Molekularni mehanizmi inzulinske rezistencije, pretilosti i metaboličkog sindroma
Molecular Mechanisms of Insulin Resistance, Obesity and Metabolic Syndrome

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Sažetak

Inzulinska rezistencija je stanje poremećene sposobnosti odgovora na djelovanje inzulina. Najčešći osnovni uzrok je središnja pretilost, iako je primarna inzulinska rezistencija moguća i u osoba s normalnom težinom. Suvišno abdominalno masno tkivo otpušta povećane količine faktora tumorske nekroze α i slobodnih masnih kiselina, što izravno utječe na inzulinsko signaliziranje, smanjuje preuzimanje glukoze u mišićima, dovodi do pretjerane sinteze triglicerida i izaziva glukoneogenezu u jetri. Ostali čimbenici za koje se pretpostavlja da igraju ulogu u inzulinskoj rezistenciji su adiponektin (sniženje), leptin, IL-6 i neki drugi adipokini. Smatra se da je obična pretilost poligenog podrijetla uz utjecaj "pretilogene" okoline – povećan unos hrane i nedostatak tjelesne aktivnosti. Današnja visoka učestalost pretilosti mogla bi se objasniti evolucijskim pritiskom za odabir gena koji promiču pohranu masti za preživljenje u vrijeme gladovanja. Inzulinska rezistencija je prisutna zajedno sa središnjom pretilosti, hipertenzijom i dislipidemijom, koje se skupno označavaju kao metabolički sindrom. Ove pojavnosti predstavljaju snažne čimbenike rizika za šećernu bolest tipa 2 i kardiovaskularnu bolest.

Ključne riječi: inzulinska rezistencija, pretilost, metabolički sindrom, adipokini

Abstract

Insulin resistance is a state of impaired responsiveness to insulin action. The most common underlying cause is central obesity although primary insulin resistance in normal-weight individuals is also possible. Excess abdominal adipose tissue has been shown to release increased amounts of tumor necrosis factor α and free fatty acids, which directly affect insulin signaling, diminish glucose uptake in the muscle, drive exaggerated triglyceride synthesis and induce gluconeogenesis in the liver. Other factors presumed to play a role in insulin resistance are adiponectin (a decrease), leptin, IL-6 and some other adipokines. Common obesity is thought to be of polygenic origin with influence of "obesogenic" environment, i.e. increased food intake and the lack of physical activity. Today's high prevalence of obesity could be explained by evolutionary pressure for selection of genes promoting fat storage to survive in starvation. Insulin resistance frequently coexists with central obesity, hypertension and dyslipidemia, which have collectively been denoted as metabolic syndrome. These manifestations represent strong risk factors for diabetes mellitus type 2 and cardiovascular disease.

Key words: insulin resistance, obesity, metabolic syndrome, adipokines

Uvod

Inzulinska rezistencija (IR) definira se kao odgovor na inzulin manji od normalnog, što dovodi do hiperinzulinemije kako bi se održali euglikemijski uvjeti (1). Stoga kompenzacijska hiperinzulinemija zbog pojačanog lučenja β-stanica obvezatno popratno obilježje uz IR. Glavne značajke IR su loše inhibirana glukoneogeneza, poremećeno preuzimanje glukoze u mišićima i loše inhibirana lipoliza u masnom tkivu. Klinički biljezi IR su visceralna pretilost, crnkasta akantoza (2), akne, prekomjerna dlakavost (3), jetrena steatoza (1).

Zlatni standard za procjenu IR je hiperinzulinemijska euglikemijska spona (engl. *clamp*): inzulin se daje po ustalje-

Introduction

Insulin resistance (IR) is defined as less than normal response to insulin, which leads to hyperinsulinemia for euglycemic conditions to be maintained (1). Compensatory hyperinsulinemia due to enhanced β-cell secretion is therefore an obligate accompanying feature in IR. The main characteristics of IR are disinhibited gluconeogenesis, impaired uptake of glucose by muscle and disinhibited lipolysis in adipose tissue.

Clinical markers of IR are visceral obesity, acanthosis nigricans (2), acne, hirsutism (3) and hepatic steatosis (1).

