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Ateroskleroza – uzrok ili posljedica?

Organizatori

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Atherosclerosis – cause or consequence?

Organizers

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Congress Hall, Zagreb Fair,
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Patofiziologija ateroskleroze

Akademik Željko Reiner

Klinika za unutrašnje bolesti Kliničkog bolničkog centra Zagreb

Danas se zna da je ateroskleroza bolest koja počinje već u mladosti i napreduje različitom brzinom, ovisno o nizu čimbenika koji djeluju na stijenku arterije. Započinje s pretjeranim očitovanjem adhezijskih molekula na endotelnim stanicama (VCAM-1, ICAM-1, selektini), te lučenjem kemotaktičkih čimbenika (MCP-1), čimbenika rasta (M-CSF) i citokina (IL-2) koji potiču nakupljanje i ulazak u arterijsku stijenku monocita koji se onda pretvore u makrofage. Kasnije, njihovom apoptozom dolazi do otpuštanja kovinoproteinaza i tkivnog čimbenika. Nakon što iz makrofaga nakupljanjem lipida u njima nastanu pjenaste stanice a glatke se mišićne stanice premjeste iz medije u intimu, stvori se vezivna kapa koja je odgovorna za stabilnost aterosklerotičkog plaka i koja razdvaja lipidnu jezgru plaka od lumena žile. Dobro je poznato da je sastav plaka, a ne njegova veličina, ono što određuje sudbinu bolesnika. Naime, većina smrtonosnih ishoda u bolesnika s aterosklerozom koronarnih arterija srca nastaje zbog pucanja ili erozije vezivne kape plaka. Upala utječe na pucanje plaka jer je povezana i sa lučenjem metaloproteinaza matriksa i s oksidacijskim stresom. Upala nije važna samo u početku procesa aterogeneze već i za stvaranje *vasa vasorum*, žilica koje snabdijevaju plak krvlju, povezana je s nastankom krvarenja unutar plaka, a tkivni čimbenik iz upalnih stanica ključan je za nastanak tromba na plaku. Stoga su upala, aterogeneza i trombogeneza međuovisna zbivanja i sva tri procesa doprinose kliničkim posljedicama bolesti.

The pathophysiology of atherosclerosis

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It is well established that atherosclerosis is a process which begins at an early age and progresses at a variable rate, depending upon a wide variety of factors acting upon the arterial wall. It begins with over expression of endothelial adhesion molecules (VCAM-1, ICAM-1, selectins), chemotactic factors (MCP-1), growth factors (M-CSF) and cytokines (IL-2) that facilitate the recruitment and internalization of monocytes which are transformed into macrophages. They may later undergo apoptosis with the release of metalloproteinases and tissue factor. After formation of foam-cells from macrophages and smooth muscle cells migration from intima to media, a fibrous cap is formed which confers the stability of the atherosclerotic plaque and separates the lipid core from the vessel lumen. Today it is clear that the composition of the plaque, rather that the percent stenosis is a predictor of the patients' destiny. Most fatal outcomes of coronary artery atherosclerosis result from the plaque fibrous cap rupture or superficial erosion. The propensity of plaque to disrupt depends upon inflammatory pathways which impinge on matrix metalloproteinases and oxidative stress. Inflammation has been implicated not only in the beginning of atherogenesis but in plaque neovascularity (*vasa vasorum*) and intraplaque hemorrhage as well, and inflammatory cell derived tissue factor is a key contributor to plaque thrombogenicity. Therefore, inflammation, atherogenesis and thrombogenesis are interdependent and all three contribute to clinical consequences.

Molekularna osnova ateroskleroze

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Brojne su epidemiološke studije pokazale da za razvoj kardiovaskularnih i cerebrovaskularnih bolesti, koje u svojoj podlozi imaju aterosklerozu, uz mnoge rizične čimbenike okoliša, genetska komponenta igra značajnu ulogu. Međutim, kompleksna etiologija ateroskleroze, kojoj je temelj poligenski poremećaj, ne dozvoljava jednoznačno povezivanje genetskih čimbenika rizika s njenim razvojem.

