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PREKOMJERNA KONZUMACIJA KALCIJUMA KAO FAKTOR RIZIKA KARDIOVASKULARNIH BOLESTI

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Sažetak: Kalcijum je najzastupljeniji mineral u ljudskom tijelu koji učestvuje u izgradnji kostiju i zuba, prenosu nervnih impulsa, unutarćelijskoj signalizaciji, hormonskoj sekreciji, kontrakciji mišića, koagulaciji, osiguranju normalnog ritma srca i fiziološke vrijednosti krvnog pritiska Prekomjerna koncentracija kalcijuma, predominantno izazvana neprikladnom upotrebom suplemenata, predisponira razvoj kardiovaskularnih bolesti. Visoke vrijednosti kalcijuma u serumu indukuju reprogramiranje i diferencijaciju glatkih mišićnih ćelija u fenotip sličan osteoblastu, translokaciju prohipertrofičnih transkripcijskih faktora kardiomiocita, kompromitovanje dijastoličke relaksacije miokarda i nekrozu njegovog kontraktilnog pojasa, poticanje reakcija koagulacije, stimulaciju agregacije trombocita, hemodinamskih promjena i metaboličkih abnormalnosti. Akutna intoksikacija suplementima kalcijuma rezultuje povećanjem krvnog pritiska. Hronično konzumiranje prekomjerne količine kalcijuma predisponira aterosklerozu i kalcifikaciju krvnih sudova, srčani i moždani udar, hipertrofiju i insuficijenciju srca i poremećaje srčanog ritma. Postoji potreba za jačanjem odgovora i uloge zdravstvenog sistema u informisanju javnosti o nuspojavama prekomjerne konzumacije kalcijuma, ograničavanju širokog propisivanja suplemenata, kao i njihovoj eventualnoj sveobuhvatnoj ponovnoj procjeni.
Ključne riječi: kalcijum, toksičnost, suplementi kalcijuma, kardiovaskularni sistem

Kalcijum u tijelu čovjeka

Kalcijum je najzastupljeniji mineral u ljudskom tijelu (1,5-2% ukupne tjelesne mase, otprilike 1200 g) [1,2]. Oko 98% ukupnog kalcijuma u tijelu nalazi se u kostima [1,2]. Ostatak je lokalizovan u zubima (1%), tjelesnim tečnostima, mišićima i drugim tkivima (1%) [1,2]. U kostima je kalcijum prisutan u obliku kalcijum-fosfatnih kompleksa, prvenstveno hidroksiapatita koji čini gotovo 40% težine kosti [2]. Kosti predstavljaju lako dostupan izvor kalcijuma (50% jonizovanog i fiziološki aktivnog kalcijuma) [1]. U tjelesnim tečnostima može postojati kao slobodni katjon kalcijuma (50%), vezan za proteine (albumin, globulin, kalmodulin i drugi proteini, 40%) i druge jone (kalcijum fosfat, kalcijum karbonat i kalcijum oksalat, 10%) [3,4]. Koncentracija kalcijuma u serumu zdravih ljudi se nalazi u opsegu od 2,2 do 2,7 mmol/l- (milimola na litar krvi) ili 8,9 - 10,4 mg/dl [4].

Apsorpcija, izlučivanje i homeostaza kalcijuma

Kalcijum se apsorbuje aktivnim transportom (niski i umjereni nivo unosa) i pasivnom difuzijom (veliki unos)u tankom crijevu [2]. Aktivni transport regulišu 1,25-dihidroksivitamin D i njegovi crijevni receptori, dok pasivna difuzija podrazumjeva kretanje ovisno o gradijentu koncentracije [2]. Apsorpcija kalcijuma je obrnuto proporcionalna unosu (najviša je u dojenačkoj dobi i ranom pubertetu, sa starenjem postepeno opada) i nešto niža kod osoba ženskog pola [2]. Oko 50% kalcijuma u plazmi (jonizovani i složeni oblik, ultrafiltrabilna frakcija, isključujući oblik vezan na proteine) slobodno se filtrira kroz bubrežni glomerul, približno 99% istog se reapsorbuje duž tubula [5]. 24 sata urin odrasle osobe sadrži oko 200 mg kalcijuma [5]. U toku 24h fecesom se izluči 140 mg kalcijuma (mješavina neresorbovanog kalcijuma, kalcijuma iz ćelija sluznice i crijevnog sekreta), znojem 35±4 mg [6]. U homeostazi kalcijuma (u nivou koštanog sistema, bubrega i tankog creva) učestvuju paratiroidni hormon, kalcitriol (1,25-dihidroksiholekalciferol) i kalcitonin [7]. Paratiroidni hormon podstiče mobilizaciju kalcijuma iz kosti (stimulacija aktivnosti osteoklasta i osteocita), reapsorpciju kalcijuma u tubulima bubrega i sintezu kalcitriola u istom [7]. Kalcitriol povećava koncentraciju kalcijum-vezujuceg proteina u

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tankom crijevu, kalcitonin smanjuje resorpciju koštanog tkiva (inhibiranje aktivnosti osteoklasta) [7]. Homeostazi kalcijuma mogu doprinijeti estrogen, testosteron, hormoni nadbubrežne žlijezde, tiroksin, somatotropin i glukagon [6,7].

Preporučeni dnevni unos kalcijuma

U novorođenačkoj dobi se preporučuje unos 400 mg kalcijuma dnevno [6]. U uzrastu 1–3 godine 500 mg/dan, u uzrastu 4–6 godina 600 mg/dan, u uzrastu 7–9 godina 700 mg/dan [6]. U adolescenciji (uzrast 10–18 godina) se preporučuje unos 1300 mg kalcijuma dnevno, u uzrastu 19-65 godina oko 1000 mg/dan [6]. U uzrastu preko 65 godina preporučuje se unos 1300 mg kalcijuma dnevno, u trudnoći i dojenju 1200 mg/dan [6]. Preporučeni dnevni unos se povećava sa smanjenjem bioraspoloživosti (u situacijama prekomjenog konzumiranja hrane bogate oksalnom i fitinskom kiselinom: špinat, slatki krompir, rabarbara, grah, beskvasni hljeb, sirovi grah, sjemenke, orašasti plodovi, žitarice), ekstremnom fizičkom aktivnošću i mehaničkim opterećenjem, prekomjernom konzumacijom natrijum hlorida, amenorejom (anoreksija nervoza), intolerancijom na glukozu i vegetarijanskom ishranom [8].

Izvori kalcijuma

Unos kalcijuma obično je povezan sa konzumiranjem mliječnih proizvoda (100-180 mg kalcijuma u 100 g mlijeka i jogurta, 1 g kalcijuma u 100 g tvrdog sira) [8]. U 100 grama žitarica nalazi se 30 mg kalcijuma (obogaćenim, 100-180 mg) [8]. Orašasti plodovi i sjemenke (u prvom redu badem i sezam) su bogati kalcijumom (250-600 mg kalcijuma u 100 g). U 100 g kelja, brokule i potočarke, nalazi se 100-150 mg kalcijuma [8]. Ukupan unos kalcijuma iz pojedinih namirnica se mjenja u skladu sa obrascima potrošnje hrane u određenoj populaciji (mliječni proizvodi obezbjeđuju 72 i 58% ukupnog unosa kalcijuma u Sjedinjenim Američkim Državama i Holandiji, povrće obezbjeđuje 46,9% ukupnog unosa kalcijuma u Kini) [8].