The golden standard for evaluation of IR is hyperinsulinemic euglycemic clamp: insulin is infused at a con-

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noj stopi infuzijom, a glukoza se održava na bazalnim razinama infuzijom glukoze. Stopa infuzije glukoze daje mjeru preuzimanja glukoze u svim tkivima (4). Alternativne mjere za IR su koncentracije inzulina u plazmi natašte (2) i procjena modela homeostaze (engl. *homeostasis model assessment*, HOMA) izvedena iz koncentracija inzulina i glukoze u plazmi natašte (5).

Etiologija IR uključuje genetske čimbenike koji rezultiraju sindromnim oblicima IR, te čimbenike okoline: unos hrane, nedostatna tjelesna aktivnost, starenje, pušenje ili uzimanje lijekova – tiazidnih diuretika, beta adrenergičnih antagonista, glukokortokoida, koji mogu uzrokovati IR ili doprinijeti njegovu nastanku (2). Najvažniji čimbenik je pretilost koja je obično složenog poligenetskog i okolinskog podrijetla (2, 6). Abdominalno masno tkivo je izvor slobodnih masnih kiselina (engl. *free fatty acids*, FFA) i različitih hormona (adipokina) koji su upleteni u razvoj IR. Nasuprot tome, ograničen unos kalorija, smanjenje težine i tjelesna aktivnost poboljšavaju inzulinsku osjetljivost (2, 3, 7).

U radu se objašnjavaju mehanizmi IR koji uključuju: poremećeno lučenje adipokina i povećan dotok FFA iz središnjeg masnog tkiva, te druge poremećaje inzulinskih predreceptora, receptora i postreceptora.

Mehanizmi inzulinske rezistencije

Faktor tumorske nekroze α i slobodne masne kiseline

Udruženost IR s povišenim faktorom tumorske nekroze α (engl. *tumor necrosis factor* α, TNF-α), interleukinom 6 (IL-6), makrofazima i monocitnim kemoatraktantnim proteinom-1 (engl. *monocyte chemoattractant protein-1*, MCP-1), inhibitorom-1 aktivatora plazminogena (engl. *plasminogen activator inhibitor-1*, PAI-1), adipsinom te sniženim adiponektinom utvrđena je u mnogim studijama (8). IR je popratno obilježje u mnogih pretilih bolesnika. Masno tkivo otpušta velike količine TNF-α, koji je barem djelomice odgovoran za razvoj IR kod pretilosti (9). S druge strane, poznato je da se s gubitkom na težini povećava inzulinska osjetljivost; smatra se kako tome dijelom posreduje smanjeno lučenje adipoznog TNF-α (10). TNF-α je glavni autokrini/parakrini čimbenik koji pokreće lučenje slobodnih masnih kiselina (FFA) iz masnog tkiva u krvotok (9). Međutim, ostaje nejasno koji čimbenici doista pokreću otpuštanje adipokina iz masnog tkiva.

TNF-α posreduje potiskivanje mnogih gena odgovornih za preuzimanje i pohranu glukoze i FFA. Za adipocite 3T3-L1 je pokazano kako se regulacija naviše i naniže gena ovisnih o TNF-α odvija obveznim aktiviranjem faktora nuklearne transkripcije κB (11). Djelovanjem TNF-α dolazi do pojačane lipolize uz otpuštanje FFA i citokina.

TNF-α i FFA remete inzulinsko signaliziranje u tkivima koja odgovaraju na inzulin, poglavito u mišićima. Prema hipotezi o opskrbi lipidima (Randleova hipoteza), otpuštene FFA djeluju kao prevladavajući supstrat u intermedi-

stant rate and glucose is held at basal levels by glucose infusion. The rate of the latter is a measure of all tissues' glucose uptake (4). Alternative measures of IR are fasting plasma insulin concentrations (2) and homeostasis model assessment (HOMA) derived from fasting plasma insulin and glucose concentrations (5).

The etiology of IR includes genetic factors resulting in syndromic forms of IR, and environmental factors: food intake, poor physical activity, aging, smoking or administration of drugs – thiazide diuretics, beta adrenergic antagonists and glucocorticoids, which can cause or contribute to IR (2). The most important factor is obesity, which is usually of combined polygenetic and environmental origin (2, 6). Abdominal adipose tissue is a source of free fatty acids (FFA) and various hormones (adipokines) implicated in the development of IR. Conversely, restricted calorie intake, weight reduction and physical activity improve insulin sensitivity (2, 3, 7).

The present paper explains the mechanisms of IR which include disregulated secretion of adipokines and increased efflux of FFA from central adipose tissue, and other insulin prereceptor, receptor and postreceptor impairments.