The molecular basis of atherosclerosis

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Numerous epidemiological studies have demonstrated the genetic component, along with many environmental risk factors, to play an important role in the development of cardiovascular and cerebrovascular diseases underlain by atherosclerosis. However, straight association between the genetic risk factors and the development of atherosclerosis cannot be determined due to the complex etiology of the latter.

Najznačajniji geni za koje se pretpostavlja da predstavljaju rizik za razvoj ateroskleroze su geni uključeni u metabolizam lipida, regulaciju tlaka, metabolizam homocisteina, trombozu, adheziju leukocita, upalnih molekula te geni metaloproteinaza matriksa, odgovornih za vaskularno remodeliranje. Najveći broj ispitivanja molekularne osnove ateroskleroze i disfunkcije endotela tijekom protekla dva desetljeća vezan je uz gene kandidate uključene u poremećaj metabolizam lipoproteina, regulaciju tlaka ili hemostaze, dok se danas istraživanja sve više usmjeravaju prema genima metaloproteinaza matriksa (MMP), renin-angiotenziskog sustava (RAS) odgovornog za regulaciju tlaka, adhezijske molekule te interleukina, koji su posredno ili neposredno povezani s aterosklerotskim lezijama.
U studijama o povezanosti gena s razvojem ateroskleroze do sada je testirano više od 850 varijanta različitih gena, međutim, rezultati ispitivanja su često proturječni. Razlozi za takva razmimoilaženja mogu se objasniti upravo kompleksnom etiologijom ateroskleroze, genetskim čimbenicima uključenim u njen razvoj, specifičnim populacijskim naslijeđem, međutim, i metodološkim pristupom ispitivanju, odabiru rizičnih skupina i dizajnu ispitivanja. To ukazuje da je ispitivanje genetske povezanosti poligenskih poremećaja vrlo teško jer su genetski učinci mali, vrlo teško mjerljivi i očituju se tek u međusobnoj interakciji više gena koji nastaju u bolesti. Kako bi se povećala snaga ispitivanja genetske povezanosti s nastankom ateroskleroze i osnažila klinička točnost ispitivanja, to se danas sve više koriste meta-analize, koje sakupljaju rezultate velikog broja objavljenih ispitivanja. U meta-analizi se rezultati takvih neovisnih ispitivanja grupiraju i analiziraju zajedno kao da je provedeno jedno veliko istraživanje s dovoljno velikim brojem ispitanika da bi se mogao prepoznati genetski učinak. Takav pristup u ispitivanju genetske povezanosti s aterosklerozom iznjedriti će realnu sliku genetskog profila gena kandidata koji predstavljaju stvarno značenje u prepoznavanju molekularne osnove ateroskleroze.

The most relevant genes postulated to pose a risk for the development of atherosclerosis are the genes involved in the metabolism of lipids, blood pressure and homocysteine; those involved in thrombosis, inflammation and leukocyte adhesion; and the genes of the matrix metalloproteinase family responsible for vascular remodeling. Along with the candidate genes involved in impairments of the lipoprotein metabolism, blood pressure regulation or hemostasis, which were in the past two decades associated with atherosclerosis and endothelial dysfunction, research has currently been focused on the genes of matrix metalloproteinases, of renin-angiotensin system involved in hypertension, adhesion molecules and of interleukins that are directly or indirectly related to atherosclerotic lesions.
To date, more than 850 different gene variants have been tested in the studies of gene to atherosclerosis association; however, quite frequently yielding contradictory results. These discrepancies can be readily explained by the complex etiology of atherosclerosis, genetic factors involved in its development, population specific heredity as well as by the methodological approach in selection of risk groups and in particular study design. This implicates that studying genetic associations in such polygenic disorders is extremely difficult, because the genetic effects are small, hardly measurable and only manifesting in the interaction of multiple genes occurring in the course of the disease. To improve the strength of the studies investigating gene associations with the genesis of atherosclerosis and to upgrade clinical precision of the studies, nowadays, meta-analyses that process pooled results of a great number of published studies have been increasingly used In a meta-analysis, results of such independent studies are pooled and analyzed together as if yielded by a single large study including a population large enough to recognize the gene impact. Such an approach in genetic association studies with atherosclerosis as s polygenic disease will provide a reliable overview and a realistic picture of genetic profile of candidate genes that presents the true significance in recognition the molecular basis of atherosclerosis.