Suplementi kalcijuma

Suplementi za oralnu upotrebu uključuju kalcijum u obliku kalcijum karbonata, kalcijum citrata, kalcijum glukonata, kalcijum laktata i kalcijum fosfata [9-12]. Kalcijum karbonat je najčešći i najisplativiji dodatak kalcijuma [9]. Kalcijum iz ovog jedinjenja ima apsorpciju sličnu kalcijumu iz mlijeka (uzima se uz obrok, ovisan je o niskoj vrijednosti ph) [9-12]. Kalcijum citrat se može uzimati bez hrane (predominantno kod osoba sa ahlorhidrijom, osoba koje koriste antagoniste receptora histamina tipa 2 ili inhibitore proteinske pumpe) [9]. Ima veću cijenu i manju efikasnostod kalcijum-karbonata (210 mg Ca u 1000 mg suplementa) [9-12]. Kalcijum glukonat i kalcijum laktat su manje koncentrovani oblici kalcijuma [9]. Upotreba kalcijum fosfata nije preporučena (ograničen broj istraživanja) [9]. U Sjedinjenim Američkim Državama i Kanadi 40% osoba uzrasta 19-65 godina i 70% žena uzrasta preko 65 godina koristi suplemente kalcijuma [8].

Uloga kalcijuma u tijelu čovjeka

Kalcijum učestvuje u izgradnji kostiju i zuba, prenosu nervnih impulsa, unutarćelijskoj signalizaciji, hormonskoj sekreciji, kontrakciji mišića, koagulaciji, osiguranju normalnog ritmasrca i fizološke vrijednosti krvnog pritiska [13].

Uloga kalcijuma u regulaciji krvnog pritiska

Kalcijum reguliše krvni pritisak putem vazokonstrikcije (promjene u koncentraciji unutarćelijskog kalcijuma u vaskularnim glatkim mišićnim) i povećanja vaskularnog volumena [14]. Svoje dejstvo ostvaruje putem paratiroidnog hormona, vitamina D i sistema renin-angiotenzin-aldosteron [14]. Unos kalcijuma je obrnuto proporcionalan koncentraciji paratiroidnog hormona u plazmi i visini krvnog pritiska [14]. Paratiroidni hormon reguliše krvni pritisak putem povećanja koncentracije slobodnog kalcijuma u citosolu (povećanja vaskularne reaktivnosti, perifernog vaskularnog otpora, reakcije na sistem renin-angiotenzin-aldosteron i simpatički nervni sistem) i receptora paratiroidnog hormona tipa 1 (spaja signalne puteve Gαs adenilat ciklaze, protein kinaze A, Gαq fosfolipaze C, β inozitol trifosfata, unutarćelijskog kalcijuma, protein kinaze C, Gα12/13 fosfolipaze D, RhoA i signalne kaskade aktivirane mitogenom protein kinazom) [14]. Povećana koncentracija kalcitriola modulira krvni pritisak genomskim (modifikacija transkripcijskih faktora ekspresije gena unutarćelijskih receptora vitamina D) i negenomskim mehanizmima (stimulacijom kalcijumskih kanala L-tipa putem cikličnog adenozin monofosfata, signalne kaskade adenilat

ciklaze/*cikličnog* adenozin monofosfata/protein kinaze A/fofolipaze C/inozitol fosfata i aktivacijom sistema za prenos kalcijuma) [14]. Unos kalcijuma je obrnuto proporcionalan aktivnosti sistema renin-angiotenzin-aldosteron (nizak unos stimuliiše oslobađanje renina, i posljedičnu sintezu angiotenzina II i aldosterona) [14].

Uloga kalcijuma u regulaciji srčanog rada

Normalna funkcija srca zahtijeva dovoljno visoku koncentraciju kalcijuma u sistoli i nisku u dijastoli [15,16]. Kalcijum predstavlja važan regulator srčane funkcije koji povezuje električnu depolarizaciju sa kontrakcijom kardiomiocita [15,16]. Intracelularni porast kalcijuma omogućava kontraktilnim nitima aktina i miozina da se aktiviraju i klize jedna pored druge, čime skraćuju ćelije i stvaraju snagu za pokretanje krvi [15,16]. Depolarizacija uzrokovana akcionim potencijalom aktivira kalcijumove kanale pod naponom, što omogućava njegov protok preko sarkoplazmatskog retikuluma u citoplazmu [15,16]. Difundovanje kalcijumovih jona pokreće kontrakciju vezujući se za troponin C unutar miofibrila [15,16]. Zahvaljujući sekvestraciji u sarkoplazmatskom retikulumu (enzimskom procesu zavisnom od adenozin trifosfata) kalcijum se oporavlja do nivoa mirovanja (dijastole) [15,16]. Miociti također posjeduju sarkoplazmatsku kalcijum adenozin trifosfatazu(mali doprinos ekstruziji kalcijuma) [15,16]. Bliska povezanost između poprečnih tubula i sarkoplazmatskog retikulumau ventrikularnim miocitima osigurava sinhroni porast kalcijuma tokom sistole (što dokazujeizrazito heterogeni prijelaz kalcijuma od površine sarkoleme do ćelijskog centra kao posljedica hemijske detubulacije s formamidom) [15,16].

Uloga kalcijuma u koagulaciji

Kalcijumovi joni igraju važnu ulogu u regulaciji koagulacije. Osim aktivacije trombocita,odgovorni su za aktivaciju nekoliko faktora koagulacije, uključujući faktor koagulacije XIII (odgovoran za kovalentno umrežavanje formiranih ugrušaka fibrina, sprečavajući njihovu prevremenu fibrinolizu). Faktor koagulacije XIII cirkuliše u plazmi kao heterotetramerna protransglutaminaza sastavljena od dimernih podjedinica katalitičkog faktora koagulacije A i zaštitnih, regulatornih podjedinica faktora koagulacije B. Faktor koagulacije A se aktivira kombinacijom vezivanja kalcijuma i proteolitičkog cjepanja trombina N-terminalne 37-aminokiselinske regije [17]. U ekstrizičnom putu koagulacije krvi, faktor X aktivira se kompleksom tkivnog faktora, faktora VIIa i jona kalcijuma [18].

