bio značajno viši tijekom uzimanja hrane niskog glikemijskog indeksa u usporedbi s razdobljem hranjenja s visokim glikemijskim indeksom. Poboljšanje u totalnom antioksidativnom kapacitetu plazme nastupa nakon 1 tjedna dijete s niskim glikemijskim indeksom.

Studija iz 2008. godine[7] ukazuje na činjenicu da prehrana s niskim glikemijskim indeksom snižava PAI-1 (marker upale) natašte, stoga može biti korisna za smanjenje krvožilnih pojavnosti oksidativnog stresa. Dodatni dokaz smanjenju oksidativnog stresa pruža kanadska studija[8]. Cilj te studije je bio usporediti učinak hrane s različitim glikemijskim indeksom ili količinom ugljikohidrata na glikolizirani hemoglobin (HbA1c), glukozu u plazmi, vrijednosti lipida i CRP u dijabetičara tipa 2. Studija je zabilježila smanjenje postprandijalne glikemije i CRP u korelaciji sa nižim glikemijskim indeksom.

Postprandijalna hiperglikemija i oksidativni stres

Postprandijalna hiperglikemija predstavlja jedan od čimbenika rizika za nastajanje oštećenja zida krvne žile i karakterizirana je skokovima glikemije koji induciraju oštećenje endotela, upalnu reakciju i oksidativni stres. Postoje dokazi da glikemija natašte, za razliku od postprandijalne hiperglikemije, nije neovisan čimbenik rizika za neželjeni kardiovaskularni događaj[4].

Postprandijalni oksidativni stres, kao podoblik nutritivnog oksidativnog stresa, karakterizira povećana osjetljivost organizma na oksidativno oštećenje nakon uzimanja hrane bogate lipidima i ugljikohidratima. Ovi makronutrijenti su u hrani ili u prooksidativnoj formi ili podliježu oksidativnoj modifikaciji nakon apsorpcije. Postprandijalno opterećenje ugljikohidratima i lipidima povećava ok-

Effects of dietary glycemic index on oxidative stress

The Dietary Glycemic Index is a capability of a certain meal (50 grams of carbohydrates) to increase the glucose level in blood in comparison with the reference food (50 grams of glucose or white bread). Food is considered to have a low glycemic index if it is lower than 55, an average one is from 55 to 70, and a high index is higher than 70.

Oxidative stress induced by taking food with a high glycemic index is the first event in the metabolic cascade of increased risk for cardiovascular events. Interventional studies suggest that a diet with the high glycemic index compared with a diet with the low glycemic index causes insulin resistance, an increase in triglycerides, a decrease in LDL, an increase in CRP and an increase in plasminogen activator inhibitor-1[6].

The study by Diego Botero et al[6] conducted in 2009 was aimed at examining the effect of a diet with a different glycemic index on antioxidative capacity, oxidative stress and risk factors for cardiovascular diseases and diabetes with obese healthy people. Measurements included antioxidative capacity, (total antioxidative capacity and oxygen radicals absorbtion capacity, ORAC), oxidative stress (urine F 2 alpha isoprostane), endothelial function, NO production, insulin sensitivity, beta cell function, lipidogram, PAI-1, fibrinogen and CRP. After fasting, the total antioxidative capacity was significantly higher during the diet with the lower glycemic index compared to the period of the diet with the high glycemic index. An improvement in the total plasma antioxidative capacity appears after 1 week of dieting with the low glycemic index.

Another study[7] conducted in 2008 suggests that diet with low glycemic index reduces fasting plasma PAI-1 (inflammatory marker) activity and therefore may be useful for diminishing the adverse cardiovascular effects of oxidative stress. Additional proof of reduction of oxidative stress (inflammation) provides study conducted in Canada[8]. The aim of the study was to compare the effects of altering the glycemic index or the amount of carbohydrate on glycated hemoglobin (HbA1c), plasma glucose, lipids, and C-reactive protein in Type 2 diabetic patients. The study recorded sustained reductions in postprandial glucose and CRP (inflammatory marker).

Postprandial hyperglycemia and oxidative stress

Postprandial hyperglycemia is one of the factors for blood vessel wall damage and it is characterized by glycemia fluctuations which induce endothelium damage, inflammatory reaction and oxidative stress. There is evidence that glycemia on an empty stomach, as opposed to postprandial hyperglycemia, is not an independent risk factor for an undesired cardiovascular event[4].