Upala i ateroskleroza

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Inflammation and atherosclerosis

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Najnovije spoznaje o aterosklerozi upućuju da je ona dinamična progresivna bolest koja nastaje kombinacijom disfunkcije endotela i upale. Upalni je mehanizam odgo-

Recent evidences suggested atherosclerosis as a dynamic progressive disease arising from combination of endothelial dysfunction and inflammation. Inflammation rep-

voran za nastanak ateroma, destabilizaciju vulnerabilnog plaka i nastanak okluzijske bolesti krvne žile. Pro-upalni citokini uključeni u prvu fazu upalne reakcije koja se odvija na stjenci krvne žile potiču endotelne stanice na ispoljavnje adhezijskih molekula, lučenje proteaza i drugih posrednika upale koji se u topljivom obliku izlučuju u sistemsku cirkulaciju. Tako, primarno izlučeni citokini induciraju nastanak inerleukina 6 (IL-6), koji u jetri potiče nastanak reaktanata akutne faze poput C-reaktivnog proteina. Trombociti i masno tkivo, također, potiču nastanak upalnih posrednika koji se smatraju ključnim u nastanku aterotromboze. Brojna istraživanja ukazuju da su i male promjene u koncentraciji CRP, (izmjere visokoosjetljivom metodom, hsCRP) u zdravih i u osoba pogođenih aterosklerozom vrlo koristan prediktor krvožilnih i moždano-žilnih bolesti. U osoba s jednakim, (a često puta i normalnim koncentracijama) LDL-kolesterola i razinama arterijskog tlaka, baš su razlike u koncentraciji CRP, ključne u predviđanju rizika za krvožilni incident.
U osoba koje su već imale krvožilni incident, primjerice akutni infarkt miokarda, terapija statinima dovodi i do značajnog sniženja CRP, potvrđujući važnost praćenja koncentracije CRP s važnosti praćenja koncentracije LDL-kolesterola.
Od ostalih upalnih biopokazatelja potencijal za praćenje faze ateroskleroze i predviđanje rizika za krvožilni incident imaju: adhezijske molekule, citokini i kemokini, mijeloperoksidaza, topljivi CD40 ligand, adiponektin i metaloproteinaze matriksa, ali su potrebna dodatna istraživanja i meta-analize kako bi se potvrdila njihova korisnost.

resents the underlying mechanism leading to the formation of human atheroma and favouring both the destabilization of vulnerable plaques and the formation of occlusive thrombi. Inflammatory cytokines involved in vascular inflammation stimulate the generation of endothelial adhesion molecules, proteases, and other mediators, which may enter the circulation in soluble form. These primary cytokines also induce production of the messenger cytokine interleukin-6, which stimulates the liver to increase production of acute-phase reactants such as C-reactive protein. In addition, platelets and adipose tissue can generate inflammatory mediators relevant to atherothrombosis. Numerous studies indicated that modest changes in circulating CRP levels, as detected by highly sensitive methods (hsCRP), can be extremely useful in predicting cardiovascular and perhaps cerebrovascular diseases in apparently healthy individuals as well as in patients affected by atherosclerosis. Subjects manifesting with identical low density cholesterol and/or blood pressure levels have different rates of cardiovascular accidents on the basis of different circulating CRP concentrations. In high-risk secondary prevention settings such as acute coronary syndrome patients being treated with statin therapy, achieving low levels of plasma hsCRP concentration appears to be of similar importance as achieving low levels of LDL cholesterol.
In addition, cellular adhesive molecules, cytokines and chemokines, myeloperoxidase, soluble CD40 ligand, adiponectin, and matrix metalloproteinase 9 may provide additional information for cardiovascular risk stratification and prediction but requires confirmation in additional studies.