Smanjena konzumacija kalcijuma

Neadekvatan unos dijetalnog kalcijuma kratkoročno ne daje simptome [18-20]. Hipokalcemija nastaje kao rezultat medicinskih problema ili njihovog tretmana (hipoparatireoidizma, bubrežne insuficijencije, pseudohipoparatireoidizma, insuficijencija jetre, hirurškog uklanjanja želuca, nedostatka vitamina D, hipomagnezijemije, hipermagnezijemije, Fankonijevog sindroma, visoke doze intravenskih bifosfonata, visoke doze diuretika) [18-20]. Dugoročno, neadekvatan unos kalcijuma uzrokuje osteopeniju, osteoporozu i povećava rizik od prijeloma kostiju (osobe starije životne dobi) [18-20].

Prekomjerna konzumacija kalcijuma

Prekomjerna konzumacija suplemenata kalcijuma, poznata i kao sindrom suplementacije kalcijuma, predstavlja značajan uzrok hipekalcijemija (učestalost premašuju samo primarni hiperparatireoidizam i maligne bolesti) [21-24]. Povišenu koncentraciju kalcijuma u krvi predisponiraju hronične bolesti i lijekovi koji se koriste u njihovoj terapiji (tiazidni diuretici, inhibitori angiotenzin konvertujućeg enzima, blokatori angiotenzinskih receptora i nesteroidni antiupalni lijekovi) [21-24]. Hiperkalcemija predisponira smanjenje glomerularne filtracije, aterosklerozu, nekontrolisanu hipertenziju, progresivnu srčanu disfunkciju [21-24].

Prekomjerna konzumacija kalcijuma i hipertenzija

Prekomjeran unos suplemenata kalcijuma uzrokuje akutno povećanje koncentracije kalcijuma u serumu, porast krvnog pritiska i ukupnog perifernog vaskularnog otpora [25]. Akutna hiperkalcijemija rezultuje povećanim minutnim volumenom koji brzo napreduje u hemodinamski obrazac s povišenim perifernim vaskularnim otporom [25]. Povećanu koncentraciju kalcijuma u serumu karakteriše neprimjereno visok srčani volumen (izostanak

kompenzacijskog smanjenja srčanog rada uzrokovan perifernom vazokonstrikcijom) [25]. Hipertenzija nastaje kao posljedica direktnog uticaja kalcijuma na vaskularne glatke mišićne ćelije (oslobađanje kalcijuma iz sarkoplazmatskog retikuluma aktivira kalmodulin i miozin kinazu, skraćuje miofilamente i uzrokuje vazokonstrikciju), dok kalcijumom posredovano povećanje oslobađanja epinefrina iz medule nadbubrežne žlijezde doprinosi njenom razvoju [25,26]. Akutna hiperkalcijemija je praćena porastom hematokrita i padom volumena plazme (povećanjem kapilarne filtracije izazvano pritiskom, povećanjem natriureze), nepromjenjenom aktivnošću noradrenalina, renina, aldosterona i dopamina [25,26]. Studija grupe autora iz Kalifornije u kojoj je učestvovalo 57 osoba (7 osoba s normalnom funkcijom bubrega i 50 osoba s blagom do teškom insuficijencijom bubrega) utvrdila je postojanje statistički značajne povezanosti akutnog povećanja koncentracije kalcijuma u serumu i porasta sistolnog i dijastolnog krvnog pritiska (razvoj ili pogoršanje hipertenzija kod jedne osobe s normalnom funkcijom bubrega i 41 osobe s blagom do teškom insuficijencijom bubrega) [27]. Hipertenzivni odgovor na povećanje serumskog kalcijuma bio je izdraženiji kod pacijenata sa uznapredovalom bubrežnom insuficijencijom (serumski kreatinin > 4 mg/100 ml ili >320 μmol/L) [27].

Prekomjerna konzumacija kalcijuma, ateroskleroza i kalcifikacija krvnih sudova

Velike opservacione studije utvrdile su da povećanje koncentracije serumskog kalcijuma uzrokovano prekomjernom konzumacijom suplemenata (1g suplementa kalcijuma povećava koncentraciju serumskog kalcijuma 1,22–1,30 mmol/L), ali ne i kalcijuma u ishrani, doprinosi razvoju ateroskleroze i kalcifikacije krvnih sudova [28-32]. Kalcifikacija intime krvnih sudova potiče iz apoptičnih glatkih mišićnih ćelija ili matrikularnih vezikula koje se oslobađaju odu blizini unutrašnje elastične lamine [28]. Njen razvoj pospješuju odlaganje lipida i upala u neointimi [28]. Kalcifikacija se može se javiti i u medijalnom sloju (duž elastičnih lamela i okolnih glatkih mišićnih ćelija) [28]. Visoke koncentracija suplemenata kalcijuma indukuju reprogramiranje i diferencijaciju glatkih mišićnih ćelija u fenotip sličan osteoblastu i generišetaloženje vezikula kalcifikovanog matriksa u zidu krvnog suda [28]. Osim toga, opterećenje kalcijumom smanjuje paratiroidni hormon (povećava rizik od adinamičke ili niske koštane obnove) [28]. Studija američkih autora koja je obuhvatila 5448 odrasle osobe bez klinički dijagnostikovane kardiovaskularne bolesti uvrdila je postojanje statistički značajne povezanosti prekomjerne upotrebe suplemenata kalcijuma sa kalcifikovanjem koronarnih arterija (relativni rizik 1,22) [29]. Dvogodišnje istraživanje sprovedeno u Sjedinjenim Američkim Državama koje je obuhvatilo 5147 osoba sa verifikovanim promjenama na koronarnim krvnim sudovima ustanovilo je da upotreba suplemenata kalcijuma dovodi do povećanja taloženja kalcijuma u istim (nezavisno od volumena plaka) [30]. Studija grupe britanskih autora je utvrdila da povišene serumske koncentracije kalcijuma i fosfora kod pacijenata na hemodijalizi povećavaju kardiovaskularni rizik i mortalitet [31]. Hiperkalcijemija indukuje gubitak funkcionalnih receptora kalcijuma na površini vaskularnih glatkih mišićnih ćelija koji direktno sprečavaju taloženje mineralnog matriksa u zidovima krvnih sudova [31]. Primjena kalcimimetika kod bubrežnih bolesnika može smanjiti taloženje minerala u glatkim mišićnim ćelijama [31]. Istraživanje grupe autora iz Kanade utvrdilo je da upotreba suplemenata kalcijuma, ali ne i kalcijuma u ishrani, rezultira statistički značajnim povećanjem kalcifikacije abdominalne aorte [33,34]. Studije grupe autora iz Italije i Japana utvrdile su postojanje statistički značajne povezanosti visoke koncentracije serumskog kalcijuma i kalcifikacije infrarenalnog segmenta adominalne aorte [35,36].