Postprandial oxidative stress, as a sub-form of the nutritional oxidative stress, is characterized by an increased susceptibility of the organism to oxidative damage after consumption of food rich in lipids and carbohydrates. These macronutrients are present in food either in a prooxidant form or they are subject to oxidative modifications after absorption. Postprandial increases of lipid and carbohydrate

sidativni stres što je povezano s povišenim rizikom razvoja kroničnih komplikacija šećerne bolesti[9]. Za vrijeme jela postoji značajno povećanje glukoze, inzulina, triglicerida i oksidacije LDL u plazmi uz pad oksidativnog kapaciteta plazme (TRAP). Uzimanje hrane koja sadrži oksidirane lipide podiže razinu lipidnih peroksida u plazmi. Isto tako koncentracija trigliceridima bogatih lipoproteina u obliku hilomikrona u plazmi, zahvaljujući zapadnjačkoj dijeti radi koje je osoba veći dio dana u postprandijalnom stanju, dovodi do kontinuiranog stresa na stijenku krvne žile, što pridonosi ubrzanju ateroskleroze[9]. Stresu stijenke krvne žile pridonosi i poremećena vazodilatacija radi poremećenog stvaranja NO. Čini se da hiperkolesterolemija uzrokuje nepravilnu funkciju NO sintetaze u endotelu krvnih žila. Stoga postprandijalna hiperglikemja i hiperlipidemija kroz oksidativni stres mogu imati izravni toksični učinak na endotel krvnih žila, neovisno o drugim čimbenicima rizika. Tako ponavljana ishemija-reperfuzija uzrokuje oksidativni stres. Ovo je vjerojatno jedan od načina na koji nastaje periferna dijabetička neuropatija. S druge strane, postoje dokazi da ljudi koji se pretežno hrane mediteranskom prehranom imaju značajno manji rizik neželjenih kardiovaskularnih događaja, metaboličkog sindroma, malignih bolesti i žive duže[10]. Mediteranska prehrana također poboljšava funkciju endotela što je vjerojatno povezano sa širokim spektrom antioksidanasa koje takva prehrana sadrži[11].

Postprandijalna hiperglikemija stoga predstavlja jedan od vrlo važnih patofizioloških stanja koje značajno pridonosi oštećenju krvožilja. Sukladno tome, kontroliranje postprandijalne hiperglikemije bi trebalo biti u žarištu terapije kao cilj u prevenciji oštećenja krvnih žila.

Uloga antioksidansa u hrani u smanjenju oksidativnog stresa

U hrani postoje mnogobrojni antioksidansi s jasnim antioksidativnim učinkom, stoga ovo područje nudi mnogobrojne mogućnosti istraživanja. Studija američkih autora iz 2006. godine učinjena na 13 dijabetičara tipa 2 koji su dobivali termički obrađenu hranu s visokim sadržajem završnih produkata glikozilacije ukazuje da uzimanje benfotiamina (1,050 mg/dan) smanjuje mikro- i makrovaskularnu disfunkciju endotela krvnih žila[12].

Terapijsko smanjenje postprandijalne hiperglikemije inzulinom na oksidativni stres može se postići uzimanjem 1 grama vitamina C dnevno[13]. Oksidativni stres je povezan sa sniženom razinom askorbata koji su posebno učinkoviti u zaštiti endotela krvnih žila. Jedan od putova ulaska C vitamina u stanicu je i pomoću transportera za glukozu (GLUT 1, GLUT 2). Ovim putem vitamin C ulazi u oksidiranom obliku dehidroksiaskorbata za vrijeme upale, pokazujući zatim svoju zaštitnu funkciju u stanici. Kako je poznato da je u šećernoj bolesti upravo oštećen mehanizam ulaska glukoze preko ovih transportera, može se postaviti pitanje dostatnog ulaska i oksidiranog vitamina C u stanicu ovim putem. Posljedično to može imati utjecaja i na razinu oksidativnog stresa u stanici[14]. Stoga podizanje nivoa vitamina C ima pozitivan učinak u bolestima uzrokovanim oksidativnim stresom.

Kao što je spomenuto ranije mediteranska prehrana koja uključuje i umjerenu konzumaciju vina ima povoljan

levels lead to increased oxidative stress, which has been associated with increased risk for the development of diabetes chronic complications[9]. During the meal there is a significant increase of glucose, insulin, triglycerides and LDL oxidation in plasma, while the oxidative capacity of plasma is falling (TRAP). Consumption of food containing oxidized lipids increases the level of lipid peroxides in plasma. Also, accumulation of triglyceride-rich lipoproteins in the form of hilomicrones in plasma, thanks to a western diet which keeps a person in postprandial state most of the day, leads to a continuous stress on a blood vessel wall, which contributes to a faster development of atherosclerosis[9]. The blood vessel wall stress is contributed by impaired vasodilation due to an impaired NO formation. The hypercholesterolemia seems to cause an impaired NO synthase in blood vessels endothelium. Therefore postprandial hyperglycemia and hyperlipidemia can have a direct toxic effect on blood vessel endothelium through oxidative stress, irrespective of other risk factors. In such a way repeated ischemia — reperfusion causes additional oxidative stress. This may be one of the ways how diabetic peripheral neuropathy occurs. On the other hand there is evidence that people who follow a Mediterranean diet are at much lower risk of cardiovascular events, metabolic syndrome, cancer, and tend to have a longer life-span[10]. A Mediterranean diet has also been shown to improve endothelial function. This may be related to the broad combination of antioxidants included in this type of diet[11].