Novi biljezi akutne ishemije miokarda

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Ishemija prethodi upalnoj vaskularnoj reakciji te oštećenju miokarda. Oko 40 % bolesnika s akutnim koronarnim sindromom (AKS) ne razvije nekrozu unatoč snažnoj koronarnoj bolesti i srčanoj ishemiji. Dinamično određivanje troponina i EKG vrlo je osjetljiva metoda za dijagnostiku infarkta miokarda, ali ne i za prepoznavanje ishemije. Stoga su razumljiva znanstvena traganja za biljegom koji će biti osjetljiv na ishemiju dok još nije započela nekroza (npr. nestabilna angina) koju prepoznajemo po porastu troponina tek nakon 4 sata.
Istraživanja ističu nekoliko različitih biljega kojima je zajednička osobina promptni porast u ishemijskom okru-

New biomarkers of acute myocardial ischemia

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Ischemia reflects both a vascular inflammatory response and myocardial injury.
About 40% of patients with ACS may not develop necrosis despite severe coronary artery disease and myocardial ischemia. Serial troponins and ECGs are very sensitive for the detection of myocardial infarction but they are insensitive for the detection of ischemia. Therefore, markers that could reliably detect ischemia even in the absence of necrosis (i.e., unstable angina) and/or before troponin level increase are desirable.
Several biomarkers are under investigation. All of them tend to be short-lived, increase promptly or within 3 h, and return to reference value within 3-24 h.

ženju (5 min do 3 sata) te brzi povratak na normalu (3 do 24 sata).
Ishemijom modificirani albumin (IMA) predskazatelj je nekroze miocita. Hipoksijom generirani slobodni radikali oštećuju i mijenjaju N-terminalni kraj albumina što mu smanjuje afinitet za kobalt. Analitička metoda upravo koristi to novo svojstvo mjereći smanjenje sposobnosti vezanja kobalta za albumin. U ranoj dijagnostici AKS kad su ostale metode neosjetljive, IMA pokazuje negativnu prediktivnu vrijednost veću od 95%, osjetljivost dvaput veću od EKG-a i 4 puta veću od troponina.
Nadalje, porast koncentracije proporcionalan ishemiji pokazuju nevezane slobodne masne kiseline (UFFA) i njihov specifični srčani vezujući protein (H-FABP). Istražuje se i polipeptidni biljeg nourin-1 (otpušta se iz miocitnog mitohondrija već nakon 5 min ishemije), kolin (stimuliran fosfolipazom D) i BNP (hormon B-natrijuretski peptid) čije koncentracije rastu nakon ishemijskog podražaja bez znakova nekroze miocita.
Primjena metabolomike uz pomoć novih tehnologija, poglavito s HPLC-MS sustavom, otkriva značajne promjene sadržaja metabolita iz ciklusa limunske kiseline (središte oksidativne fosforilacije u miokardu) i metabolita iz urea ciklusa.
Klinička vrijednost novih biljega ishemije nije još istražena. Za većinu ne postoje standardizirani analitički postupci, studije za referentne intervale, ni ujednačene kliničke evaluacije. Usto, nespecifični su za miokard – i drugi ishemični organi izvorište su istih biljega. Zbog toga je njihova valjanost ograničena i još nespremna za kliničku praksu.

Ischemia-modified albumin (IMA) is a marker of impending myocyte necrosis. During ischemia, free-radical damage alters the N-terminus of albumin and affinity to bind cobalt is reduced. Studies have shown that the negative predictive value of IMA was over 95%, the sensitivity twice higher than an ECG and four times than troponin to detect patients with ACS at time of presentation, which is difficult to diagnose with other diagnostic methods.
Monitoring increased plasma unbound free fatty acid (UFFA) and their intracellular binding protein, heart-type fatty acid-binding protein (H-FABP) concentrations has been proposed as a biomarker for myocardial ischemia.
Ischemia can cause the release of mitochondrial proteins such nourin-1 (polypeptide 3 KD released rapidly by stressed myocytes; within 5 minutes by heart tissues in response to myocardial ischemia) and increased concentration of choline (released after stimulation by phospholipase D) Hypoxia also trigger release of BNP (naturally hormone B- natriuretic peptide) in absence of necrosis.
Current technologies, especially HPLC-MS analysis, can be used to identify clinically relevant perturbations in circulating metabolites. Application of metabolomics identifies changes in levels of metabolites belonging to the citric acid pathway. (central role in oxidative phosphorylation in the myocardium) and the urea cycle.
New markers of ischemia are yet to be evaluated. For more of them there is no standardized assay and no reference interval studies or consistent assay validation. None of them is specific to the myocardium. Therefore, their use is limited since other organs in ischemia may release these biomarkers, too. At present, none of these analytes are yet appropriate for routine clinical use.