Prekomjerna konzumacija kalcijuma i infarkt miokada

Prekomjerna konzumacija kalcijuma predisponira ektopični koštani osteoid u arterijama i srčanim zaliscima i razvoj infarkta miokarda [37-42]. Studije američkih autora ustanovile su da izuzetno visok unos kalcijuma (> 2500 mg dnevno) kod osoba starije životne dobi statistički značajno povećava mogućnost infarkta miokarda [37]. Petogodišnje istraživanje u Novom Zelandu koje je obuhvatilo 2421 žena starosti 55 ili više godina, sa očekivanim životnim vijekom dužim od pet godina, utvrdilo je statistički značajno veću učestalost infarkta miokarda kod žena koje su konzumirale 1000 mg kalcijuma dnevno (u odnosu na placebo)

[38]. Osamnaestogodišnja kohortna studija u Švedskoj verifikovala je povišene vrijednosti kalcijuma u serumu kao nezavisni, prospektivni faktor rizika infarkta miokarda u muškaraca srednje životne dobi (od 2183 učesnika, miokardni infarkt je razvilo 180 osoba sa statistički značajno većom incijalnom koncentracijom serumskog kalcijuma u odnosu na ostatak kohorte, 2,37±0,09 mmol/l naspram 2,35±0,09 mmol /1, p<0,03) [39]. Dvanaestogodišnje istraživanje u Sjedinjenim Američkim Državama koje je obuhvatilo 388 229 osoba uzrasta 50-71 godina utvrdilo je statistički značajnu povezanost upotrebe suplemenata kalcijuma i razvoja infarkta miokarda kod osoba muškog pola (RR, 1,19; 95% CI, 1,03-1,37) [40]. Upotreba dijetetskih suplemenata je češća i redovnija kod žena (postignuta ravnoteža i stabilan nivo kalcijuma prije studije), koje imaju blaže izražen učinak dodatnog kalcijuma u odnosu na muškarace (koji su suplemente kalcijuma počeli uzimati u starijoj dobi) [40]. Prema istim autorima, infarkt miokarda ne predisponira ukupno opterećenje, već nagle promjene u unosu i u serumskoj koncentaciji kalcijuma [40]. Jedanaestogodišnja evropska prospektivna studija koja je obuhvatila 23 980 učesnika utvrdila je statistički značajnu povezanost upotrebe suplemenata kalcijuma i razvoja infarkta miokarda (HR=2,39; 95% CI 1,12 do 5,12) [41]. Istraživanje u Švedskoj u trajanju od 10,8 godina detektovalo je da povećanje serumskog kacijuma (gornje referentne vrijednosti) statistički značajno povećava incidencu infarkta miokarda kod muškaraca starosti ispod 50 godina [41]. Do sličnih rezultata došla je grupa američkih autora [43]. Muškarci koji su uzimali više od 1000 mg kalcijuma dnevno imali su 20% veći rizik od infarkta miokarda u odnosu na muškarce koji nisu uzimali isti (dodatni unos kalcijuma kod žena nije povezan sa razvojem infarkta miokarda) [43]. Ženska zdravstvena inicijativa utvrdila je da suplementi kalcijuma (1000 mg/dan) povećavaju rizik od infarkta miokarda kod žena koje nisu uzimale suplemente kalcijuma prije ulaska u studiju [44]. Prema istim autorima, prekomjerni unos kalcijuma iz suplemenata proizvodi privremenu hiperkalcemiju povezanu s povećanom koagulabilnošću krvi, vaskularnom kalcifikacijom i krutošću arterija koje predisponiraju infarkt miokarda [43-47].

Prekomjerna konzumacija kalcijuma, hipertrofija i insuficijencija srca

Funkcija lijeve komore osjetljiva je na poremećaje u metabolizmu kalcijuma [48]. Kontrakciju i relaksaciju kardiomiocita u velikoj mjeri određuje homeostaza citozomalnog kalcijuma [48]. Pozitivna ravnoteža kalcijuma može ubrzati kalcifikaciju mekog tkiva i krvnih sudova što predisponira hipertrofiju lijeve komore čak i bez hiperkalcemije [48]. Povećanje serumskog kalcijuma je potencijalni okidač translokacije prohipertrofičnih transkripcijskih faktora uključenih u razvoj kardiomiocita [48]. Osim toga trajno povećanje intracelularnog kalcijuma može dovesti do prekomjerne aktivacije kalcineurina (kalcineurinski kardiomiociti su neorganizovani i izrazito hipertrofični) [48]. Povećana koncentracija serumskog kalcijuma za posljedicu ima hemodinamske promjene (povećan udarni volumen lijeve komore) i razvoj hipertenzije kojanarušava metabolizam kalcijuma koji opet predisponira hipertrofiju miokarda [48]. Metaboličke abnormalnosti (intolerancija glukoze, dijabetes, centralna pretilost, dislipidemija, hiperurikemija) uzrokovane povećanom koncentracijom kalcijuma u serumu takođe predisponiraju hipertrofiju lijeve komore [48]. Povećanje koncentracije serumskog kalcijuma rezultira intracelularnom hiperkalcemijom koja narušava repolarizaciju (dijastoličku relaksaciju) miokarda i uzrokuje nekrozu njegovog kontraktilnog pojasa (prekomjerno stezanje miofibrila i naknadnu miocitolizu) što je čini važnim faktorom naprelazu iz kompenzacije u insuficijenciju srca [48,49]. Studija kineskih autora koja je obuhvatila 833 pacijenta oboljela od dijabetesa melitusa tipa 2 utvrdila je da osobe sa vrijednostima serumskog kalcijuma u gornjim referentnim granicama imaju staistički značajno veću učestalost hipertrofije lijeve komore (analiza serumskog kalcijuma korigovanog albuminom kao kontinuirane varijable, sa porastom serumskog kalcijuma 1 mg/dl, odnos vjerovatnoća (OR) za hipertrofiju lijeve komore iznosi 2,400 (1,552-3,713), p<0.001) [48].

Prekomjerna konzumacija kalcijuma i poremećaji srčanog ritma

Hiperkalcemija je povezana sa poremećajima srčanog ritma, u prvom redu skraćenim QT intervalom, i tek ponekad sa blago produženim PR segmentom i QRS intervalom

[51]. S hiperkalcijemijom povezana hipertrofična kardiomiopatija uzrokuje transkripcijsku disregulacijukalcijum zavisne protein kinaze II ili kalcineurinskog puta, konstitutivnu aktivaciju kalcijum zavisne protein kinaze IIδ i posljedičnu mutaciju u debelim i tankim nitima sarkomera, što rezultira abnormalnim upravljanjem kalcijuma i aritmogenim potencijalom [52]. Smanjenje ekspresije i aktivnosti gena sarkoplazmatske endoplazmatske retikularne kalcijum adenozin trifosfataze dokazana je na animalnom modelu ali ne i kod ljudi [52]. Opterećenje hipertrofijom i ožiljcima doprinosi razvoju aritmije [52]. U literaturi su opisani slučajevi opetovanih ventrikularnih aritmija (ventrikularne bigeminije, monomorfne i polimorfne ventrikularne fibrilacije) refrakternih na antiaritmijsku terapiju koje su nestale sa normalizovanjem vrijednosti kalcijuma u serumu [50-53]. Istraživanje američkih autora koje je obuhvatilo 871 029 učesnika sa dijagnostikovanom fibrilacijom atrijuma utvrdilo je da osobe sa povišenom koncentracijom serumskog kalcijuma imaju veću smrtnost, povećanu dužinu boravka u bolnici, kao i povećane ukupne troškove hospitalizacije u odnosu na osobe sa normalnom koncentracijom kalcijuma [54,55].