Postprandial hyperglycemia is therefore one of the very important pathophysiological states contributing to vascular failure. Accordingly, controlling postprandial hyperglycemia should be the focus of therapy as a potential target for preventing vascular failure.

Role of food antioxidants in oxidative stress decrease

There are numerous antioxidants in food with clear antioxidant effect, so this area offers numerous researching possibilities. A study by American authors was conducted in 2006 on 13 type 2 diabetics, who were given thermally processed food with a high content of glycosylation end products, shows that taking of benfotiamine (1,050 mg/day) decreases micro- and macrovascular disfunction of blood vessels endothelium[12].

Therapeutic decrease of postprandial hyperglycemia by insulin on oxidative stress can result in additional benefits by taking 1 g of vitamin C a day[13]. Oxidative stress seems to be connected with a lowered level of ascorbates. Ascorbates are especially efficient in protection of blood vessels endothelium. One of the ways vitamin C enters a cell is through a glucose transporter (GLUT 1, GLUT 2). This way, vitamin C enters in dehydroxyascorbate oxidative form during the inflammation, showing its protective function in the cell. Since it is known that diabetes deals with damaged mechanism of glucose entrance through the above mentioned transporters, we can question if there is enough glucose entered as well as oxidized vitamin C in the cell. Consequently, this can even have influence the level of oxidative stress in the cell[14]. Therefore, rising the level of vitamin C can have a positive effect in diseases which includes oxidative stress.

As mentioned above, Mediterranean diet which includes moderate wine drinking has beneficial effect on oxida-

učinak na oksidativni stres. Konzumiranje vina natašte značajno povisuje antioksidativnu sposobnost plazme[15]. Resveratrol, jedan od prirodnih polifenola, smanjuje nastajanje slobodnih kisikovih radikala (mtROS) i u stanju mirovanja i za vrijeme opterećenja glukozom u kulturama stanica endotela. Ovaj učinak može biti smanjen obaranjem bjelančevine deacetilaze SIRT 1. Pretpostavka je da resveratrol preko metaboličkog puta koji uključuje aktivaciju SIRT 1 smanjuje nastajanje slobodnih kisikovih radikala u mitohondrijima, što pobuđuje nadu u novi terapijski pristup nastajanju kroničnog oštećenja stijenke krvne žile tijekom oksidativnog stresa[16].

Jedan od najjačih prirodnih izvora antioksidanta je kakao. Antioksidativni učinak flavonoida na endotel krvnih žila posredovan je i sprečavanjem oksidativne konverzije NO u peroksinitrit. Sukladno tome flavonoidi kakaa smanjuju produkciju peroksinitrita. U odraslih kakao napitci poboljšavaju vazodilataciju posredovanu sa NO, time smanjujući stres na stijenku krvne žile[17]. Epikatehin i slični procijanidi su najzastupljeniji među polifenolima kakaa, ali se niti uloga quercetina ne zaobići. Iako je njihova koncentracija u kakau mnogo puta manja, njihov učinak na inhibiciju lipooksigenaze je mnogostruko jači[18].

Ekstrakt čaja (crni i zeleni čaj) nastaje od lišća biljke Camellia sinensis. Najčešći flavonoli i antioksidanti zastupljeni u čaju su: epigalokatehin-3-galat, epigalokatehin, epikatehin-3-galat i epikatehin. Epigalokatehin-3-galat i epikatehin imaju najjaču sposobnost skupljanja kisikovih radikala[19]. Znatan broj studija sa crnim i zelenim čajem pokazuju značajan porast antioksidativnog kapaciteta plazme otprilike 1 sat nakon uzimanja čaja[20].