Lipidi u moždanom udaru

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Lipids in stroke

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Kao što je već prikazano u nekoliko velikih perspektivnih kliničkih pokusa, terapija snižavanja koncentracije kolesterola je učinkovita primarna i sekundarna preventivna mjera u smanjenju rizika od moždanog udara. Rizik od ponovljenog udara znatno je smanjen kod bolesnika koji su nedugo nakon udara započeli s redovitom primjenom statina za snižavanje koncentracije kolesterola. Međutim određivanje koncentracije lipida i terapija s ciljem smanjenja koncentracije lipida kod bolesnika hospitaliziranih zbog ishemijskog moždanog udara, još uvijek nije ušla u široku upotrebu, niti se još u dovoljnoj mjeri razumije uloga i važnost lipida kod bolesnika koji su pretrpje-

As already shown in several major prospective clinical trials, cholesterol-lowering therapy is an efficient primary and secondary preventive measure in reducing the risk of stroke. The risk of recurrent stroke is significantly reduced in stroke patients who began regular treatment with the cholesterol-lowering statin drugs soon after the stroke. However, lipid testing and lipid lowering therapy in patients hospitalized for ischemic stroke is widely underused and the exact role and significance of lipids in stroke patients is still not well understood. Some investigators suggest a different role of HDL and LDL cholesterol in the aetiology of different stroke subtypes. Furthermore,

li moždani udar. Neki su stručnjaci mišljenja kako HDL i LDL kolesterol imaju drugačiju ulogu u etiologiji različitih podtipova moždanog udara. Nadalje, postoje izvješća o tome da se na osnovi koncentracije lipida u serumu mjerene nedugo nakon prijema bolesnika u bolnicu može predvidjeti veličina regije zahvaćene infarktom, izgledi šestomjesečnog preživljenja, podtip moždanog udara te rana smrtnost od moždanog udara. Međutim ne postoji univerzalno prihvaćena preporuka optimalnog vremena za mjerenje koncentracije lipida. Istraživanja provedena tijekom ranog akutnog stadija moždane ishemije dale su do sada proturječne rezultate. Koncentracije lipida uglavnom su bile niske neposredno nakon moždanog udara, no u literaturi postoje i navodi o povišenoj koncentraciji lipida nakon moždanog udara. Stoga je koncentracija lipida kod akutnog moždanog udara još uvijek nepouzdana mjera lipidnog statusa. Jedno od važnijih rezultata u jednom našem nedavnom istraživanju o bolesnicima koji su pretrpjeli moždani udar je da su više koncentracije triglicerida u serumu bile povezane s težom kliničkom slikom i neurološkim deficitom. Trebalo bi provesti daljnja istraživanja kako bi se istražila vremenska dinamika promjena u koncentraciji lipida kod akutnog ishemijskog moždanog udara te da se ustanovi najbolje vrijeme za mjerenje koncentracije lipida kako bi se započela terapija s ciljem snižavanja njihove koncentracije.

it has been reported that serum lipid levels measured in early period after stroke admission are predictive of infarct volume and 6-month mortality rate, brain infarction subtype and early death from stroke. Nevertheless, there is not a widely accepted recommendation on the optimal time for lipid measurement. Studies on the lipid concentrations obtained during the early acute period of brain ischemia have so far produced conflicting results. Lipid concentrations have mostly been found lower in the early period after the stroke but there are also some reports in the literature on the elevated lipids in early stroke period. Lipid level in acute stroke is therefore still the unreliable measure of lipid status. The major finding in one our recent study on stroke patients was that higher serum triglycerides were associated with more severe stroke and substantial neurological deficit. Further studies should be done to explore the time dependent changes in lipid profile in acute ischemic stroke as well as the best time for lipid measurement, with the purpose of initiating the lipid lowering therapy.