Prekomjerna konzumacija kalcijuma i embolija pluća

Smatra se da visoka koncentracija kalcijuma u krvikao posljedica prekomjerne konzumacije suplemenata kalcijuma može imati značajnu ulogu u razvoju emboliije pluća [56,57]. Hiperkalcijemija dovodi do vazokonstrikcije, pokreće i ubrzava reakcije koagulacije, stimuliše agregaciju trombocita [57]. Pored toga, ona narušava reapsorpciju natrijuma i vode u bubrezima, dok nekompenzovana poliurija zbog mučnine i anoreksije predisponira dehidraciju i hiperkoagulabilno stanje [57]. Nadalje, povišene koncentracije kalcijuma u serumu imaju citotoksične efekte odgovorne za ćelijsku apoptozu i trombozu [57].

Prekomjerna konzumacija kalcijuma i mozdani udar

Prekomjerna konzumacija kalcijuma, predstavlja značajan faktor rizika moždanog udara [58]. Pozitivna ravnoteža kalcijuma (unos>1400 g/dan) tokom dužeg perioda pospješuje vaskularnu kalcifikaciju i razvoj ateroskleroze [58]. Španska studija kontrole slučaja koje je obuhvatila osobe uzrasta 40-89 godina (2690 osoba sa prvom epizodom nefatalnog ishemijskog moždanog udara i 19 538 kontrola) utvrdila je snažnu povezanost konzumiranja visokih doza suplemenata kalcijuma (≥1000 mg/dan) i nefatalnog ishemijskog moždanog udara (odnos verovatnoća 0,76; 95% CI: 0,45–1,26) [58]. Jedanaestogodišnja studija sprovedena u Švedskoj koja je obuhvatila 34670 osobe uzrasta 49-83 godine utvrdila je da prekomjeran unos kalcijuma u ishrani nosi statistički značajan rizik od intracerebralnog krvarenja (prilagođeni relativni rizik 2,04; 95% CI: 1,24-3,35) [59]. Istraživanje australijskih autora ustanovilo je hiperkalcijemijom aktivirani arterijski spazamza etiološki faktor u žarišnim neurološkim lezijama povezanim sa hiperkalcemijom [60]. Studija korejskih autora ustanovila je da visoke koncentracije kalcijuma korigovanog albuminom rezultuju povećanom incidencijom smrtnosti nakon akutnog ishemijskog moždanog udara [61]. Priliv jonizovanog kacijuma u neuronske ćelije posredovan N metil D aspartat receptorima rezultira ishemijskom smrću iste [61]. U prilog ovome govori činjenica da inhibicija efektora toksičnosti jonizovanog kalcijuma (kalmodulina, kalcineurina, neuronske azotoksid sintaze) štiti neurone od toksičnih efekata ekscitacionih aminokiselina [61]. Odgođenoj smrti neurona doprinosi i kalcijumom uzrokovana mitohondrijska disfunkcija (oksidativni stres i akumulacija kalcijuma u mitohondrijama rezultuju bubrenjem i oslobađanjem sadržaja mitohondrija) [61].

ZAKLJUČAK

Prekomjerna koncentracija kalcijuma, uzrokovana predominantno neprikladnom upotrebom suplemenata, predisponira razvoj kardiovaskularnih bolesti. Visoke vrijednosti kalcijuma u serumu indukuju reprogramiranje i diferencijaciju glatkih mišićnih ćelija u fenotip sličan osteoblastu, translokaciju prohipertrofičnih transkripcijskih faktora kardiomiocita, kompromitovanje dijastoličke relaksacije miokarda i nekrozu njegovog kontraktilnog pojasa, poticanje reakcija koagulacije, stimulaciju agregacije trombocita, hemodinamskih promjena i metaboličkih abnormalnosti. Akutna intoksikacija suplementima kalcijuma rezultuje povećanjem krvnog pritiska. Hronično konzumiranje

prekomjerne količine kalcijuma predisponira aterosklerozu i kalcifikaciju krvnih sudova, srčani i moždani udar, hipertrofiju i insuficijenciju srca iporemećaje srčanog ritma. Postoji potreba za jačanjem odgovora i uloge zdravstvenog sistema u informisanju javnosti o nuspojavama prekomjerne konzumacije kalcijuma, ograničavanju širokog propisivanja suplemenata, kao i eventualnoj sveobuhvatnoj ponovnoj procjeni.

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EXCESSIVE CALCIUM CONSUMPTION AS A RISK FACTOR FOR CARDIOVASCULAR DISEASES

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Summary: Calcium is the most abundant mineral in the human body that participates in the construction of bones and teeth, nerve impulse transmission, intracellular signaling, hormone secretion, muscle contraction, coagulation, ensuring normal heart rhythm and physiological values of blood pressure. Excessive calcium concentration, predominantly caused by improper use of supplements, predisposes to the development of cardiovascular disease. High serum calcium induces reprogramming and differentiation of smooth muscle cells into an osteoblast-like phenotype, translocation of prohypertrophic cardiomyocyte transcription factors, compromise of diastolic relaxation of the myocardium and necrosis of its contractile girdle, stimulation of coagulation reactions, stimulation of platelet aggregation, hemodynamic changes and metabolic abnormalities. Acute intoxication with calcium supplements results in an increase in blood pressure. Chronic consumption of excessive calcium concentration predisposes to atherosclerosis and calcification of blood vessels, heart attack and stroke, hypertrophy and heart failure, and heart rhythm disorders. There is a need to strengthen the response and role of the health system in informing the public about the side effects of excessive calcium consumption, limiting the widespread prescribing of supplements, as well as a possible comprehensive reassessment of the same.
Key words: calcium, toxicity, cardiovascular system

Calcium in the human body

Calcium is the most abundant mineral in the human body (1.5-2% of total body weight, approximately 1200 g) [1,2]. About 98% of the total calcium in the body is found in the bones[1,2]. The remainder was localized in teeth (1%), body fluids, muscles, and other tissues (1%) [1,2]. In bones, calcium is present in the form of calcium-phosphate complexes, primarily hydroxyapatite, which makes up almost 40% of bone weight[2]. Bones are an easily available source of calcium (50% ionized and physiologically active calcium) [1]. It can exist in body fluids as a free calcium cation (50%), bound to proteins (albumin, globulin, calmodulin and other proteins, 40%) and other ions (calcium phosphate, calcium carbonate and calcium oxalate, 10%) [3,4]. The concentration of calcium in the serum of healthy people is in the range 8.88 - 10.4 mg / dl[4].