The Mechanisms of Insulin Resistance

Tumor necrosis factor α and free fatty acids

Numerous studies have found associations between increased tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), macrophages and monocyte chemoattractant protein-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1), adipsin, and decreased adiponectin with IR (8).

In the majority of obese patients IR is an accompanying feature. Adipose tissue releases great amounts of TNF-α, which is at least partly responsible for the development of IR in obesity (9). On the other hand, weight loss is well known to increase insulin sensitivity, which is thought to be mediated in part by decreased adipose TNF-α release (10). TNF-α is the main autocrine/paracrine factor triggering the secretion of FFA from adipose tissue into the circulation (9). However, it remains unclear which factors actually trigger the release of adipokines from adipose tissue.

TNF-α mediates repression of many genes responsible for glucose and FFA uptake and storage. For 3T3-L1 adipocytes it has been shown that TNF-α dependent gene up- and down-regulation occurs by obligatory activation of nuclear transcription factor κB (11). Upon TNF-α action, enhanced lipolysis occurs with the release of FFA and cytokines.

TNF-α and FFA impair insulin signaling in insulin responsive tissues, especially muscle. The released FFA, according to the lipid supply hypothesis (Randle hypothesis), act as a predominant substrate in intermediary metabolism. Increased NADH/NAD+ and acetyl-CoA/CoA ratios could

jarnom metabolizmu. Povišeni omjeri NADH/NAD+ i acetil-CoA/CoA mogli bi biti razlogom smanjenog preuzimanja glukoze, što znači poremećene inzulinske osjetljivosti (12, 13). Visceralno masno tkivo luči FFA izravno u portalni krvotok, čime snažno utječe na jetru, a ne na potkožno masno tkivo otpuštajući svoje proizvode u perifernu cirkulaciju (1).

U jetri velike količine FFA osiguravaju obilan supstrat za sintezu triglicerida i VLDL, te za glukoneogenezu. TNF-α potiskuje gene za preuzimanje glukoze i beta oksidaciju (14). Dolazi do *de novo* sinteze kolesterola, potom do regulacije naviše odgovarajućih gena pomoću TNF-α (8).

FFA također pokreću sintezu fibrinogena i PAI-1 u jetri (15). FFA koje iz visceralnog masnog tkiva otječu u portalnu cirkulaciju i u jetru smanjuju jetreni klirens inzulina, čime doprinose hiperinzulinemiji (13). Suvišak triglicerida se nakuplja u jetri (1). U mišićima pak visoke koncentracije FFA pogoduju beta oksidaciji, čime se smanjuje preuzimanje i oksidacija glukoze (16). No, beta oksidacija je nedostatna za djelotvorno uklanjanje FFA iz krvotoka, osobito ako nema tjelesne aktivnosti (17). Sinteza glikogena u mišićima je suspregnuta. Mišić ima glavnu ulogu u uklanjanju glukoze (80–90%), pa njezino smanjeno preuzimanje u velikoj mjeri doprinosi hiperglikemiji (9, 18). Suvišne FFA pohranjuju se kao kapljice triglicerida u mišićima (1, 7, 17). U masnom tkivu FFA suzbijaju aktivnost lipoprotein lipaze, koju inače potiče inzulin, te tako onemogućavaju klirens FFA iz krvotoka (19). Sve u svemu, lipidi otpušteni iz adipocita kao FFA prenose se kao trigliceridi pomoću VLDL i premještaju u nemasna tkiva (20).

Pokazano je kako TNF-α naniže regulira gene za adiponektin, transporter glukoze 4 (engl. *glucose transporter 4*, GLUT4), supstrat-1 inzulinskog receptora (engl. *insulin receptor substrate-1*, IRS-1), CCAAT/pojačajni vezni protein α (engl. *CCAAT/enhancer binding protein* α, C/EBP-α), peroksizomni proliferator-aktivirani receptor γ (engl. *peroxisome proliferator-activated receptor* γ, PPAR-γ) i perilipin u adipocitima (11, 14). TNF-α naviše regulira mnoge gene izražene u masnom tkivu, koji su odgovorni za upalu, imuni odgovor i energetsku ravnotežu (vaskularna stanična prianjajuća molekula-1 (VCAM-1), PAI-1, IL-6, IL-1β, angiotenzinogen, rezistin, leptin) (14).