Antioksidativna svojstva vitamina E su dugo znana i intenzivno proučavana. Skupinu vitamina E čine tokoferoli i tokotrienoli. Najučinkovitiji predstavnik je alfa tokoferol. Studija iz 2007. godine proučavala je 55 pacijenta s tipom 2 dijabetesa koji su dobivali 500 mg na dan alfa tokoferola. Mjereni su stanični tokoferoli, F2 isoprostani, antioksidativna aktivnost eritrocita, upalni parametri u plazmi. Zaključeno je da je dodatak vitamina E pacijentima s tipom 2 šećerne bolesti ima potencijalno povoljne učinke u pacijenata koji imaju loše reguliran dijabetes. Dodatak vitamina E u dobro kontroliranih dijabetičara tipa 2 nema dodatni povoljni učinak na smanjenje upale[21].

Zaključak

Trenutno se nalazimo usred pandemije šećerne bolesti i brzog rasta broja novooboljelih. Najveća potencijalna opasnost leži u porastu broja kroničnih makro- i mikrovaskularnih komplikacija, što stavlja velike zahtjeve pred zdravstvenu službu i zdravstvene fondove cijelog svijeta.

Kako je stres na endotel krvnih žila, a naročito oksidativni stres, potenciran postprandijalnom hiperglikemijom jedan od najvažnijih čimbenika nastanka ovih komplikacija, svaka mogućnost njegovog smanjivanja predstavlja zanimljiv terapeutski izazov.

Polifenoli i vitamini iz hrane potencijalno su vrlo efikasni antioksidansi te potencijalno posjeduju velike terapeutske mogućnosti. Nedostatak točnih podatka o njihovoj bioraspoloživosti u ljudi nameće potrebu daljnjih istraživanja, ali i upućuje na činjenicu da je za prevenciju kroničnih komplikacija dijabetesa najvažnija njegova dobra

tive stress. Consumption of wine on an empty stomach increases considerably antioxidant capability of plasma[15]. Resveratrol, one of the natural polyphenols, decreases formation of free oxygen radicals (mtROS) both while it stands still and while it is loaded with glucose in endothelium cells cultures. This effect can be lowered by deacetylase protein SIRT 1 knocking down. The assumption is that resveratrol, through a metabolic pathway which includes activation of SIRT 1, decreases production of mitochondrial free oxygen radicals, suggesting the potential for a new treatment approach to forming of a blood vessel wall chronic damage during oxidative stress[16].

One of the strongest natural antioxidant sources is cocoa. Antioxidant effect of flavonoids on blood vessels endothelium is also mediated by obstructing the oxidative conversion of NO into peroxynitrite. Taking this into account, flavonoids in cocoa decrease the peroxynitrite production. Cocoa beverages improve vasodilation through NO in adults which decreases the stress on the blood vessel wall[17]. Epicatechin and similar procyanidins are most present among cocoa polyphenols, but the role of quercetin must not be avoided. Although their concentration in cocoa is many times smaller, their influence on lipooxigenasis inhibition is much stronger[18].

A tea extract (black or green tea) comes from leaves of a plant called Camellia sinensis. The most common flavonols and antioxidants contained in tea are: epigallocatechin-3-gallate, epigallocatechin, epicatechin-3-gallate and epicatechin. Epigallocatechin-3-gallate and epicatechin have the strongest ability to collect oxygen radicals[19]. A considerable number of studies with black and green tea indicate a significant increase in antioxidant capacity of plasma around 1 hour after tea consumption[20].

Antioxidative characteristics of vitamin E have been known and studied for a long time. Vitamin E group consists of tocopherols and tocotrienols, and the most efficient representative is alpha tocopherol. A study from 2007 included 55 patients with type 2 diabetes who were given 500 mg of alpha tocopherol a day. Cell tocopherols, F2 isoprostanes, erythrocytes antioxidative activity, and inflammatory parameters in plasma were measured. It was concluded that vitamin E supplement in type 2 diabetes had potentially positive effects in patients with poorly regulated diabetes. Vitamin E supplement in well controlled type 2 diabetics had no additional positive effect on inflammatory process[21].

Conclusion

We are in the middle of a diabetes pandemics and fast growing of new people affected by this illness. The biggest potential danger of such a development of events lies in increasing number of chronic macro- and microvascular complications of diabetes, which requires a lot from health care and health funds all over the world.

Since the stress on blood vessel endothelium, especially oxidative stress, induced by postprandial hyperglycemia, is one of the most important factors for mentioned complications occurrence, every possibility of its reduction represents an interesting therapeutic challenge.

Polyphenols and vitamins from food are potentially very efficient antioxidants and they potentially have great therapeutic possibilities. Lack of accurate data on their bioavailability in people emphasizes the need for further

kontrola, odnosno uravnotežena prehrana kao neodvojivi dio liječenja te teške bolesti.

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research, but it also states the fact that for prevention of chronic complications in diabetes the most important is its control and a balanced diet, as an inseparable part of this dangerous illness treatment.

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