Calcium absorption, excretion and homeostasis

Calcium is absorbed by active transport (low and moderate levels of intake) and passive diffusion (high intake) in the small intestine[2]. Active transport is regulated by 1,25-dihydroxyvitamin D and its intestinal receptors, while passive diffusion involves movement depending on the concentration gradient[2]. Calcium absorption is inversely proportional to intake (highest in infancy and early puberty, gradually declining with age) and somewhat lower in females[2]. About 50% of plasma calcium (ionized and complex form, ultrafiltrable fraction, excluding protein-bound form) is freely filtered through the renal glomerulus, approximately 99% of which is reabsorbed along the tubule[5]. 24h adult urine contains about 200 mg of calcium[5]. During 24 h, 140 mg of calcium (a mixture of unsorbed calcium, calcium from mucosal cells and intestinal secretions) is excreted in the faeces, with sweat 35 ± 4 mg[6]. Parathyroid hormone, calcitriol (1,25-dihydroxycholecalciferol) and calcitonin7 participate in calcium homeostasis (at the level of the skeletal system, kidneys and small intestine)[6,7]. Parathyroid hormone stimulates the mobilization of calcium from the bones (stimulation of osteoclast and osteocyte activity), reabsorption of calcium in the renal tubules and the synthesis of calcitriol in the same[7]. Calcitriol increases the concentration of calcium-binding protein in the small intestine, calcitonin reduces

the resorption of bone tissue (inhibition of osteoclast activity) [7]. Calcium homeostasis may be contributed by estrogen, testosterone, adrenal hormones, thyroxine, somatotropin, and glucagon[6,7].

Recommended daily calcium intake

In newborns, it is recommended to take 400 mg of calcium per day[6]. At the age of 1–3 years 500 mg / day, at the age of 4–6 years 600 mg / day, at the age of 7–9 years 700 mg / day[6]. In adolescence (age 10–18 years) it is recommended to take 1300 mg of calcium per day, in the age of 19-65 years 1000 mg / day[6]. At the age of 65, it is recommended to take 1300 mg of calcium per day, in pregnancy and breastfeeding 1200 mg / day[6]. The recommended daily intake increases with decreasing bioavailability (in the cases of excessive consumption of foods rich in oxalic and phytic acid: spinach, sweet potatoes, rhubarb, beans, unleavened bread, raw beans, seeds, nuts, cereals), extreme physical activity and mechanical stress, excessive consumption of sodium chloride, amenorrhea, glucose intolerance and vegetarian diet[8].

Sources of calcium

Calcium intake is usually associated with the consumption of dairy products (100-180 mg of calcium in 100 g of milk and yogurt, 1 g of calcium in 100 g of hard cheese) [8]. In 100 grams of cereals there is 30 mg of calcium (enriched with 100-180 mg) [8]. Nuts and seeds (primarily almonds and sesame) are rich in calcium (250-600 mg of calcium per 100 g)[8]. 100 g of kale, broccoli and watercress contain 100-150 mg of calcium[8]. Total calcium intake from certain foods varies according to food consumption patterns in a given population (dairy products provide 72 and 58% of total calcium intake in the United States and the Netherlands, vegetables provide 46.9% of total calcium intake in China) [8].

Calcium supplements

Supplements for oral use include calcium in the form of calcium carbonate, calcium citrate, calcium gluconate, calcium lactate, and calcium phosphate[9-12]. Calcium carbonate is the most common and most cost-effective calcium supplement[9]. Calcium from this compound has an absorption similar to calcium from milk (taken with a meal, it depends on the low pH value) [9-12]. Calcium citrate can be taken without food (predominantly in people with achlorhydria, people using type 2 histamine receptor antagonists or protein pump inhibitors) [9]. It has a higher cost and lower efficacy than calcium carbonate (210 mg Ca in 1000 mg supplement) [9-12]. Calcium gluconate and calcium lactate are less concentrated forms of calcium[9]. The use of calcium phosphate is not recommended (limited number of studies) [9]. In the United States and Canada, 40% of people aged 19-65 and 70% of women over the age of 65 use calcium supplements[8].

The role of calcium in the human body

Calcium participates in the construction of bones and teeth, transmission of nerve impulses, intracellular signaling, hormonal secretion, muscle contraction, coagulation, ensuring normal heart rhythm and physiological value of blood pressure[13].

The role of calcium in the regulation of blood pressure

Calcium regulates blood pressure through vasoconstriction (changes in the concentration of intracellular calcium in vascular smooth muscle) and an increase in vascular volume[14]. It exerts its action through parathyroid hormone, vitamin D and the renin-angiotensin-aldosterone system[14]. Calcium intake is inversely proportional to the concentration of parathyroid hormone in plasma and the level of blood pressure[14]. Parathyroid hormone regulates blood pressure by increasing the concentration of free calcium in the cytosol (increased vascular reactivity, peripheral vascular resistance, reactions to the renin-angiotensin-aldosterone system and the sympathetic nervous system) and parathyroid hormone receptor type 1 (connects Gαs adenylate cyclase signaling pathways A, Gαq phospholipase C, β inositol triphosphate, intracellular calcium, protein kinase C, Gα12 / 13 phospholipase D, RhoA and signaling cascades activated by mitogenic protein kinase) [14]. Increased concentration of calcitriol modulates blood pressure by genomic (modification of transcription factors of intracellular vitamin D receptor gene expression) and non-genomic mechanisms (stimulation of L-type calcium channels by cyclic adenosine mono phosphate, signaling cascade adenylate cyclase / cyclic adenosine mono phosphate/ proteinprotein kinase A/fofolipase C / inositol phosphate and activation of the calcium transfer system) [14]. Calcium intake is inversely proportional to the activity of the renin-angiotensin-aldosterone system (low intake

stimulates renin release, and consequent synthesis of angiotensin II and aldosterone) [14].

The role of calcium in the regulation of cardiac work

Normal heart function requires a sufficiently high concentration of calcium in systole and low in diastole [15,16]. Calcium is an important regulator of cardiac function that links electrical depolarization with cardiomyocyte contraction[15,16]. Intracellular increase of calcium allows the contractile threads of actin and myosin to be activated and slide next to each other, which shortens the cells and creates the power to move the blood[15,16].Depolarization caused by action potential activates calcium channels under voltage, which allows its flow through the sarcoplasmic reticulum into the cytoplasm (dyadic or triadic cleft) [15,16]. Diffusion of calcium ions initiates contraction by binding to troponin C within the myofibril[15,16]. Thanks to sequestration in the sarcoplasmic reticulum (an adenosine triphosphate-dependent enzyme process), calcium recovers to resting levels (diastole) [15,16]. Myocytes also possess sarcoplasmic calcium adenosine triphosphatase, (small contribution to calcium extrusion) [15,16]. Close connection between transverse tubules and sarcoplasmic reticulum in ventricular myocytes provide a synchronous increase in calcium during systole (which proves highly heterogeneous transition of calcium from the surface of the sarcolemma to the cell center as a consequence of chemical detubulation with formamide) [15,16]. Although without transverse tubules, the passage of calcium through atrial myocytes has similar spatial properties[15,16].