Leptin

Leptin je hormon što ga u najvećoj mjeri luči masno tkivo, a označava dostatnu količinu energije. Leptin smanjuje unos hrane i povećava potrošnju energije (21). Ovi učinci nastupaju djelovanjem leptina na hipotalamus i izravno na ciljna tkiva (mišić, gonade, β-stanice, jetru) (22).

U normalnim uvjetima održavanja težine koncentracije leptina pozitivno koreliraju s ukupnom tjelesnom masnom masom. Kod kratkotrajnog uskraćivanja hrane serumske razine leptina se snižavaju, dok se obrnuto događa kod kratkotrajnog prekomjernog hranjenja (23).

be the reason for the decreased glucose uptake, which means impaired insulin sensitivity (12, 13). Visceral adipose tissue secretes FFA directly to the portal blood flow thereby exerting potent effects on the liver rather than subcutaneous adipose tissue releasing its products to peripheral circulation (1).

In the liver, high amounts of FFA provide an abundant substrate for triglyceride and VLDL-synthesis, and gluconeogenesis. TNF-α represses genes for glucose uptake and beta oxidation (14). *De novo* cholesterol synthesis occurs followed by TNF-α up-regulation of the corresponding genes (8).

FFA also trigger fibrinogen and PAI-1 synthesis in the liver (15). FFA draining from visceral adipose tissue to portal circulation and to the liver decrease hepatic insulin clearance, thereby contributing to hyperinsulinemia (13). Excess triglycerides are accumulating in the liver (1).

In the muscle, high FFA concentrations favor beta oxidation, which diminishes glucose uptake and oxydation (16). However, beta oxidation is inadequate to clear FFA efficiently from the circulation, even more in the lack of physical activity (17). Glycogen synthesis in the muscle is inhibited. Muscle is in force as the main glucose disposer (80%–90%) and diminished uptake contributes largely to hyperglycemia (9, 18). Excess FFA are stored as triglyceride droplets in the muscle (1, 7, 17).

In adipose tissue, FFA inhibit lipoprotein lipase activity which is otherwise stimulated by insulin, and thereby render clearance of FFA from circulation impossible (19). Overall, lipids released from adipocytes as FFA are transported as triglycerides by VLDL and shifted to non-adipose tissues (20).

TNF-α has been shown to down-regulate the genes for adiponectin, glucose transporter 4 (GLUT4), insulin receptor substrate-1 (IRS-1), CCAAT/enhancer binding protein α (C/EBP-α), peroxisome proliferator-activated receptor γ (PPAR-γ) and perilipin in adipocytes (11, 14). TNF-α upregulates many genes expressed in adipose tissue, which are responsible for inflammation, immune response and energy balance (vascular cell adhesion molecule-1 (VCAM-1), plasminogen activator inhibitor-1 (PAI-1), IL-6, IL-1β, angiotensinogen, resistin, leptin) (14).

Leptin

Leptin is a hormone secreted predominantly by adipose tissue and is a signal of energy sufficiency. It decreases food intake and increases energy expenditure (21). These effects are mediated by leptin action on the hypothalamus and directly on target tissues (muscle, gonads, β-cells, liver) (22). In normal conditions of weight maintenance leptin concentrations positively correlate with total body fat mass. In short term food deprivation serum leptin levels decrease and the opposite is true for short term overfeeding (23).

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Leptin predstavlja bitan čimbenik fertiliteta, jer se je pokazalo kako su snižene koncentracije leptina nakon uskraćivanja hrane odgovorne za suzbijanje hipotalamo-hipofizno-gonadne osi (24).

Klinička stanja sa smanjenom masnom masom (lipodistrofije) obilježena su sniženim koncentracijama leptina u plazmi i IR. Davanjem leptina značajno se poboljšava inzulinska osjetljivost u ovim stanjima (25), što pokazuje da je normalna količina masnog tkiva presudna za normalnu inzulinsku osjetljivost, a to se barem djelomice ispunjava kroz lučenje leptina i njegovim učincima.

Važan učinak leptina je simpatička stimulacija putem neurona koji odgovaraju na leptin u hipotalamusu (8). To bi moglo djelomice objasniti razvoj hipertenzije kod visceralne pretilosti te u nepretilim stanjima. U skladu s tim, mišićna simpatička aktivnost kod nepretilih normotenzivnih muškaraca dobro korelira s koncentracijama leptina vezanog za bjelančevine (26).