Ateroskleroza i procjena rizika kod akutnog infarkta miokarda

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Troponin, mijeloperoksidaza (MPO) i homocistein su dijagnostički biljezi koronarnih bolesti. Dok je Troponin etabliran test za isključivanje koronarne etiologije bolesti, MPO je potpuno novi test za identifikaciju visokorizičnih pacijenata kojima prijeti ruptura aterosklerotskog plaka.
Abbott Dijagnostika nudi potpuno automatizirani Troponin i Homocistein test na AxSYM-u (Trp I, Hcy) a na Architect-u Trp I, Hcy i MPO.
Danas se troponin smatra biljegom izbora za infarkt miokarda (MI). Srčani troponini (Trp I) i Trp T su miofibrilarni proteini srčanih mišićnih stanica. Prema preporukama ESC/ACC (*European Society of Cardiology/American College of Cardiology*) 99-percentila je preporučeni cut-off. Čini se da je umetanje barem dva monoklonalna protutijela usmjerena na epitope N-terminalnog kraja specifične regije troponinskog testa posebno važno za postizanje optimalnosti testa. Značajno nadmoćnija klinička osjetljivost pos-

Atherosclerosis and risk stratification in acute myocardial infarction

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Troponin, myeloperoxidase (MPO) and homocysteine are markers for the diagnosis of cardiac diseases. While cardiac troponin assays are established tool for exclusion of coronary disease, MPO is a brand new marker for identifying high risk patients with arterosclerotic plaque ruptures.
Abbott Diagnostics offers fully automated troponin, homocysteine and MPO assays on AxSYM (Trp I, Hcy) and Architect platforms (Trp I, Hcy and MPO).
Nowadays Troponin is regarded as myocardial infarction (MI) marker of choice. Cardiac troponins I (TnI) and (TnT) are myofibrillar proteins of heart muscle cells. According to the ESC/ACC (European Society of Cardiology/American College of Cardiology) Consensus Guidelines the 99th percentile is recommended as cut-off.
Inclusion of at least two monoclonal antibodies against epitopes at the N-terminal part of the heart specific re-

tignuta je s Architect-ovim Trp I u odnosu na Roche TrpT i u odnosu na Immulite TnI test (GUSTO IV studija).
MPO ima glavnu ulogu u regulaciji upalnih procesa. MPO je hemoprotein pohranjen u leukocitima. Za vrijeme fagocitoze biva izbačen iz stanice leukocita.
MPO ima važnu ulogu u aterosklerotskim procesima. On je ujedno biljeg bolesti kod ateroskleroze s vulnerabilnim plakom, ali i akutni biljeg za otkrivanje rupture plaka.
To uvelike pomaže u postavljanju rane dijagnoze akutnog infarkta miokarda.
Homocistein (Hcy) je sumporna aminokiselina i kao takva dio je metioninskog metaboličkog puta. Povišena razina homocisteina ima prooksidativan učinak i povećava rizik za razvoj aterotrombotskih bolesti, demencije, Alzheimerove bolesti, depresije i osteoporoze.

gion of troponin seemed critical for optimum performance. Significantly superior clinical sensitivity was obtained with the Architect TnI assay vs. Roche TnT and Immulite TnI assays (GUSTO IV study).
MPO plays a major role in the regulation and termination of inflammatory processes. It is a hemoproteine stored in the leukocytes and will be secreted during phagocyte activation. MPO has important role in the atherosclerotic process. It is both a disease marker in atherosclerosis with vulnerable plaques and an event marker for plaque rupture and thus helps in the early diagnosis of acute myocardial infarction.
Homocysteine (Hcy) is a sulphur containing amino acid and part of methionine metabolic pathways. Elevated Hcy levels have a pro-oxidative effect and increase the risk for atherothrombotic disease, dementia, Alzheimer's disease, depression and osteoporosis.