The role of calcium in coagulation

Calcium ions play an important role in the regulation of coagulation. In addition to platelet activation, they are responsible for the activation of several coagulation factors, including coagulation factor XIII (responsible for covalent cross-linking of formed fibrin clots, preventing their premature fibrinolysis). Coagulation factor XIII circulates in plasma as a heterotetrameric protransglutaminase composed of dimeric subunits of catalytic coagulation factor A and protective, regulatory subunits of coagulation factor B. Coagulation factor A is activated by a combination of calcium binding and the proteolytic cleavage of thrombin of the N-terminal 37-amino acid region[17]. In the extrinsic blood coagulation pathway, factor X is activated by a complex of tissue factor, factor VIIa, and calcium ions[18].

Reduced calcium consumption

Inadequate dietary calcium intake does not cause symptoms in the short term[18-20]. Hypocalcemia occurs as a result of medical problems or their treatment (hypoparathyroidism, renal failure, pseudohypoparathyroidism, liver failure, surgical removal of the stomach, vitamin D deficiency, hypomagnesemia, hypermagnesemia, Fanconi's syndrome, high doses of intravenous bisphosphonates, high-dose diuretics). In the long run, inadequate calcium intake causes osteopenia, osteoporosis and an increased risk of bone fractures (elderly people) [18-20].

Excessive calcium consumption

Excessive consumption of calcium supplements, also known as calcium supplementation syndrome, is a significant cause of hypercalcemia (frequency exceeded only by primary hyperparathyroidism and malignancies) [21-24]. Elevated blood calcium levels are predisposed to chronic diseases and drugs used in their treatment (thiazide diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers and nonsteroidal anti-inflammatory drugs) [21-24]. Hypercalcemia predisposes to decreased glomerular filtration, atherosclerosis, uncontrolled hypertension, progressive cardiac dysfunction[21-24].

Excessive calcium consumption and hypertension

Excessive intake of calcium supplements causes an acute increase in serum calcium concentration, increase in blood pressure and total peripheral vascular resistance[25]. Acute hypercalcemia results in increased minute volume that rapidly progresses to a hemodynamic pattern with increased peripheral vascular resistance[25]. Increased serum calcium concentration is characterized by inappropriately high cardiac volume (absence of compensatory decrease in cardiac output caused by peripheral vasoconstriction) [25]. Hypertension occurs as a consequence of the direct effect of calcium on vascular smooth muscle cells (release of calcium from the sarcoplasmic reticulum activates calmodulin and myosin kinase, shortens myofilaments and causes vasoconstriction), while calcium-mediated increase in the release of epinephrine from the medulla of the adrenal gland contributes to its development [25]. Acute hypercalcemia is

accompanied by an increase in hematocrit and a decrease in plasma volume (increased capillary filtration caused by pressure, increased sodium diuresis), unchanged activity of norepinephrine, renin, aldosterone and dopamine [25,26]. A study by a group of authors from California involving 57 subjects (7 subjects with normal renal function and 50 subjects with mild to severe renal insufficiency) found a statistically significant association between an acute increase in serum calcium and an increase in systolic and diastolic blood pressure (development or worsening of hypertension in 1 person with normal renal function and 41 people with mild to severe renal insufficiency) [27]. The hypertensive response to increased serum calcium was more pronounced in patients with advanced renal failure (serum creatinine> 4 mg / 100 ml) [27].

Excessive calcium consumption, atherosclerosis and calcification of blood vessels

Large observational studies have found that an increase in serum calcium concentration caused by excessive consumption of supplements (1 g of calcium supplement increases the concentration of serum calcium 1.22–1.30 mmol / L), but not dietary calcium, contributes to the development of atherosclerosis and calcification of blood vessels[28-32]. Calcifications of the intima of blood vessels originate from apoptotic smooth muscle cells or matricular vesicles that are released from near the inner elastic lamina[28]. Its development is enhanced by lipid deposition and inflammation in the neointima[28]. Calcification can also occur in the medial layer (along the elastic lamellae and surrounding smooth muscle cells) [28]. High concentrations of calcium supplements induce reprogramming and differentiationof smooth muscle cells into an osteoblast-like phenotype and generates deposition of calcified matrix vesicles in the blood vessel wall[28.] In addition, calcium load reduces parathyroid hormone (increases the risk of adynamic or low bone regeneration) [28]. A study by American authors, which included 5448 adults without clinically diagnosed cardiovascular disease, found a statistically significant association between overuse of calcium supplements and calcification of coronary arteries (relative risk 1.22) [29]. A two-year study conducted in the United States, which included 5,147 people with verified changes in coronary blood vessels, found that the use of calcium supplements led to the increase in calcium deposition in them (regardless of plaque volume) [30]. A study by a group of British authors concluded that elevated calcium and phosphorus serum concentrations in hemodialysis patients increase cardiovascular risk and mortality [31]. Hypercalcemia induces loss of functional calcium receptors on the surface of vascular smooth muscle cells that directly prevent the deposition of mineral matrix in blood vessel walls [31] The use of calcimimetics in people with chronic renal failure can reduce the deposition of minerals in smooth muscle cells[31]. A study by a group of authors from Canada found that the use of calcium supplements, but not calcium in the diet, resulted in a statistically significant increase in abdominal aortic calcification[33,34]. Studies by a group of authors from Italy and Japan determined the existence of a statistically significant association between high serum calcium concentration and calcification of the infrarenal segment of the adominal aorta [35.36].

Excessive calcium consumption and myocardial infarction

Excessive calcium consumption predisposes to ectopic bone osteoid in arteries and heart valves and the development of myocardial infarction[37-42]. Studies by American authors have found that extremely high calcium intake (> 2500 mg per day) in the elderly statistically significantly increases the possibility of myocardial infarction[37]. A five-year study in New Zealand of 2,421 women aged 55 or over, with a life expectancy of more than five years, found a statistically significantly higher incidence of myocardial infarction in women who consumed 1000 mg of calcium per day (compared to placebo) [38]. An 18-year cohort study in Sweden verified elevated serum calcium values as an independent, prospective risk factor for myocardial infarction in middle-aged men (out of 2183 participants, 180 people developed a myocardial infarction with a statistically significantly higher initial serum calcium concentration than the rest). 2.37 ± 0.09 mmol/l versus 2.35 ± 0.09 mmol / l, p <0.03) [39]. A twelve-year study in the United States of 388.229 people aged 50-71 found a statistically significant association between the use of calcium supplements and the development of myocardial infarction in males (RR, 1.19; 95% CI, 1.03-1.37) [40]. The use of dietary supplements is more frequent and regular in women (achieved balance and stable calcium levels before the study) who have a milder effect of supplemental

calcium compared to men (who started taking calcium supplements at old age) [40]. According to the authors, myocardial infarction does not predispose to the total load, but to sudden changes in calcium intake and serum concentration[40]. An eleven-year European prospective study of 23.980 participants found a statistically significant association between the use of calcium supplements and the development of myocardial infarction (HR = 2.39; 95% CI 1.12 to 5.12) [41]. A 10.8-year study in Sweden found that an increase in serum calcium (upper reference values) statistically significantly increased the incidence of myocardial infarction in men under the age of 50[41]. A group of American authors came to similar results43. Men who took more than 1,000 mg of calcium per day had a 20% higher risk of myocardial infarction than men who did not take the same (additional calcium intake in women was not associated with the development of myocardial infarction) [43]. The Women's Health Initiative found that calcium supplements (1000 mg / day) increased the risk of myocardial infarction in women who did not take calcium supplements before entering the study[44] According to the same authors, excessive calcium intake from supplements produces temporary hypercalcemia associated with increased blood coagulation, vascular calcification and stiffness of the arteries predisposing to myocardial infarction [43-47].