Adiponektin

Adiponektin pokazuje snažnu obrnutu korelaciju s IR u lipodistrofiji i pretilosti, te s upalnim stanjima (27, 28). Adiponektin luče isključivo adipociti (27). Adiponektin poboljšava inzulinsku osjetljivost kroz različite mehanizme. U jetri izaziva oksidaciju masnih kiselina, smanjuje sintezu lipida, smanjuje preuzimanje FFA i suzbija glukoneogenezu regulirajući enzime naniže (8, 23, 29). U mišiću adiponektin pogoduje oksidaciji glukoze i FFA. Ove učinke dijelom omogućuje aktiviranje AMP-kinaze (28). Tako adiponektin snižava razine FFA i glukoze u plazmi (8, 23). Katabolizam FFA se potiče izravno ili kroz poticanje nuklearnih receptora PPAR-γ (30).

Adiponektin smanjuje izraženost prianjajućih molekula na stijenci krvnih žila, suzbija kemotaksu makrofaga i njihovu pretvorbu u pjenaste stanice, proliferaciju glatkomišićnih stanica i upalne događaje u aterogenezi što ih promiču IL-6, PAI-1 itd. (8). Adiponektin također suzbija lučenje TNF-α (31).

Razine adiponektina povećavaju se s gubitkom težine (32) i liječenjem tiazolidinedionima (engl. *thiazolidinediones*, TZD) (33), koji su agonisti PPAR-γ. Sinteza adiponektina je poremećena u stanjima suviška kalorija, što bi moglo biti povezano s rezistencijom ili nedostatkom leptina (23). Inzulin i inzulinu sličan faktor rasta (engl. *insulin-like growth factor-1*, IGF-1) potiču sintezu adiponektina (23).

Slično tome, IL-10 isto tako ima antidijabetogeni učinak: kod pretilosti bez metaboličkog sindroma razine IL-10 u plazmi su povišene, ali je IL-10 snižen u metaboličkom sindromu (34).

Rezistin

Visceralno masno tkivo luči rezistin u daleko većoj mjeri nego potkožno masno tkivo (8). Kod pretilosti u glodavaca su serumske razine rezistina povišene, a neki su pokusi

Leptin represents an essential fertility factor as decreased leptin concentrations following food deprivation have been shown to be responsible for the suppression of the hypothalamic-pituitary-gonadal axis (24).

Clinical states with diminished adipose mass (lipodystrophies) are characterized by reduced plasma leptin concentrations and IR. Leptin administration significantly improves insulin sensitivity in these conditions (25), indicating that normal amount of adipose tissue is critical for normal insulin sensitivity, and this is at least partly fulfilled *via* leptin secretion and its effects.

An important leptin effect is sympathetic stimulation achieved by eliciting leptin-responsive neurons in the hypothalamus (8). This could in part explain the development of hypertension in visceral obesity and non-obese states. In accordance with this, muscle sympathetic activity in non-obese normotensive men correlates well with protein-bound leptin concentrations (26).

Adiponectin

Adiponectin shows strong inverse correlation to IR in lipodystrophy and obesity, and to inflammatory states (27, 28). It is secreted exclusively by adipocytes (27). Adiponectin improves insulin sensitivity by various mechanisms: in the liver, it induces fatty acid oxidation, decreases lipid synthesis, decreases uptake of FFA and represses gluconeogenesis by enzyme down-regulation (8, 23, 29). In muscle, adiponectin favors glucose and FFA oxidation. These effects are partly due to the activation of AMP-kinase (27). Thereby, adiponectin decreases plasma FFA and glucose levels (8, 23). FFA catabolism is stimulated either directly or through stimulation of PPAR-γ nuclear receptors (30).

Adiponectin decreases the expression of adhesion molecules on blood vessel wall, inhibits chemotaxis of macrophages and their conversion to foam cells, proliferation of smooth muscle cells and inflammatory events in atherogenesis, which are promoted by IL-6, PAI-1 etc. (8). Adiponectin also suppresses secretion of TNF-α (31).

Adiponectin levels increase with weight loss (32) and treatment with thiazolidinediones (TZD) (33), which are PPAR-γ agonists. The synthesis of adiponectin is impaired in the states of calorie excess, which might be associated with leptin resistance or deficiency (23). Insulin and insulin-like growth factor (IGF-1) stimulate adiponectin synthesis (23).