Glikirani Hemoglobin A1c

Lucija Božić
Abbott Laboratories

Prema Svjetskoj zdravstvenoj organizaciji razlikuju se tri tipa šećerne bolesti:
- tip 1–10% od ukupnog broja dijabetičara ima tip 1. Uzrok je nedovoljna proizvodnja inzulina na razini beta Langerhansovih stanica pankreasa.
- tip 2 – kombinacija nedostatne proizvodnje inzulina i rezistencije receptora na inzulin
- gestacijska šećerna bolest (pogađa 2-5% svih trudnica). Nakon poroda najčešće dolazi do poboljšanja stanja ili do potpunog nestanka simptoma.

Šećerna bolest je karakterizirana povratnom ili perzistentnom hiperglikemijom.
Dijagnoza se postavlja temeljem prisustva bilo kojeg od slijedećih stanja:
- koncentracija glukoze u plazmi izmjerena natašte ≥ 7 mmol/L.
- koncentracija glukoze u plazmi ≥ 11,1 mmol/L dva sata nakon oralne primjene 75g glukozne otopine (OGTT test)
- izmjerena koncentracija glukoze u plazmi ≥ 11,1 mmol/L.

U ovisnosti o testu, HbA1c je najčešće 4 do 6% kod nedijabetičara, 6 do 8% u dijabetičara s kontroliranom šećernom bolesti, dok može biti i 20% u nekontroliranih dijabetičara.

Glycated Hemoglobin A1c

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WHO (World Health Organization) recognizes three main forms of diabetes:
- type 1–10% of total diabetes cases has type 1. Cause is in loss of the insulin-producing beta cells of the islets of Langerhans of the pancreas leading to a deficiency of the insulin
- type 2 – combination of defective insulin secretion and insulin resistance
- gestational diabetes (comprises 2–5% of all pregnant women). Diabetes symptoms usually improve or disappear after delivery.

Diabetes mellitus is characterised by recurrent or persistent hyperglycemia and is diagnosed by any one of the following:
- fasting plasma glucose level at or above 7 mmol/L.
- fasting plasma glucose level at or above 11,1 mmol/L two hours after 75g oral glucose load as in a glucose tolerance test.
- random plasma glucose level at or above 11,1 mmol/L.

Depending on the assay used, HbA1c is approximately 4 to 6% in nondiabetics, 6 to 8% in controlled diabetics and can be as much as 20% in uncontrolled diabetics
The current recommended goal for HbA1c in patients with diabetes is < 7.0%, which as defined as "good glycemic control" (American Diabetes Association Guidelines).

Najbolja kontrola šećerne bolesti postiže se održavanjem postotka glikiranog hemoglobina manjim od 7% [preporuke ADA-e (*American Diabetes Association*)].
Tvrtka Abbott Dijagnostika je u 2007.g. predstavila novi, potpuno automatizirani test AxSYM HbA1c (bez pretretmana) za određivanje glikiranog hemoglobina.
Uzorak je puna krv [natrijev fluorid/kalij oksalat (fluorid oksalat) i natrijev fluorid/natrij EDTA (fluorid EDTA)]. Test se izvodi na Abbott-ovom analizatoru AxSYM-u. Mjerenje postotka HbA1c se koristi u kliničkom praćenju šećerne bolesti, tj. u procjeni efikasnosti kontrole šećerne bolesti u proteklih 100-120 dana.
Standardni kalibrator za HbA1c na AxSYM-u je u skladu s NGSP/DCCT (*National Glycohemoglobin Standardization Program/Diabetes Control and Complications Trial*) kao i s IFCC stadardnim materijalom što osigurava veliku pouzdanost rezultata.

In 2007 Abbott Diagnostics launched new, fully automated immunoassay AxSYM HbA1c for the quantitative determination of percent hemoglobin A1c (HbA1c)-without pretreatment.
The Sample is whole blood [sodium fluoride/potassium oxalate (fluoride oxalate) and sodium fluoride/sodium EDTA (fluoride EDTA)]. Test is performed on Abbott analyzer AxSYM. Percent HbA1c measurements are used in the clinical management of diabetes to assess the long-term efficacy of diabetic control.
Standard AxSYM HbA1c calibrators are traceable to the IFCC reference calibrators and are aligned with the NGSP/DCCT (National Glycohemoglobin Standardization Program/Diabetes Control and Complications Trial) which ensure good reliability and confidence in result.