Excessive calcium consumption, hypertrophy and heart failure

Left ventricular function is sensitive to disturbances in calcium metabolism[48]. Cardiomyocyte contraction and relaxation are largely determined by cytosomal calcium homeostasis[48]. A positive calcium balance can accelerate soft tissue and blood vessel calcification that predisposes to left ventricular damage and relaxation even without hypercalcemia[48]. Increased serum calcium is a potential trigger for translocation of prohypertrophic trencryption factors involved in the development of cardiomyocytes[48]. In addition, a permanent increase in intracellular calcium can lead to excessive activation of calcineurin (calcineurin cardiomyocytes are disorganized and markedly hypertrophic) [48]. Increased serum calcium concentration results in hemodynamic changes (increased left ventricular stroke volume) and the development of hypertension that disrupts calcium metabolism which in turn predisposes to myocardial hypertrophy[48]. Metabolic abnormalities (glucose intolerance, diabetes, central obesity, dyslipidemia, hyperuricaemia) caused by increased serum calcium concentrations also predispose to left ventricular hypertrophy[48]. An increase in serum calcium concentration results in intracellular hypercalcemia, which impairs myocardial repolarization (diastolic relaxation) and causes necrosis of its contractile girdle (excessive myofibril shrinkage and subsequent myocytolysis), which makes it an important factor in heart failure[48]. A Chinese authors' study of 833 patients with type 2 diabetes mellitus found that individuals with serum calcium values in the upper reference range had a statistically significantly higher incidence of left ventricular hypertrophy (analysis of serum calcium adjusted by albumin as a continuous variable, with an increase in serum calcium 1 mg/dl, the probability ratio for left ventricular hypertrophy is 2.400 (1,552-3,713) $p<0.001$) [48].

Excessive calcium consumption and heart rhythm disorders

Hypercalcemia is associated with cardiac arrhythmias, primarily with shortened QT interval, and only sometimes with slightly prolonged PR segment and QRS interval[50.51]. Hypercalcemia-associated hypertrophic cardiomyopathy causes transcriptional dysregulations of calcium-dependent protein kinase II or the calcineurin pathway, constitutive activation of calcium-dependent protein kinase IIδ, and consequent mutation in thick and thin strands of sarcomeres, which results in abnormal management of calcium and arrhythmogenic potential [50-52]. Decreased expression and activity of the sarcoplasmic endoplasmic reticular calcium adenosine triphosphatase gene has been demonstrated in an animal model but not in humans[52]. Hypertrophy loading and scarring contributes to the development of arrhythmia[52]. The literature describes cases of repeated ventricular arrhythmias (ventricular bigemia, monomorphic and polymorphic ventricular fibrillation) refractory to antiarrhythmic therapy, which disappeared with normalization of serum calcium values[50-53]. A study by American authors that included 871.029 participants diagnosed with atrial fibrillation found that people with elevated serum calcium concentrations had higher mortality, increased length of hospital

stay, and increased total hospitalization costs compared to those who had normal calcium concentrations [54, 55].

Excessive calcium consumption and pulmonary embolism

It is thought that a high concentration of calcium in the blood as a consequence of excessive consumption of calcium supplements may play a significant role in the development of pulmonary embolism [56.57]. Hypercalcemia leads to vasoconstriction, initiates and accelerates coagulation reactions, stimulates platelet aggregation[57]. In addition, it impairs the reabsorption of sodium and water in the kidneys, while uncompensated polyuria due to nausea and anorexia predisposes to dehydration and hypercoagulable conditions[57]. Furthermore, elevated serum calcium concentrations have cytotoxic effects responsible for cellular apoptosis and thrombosis[57].

Excessive calcium consumption and stroke

Excessive calcium consumption is a significant risk factor for stroke[58]. A positive calcium balance (intake> 1400 g / day) over a long period of time promotes vascular calcification and the development of atherosclerosis[58]. A Spanish case control study involving people aged 40-89 years (2690 people with the first episode of non-fatal ischemic stroke and 19.538 controls) found a strong association between consuming high doses of calcium supplements (≥1000 mg / day) and non-fatal ischemic stroke (probability ratio 0.76; 95% CI, 0.45–1.26) [58]. An eleven-year study conducted in Sweden involving 34.670 people aged 49-83 found that excessive dietary calcium intake carried a statistically significant risk of intracerebral hemorrhage (adjusted relative risk 2.04; 95% CI: 1.24– 3.35). [59]. A study by Australian authors found hypercalcaemia-activated arterial spasm for an etiological factor in focal neurological lesions associated with hypercalcemia[60]. A study by Korean authors found that high concentrations of albumin-adjusted calcium result in an increased incidence of mortality after acute ischemic stroke[60]. The influx of ionized calcium into neuronal cells mediated by N methyl D aspartate receptors results in ischemic death of those [61]. This is supported by the fact that the inhibition of the toxicity effectors of ionized calcium (calmodulin, aslcineurin, neuronal nitric oxide synthase) protects neurons from the toxic effects of excitatory amino acids[61]. Calcium-induced mitochondrial dysfunction also contributes to delayed neuronal death (oxidative stress and calcium accumulation in mitochondria result in swelling and release of mitochondrial contents)[61].

CONCLUSION

Excessive calcium concentration, caused by predominantlyimproper use of its supplements, predisposes to the development of cardiovascular diseases. High serum calcium induces reprogramming and differentiation of smooth muscle cells into an osteoblast-like phenotype, translocation of prohypertrophic cardiomyocyte transcription factors, compromise of diastolic relaxation of the myocardium andnecrosis of its contractile girdle, stimulation stimulation of coagulation reactions, stimulation of platelet aggregation, hemodynamic changes and metabolic abnormalities. Acute intoxication with calcium supplements results in an increase in blood pressure. Chronic consumption of excessive calcium concentration predisposes to atherosclerosis and calcification of blood vessels, heart attack and stroke, hypertrophy and heart failure, and heart rhythm disorders. There is a need to strengthen the response and role of the health system in informing the public about the side effects of excessive calcium consumption, limiting the broad prescribing of supplements, as well as possible comprehensive reassessment of the same.

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