Similarly, IL-10 also exerts an antidiabetogenic effect: in obesity without the metabolic syndrome IL-10 plasma levels are increased, but in the metabolic syndrome IL-10 is decreased (34).

Resistin

Resistin is secreted to a much greater extent by visceral than by subcutaneous adipose tissue (8). In rodent obe-

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potvrdili da rezistin uzrokuje IR (35). Međutim, druga pak ispitivanja nisu potvrdila takve rezultate (8, 36).

Ljudski rezistin pokazuje tek 64%-tnu homolognost s rezistinom glodavaca (37) i izraženost rezistina u ljudskim adipocitima nije jednako udružena s IR ili pretilošću (23). S druge strane, tiazolidindioni (TZD) možda svoje učinke djelomice ostvaruju kroza smanjeno djelovanje rezistina, jer se njegovo lučenje smanjuje tijekom liječenja TZDima (23). Sve u svemu, ulogu rezistina u ljudi tek treba podrobnije razjasniti.

Ostali adipokini

Makrofazi i monocitni kemoatraktantni protein-1 (MCP-1) su izravno uzročno povezani s IR: MCP-1 remeti ulazak glukoze i inzulinske signale u stanicama (38). Adipociti luče MCP-1; on privlači makrofage u masno tkivo i promiče njihovo otpuštanje IL-1 i TNF-α (8). On isto tako suzbija rast i diferencijaciju adipocita. MCP-1 promiče aterosklerozu privlačeći makrofage i pogodujući njihovom nakupljanju u staničnim stijenkama (39).

PAI-1 je više izražen u visceralnom u usporedbi s potkožnim masnim tkivom (40). On je snažno udružen s visceralnom pretilošću, IR i metaboličkim sindromom. Pretpostavlja se da PAI-1 doprinosi pretilosti i IR, te da ima uzročnu ulogu u daljnjem razvoju kardiovaskularne bolesti zbog svog protrombotskog djelovanja (8). Razine PAI-1 u plazmi snižavaju se s gubitkom težine (8) i liječenjem tvarima za inzulinsku senzibilizaciju (41).

Studije s IL-6 ukazuju na njegovu uzročnu ulogu u IR, jer plazmatske koncentracije i izraženost u masnom tkivu te polimorfizam IL-6 dobro koreliraju s pretilošću i IR. Pokazano je kako IL-6 remeti inzulinsko signaliziranje (42), suzbija adipogenezu i lučenje adiponektina (8). Isto tako, IL-6 izaziva IR u jetri i adipocitima (43).

U središnjem živčanom sustavu IL-6 ima suprotne učinke – što ukazuje na to da on pogoduje potrošnji energije. Davanje IL-6 transgeničnim glodavcima kojima je uklonjen gen za IL-6 poništilo je razvoj pretilosti (44).

Glukokortikoidi

Glukokortikoidi su dobro poznati antagonisti inzulina. Oni se suprotstavljaju učincima inzulina i time mogu izazvati IR. Oni djeluju na objema razinama IR: pojačavaju jetrenu glukoneogenezu i otpuštanje glukoze iz jetre, te remete preuzimanje glukoze u perifernim tkivima. Prethodno spomenute visoke razine FFA predstavljaju mehanizam za ovaj potonji učinak, a najmanje su tri moguća puta kojima može nastupiti lipoliza:

1. glukokortikoidi povećavaju pretvorbu noradrenalina u adrenalin (fenil-etanolamin N-metiltransferaza u skeletnim mišićima), koji djeluje na hormonski osjetljivu lipazu u masnom tkivu i provodi lipolizu (45);

2. oni posreduju lipolizu kroz reguliranje naviše PPAR-γ (46);

sity, serum resistin levels are increased and some experiments have confirmed resistin as causing IR (35). However, some other studies failed to confirm these results (8, 36). Human resistin shows only 64% homology with rodent resistin (37) and expression of resistin in human adipocytes is not uniformly associated with IR or obesity (23). On the other hand, TZD may exert their effects partly through a diminished action of resistin as its secretion is decreased during TZD therapy (23). Taken together, the role of resistin in humans remains to be further elucidated.

Other adipokines

Macrophages and monocyte chemoattractant protein-1 (MCP-1) are directly causally associated with IR: MCP-1 impairs glucose entrance and insulin signaling in cells (38). MCP-1 is secreted by adipocytes; it attracts macrophages to adipose tissue and promotes their IL-1 and TNF-α release (8). It also inhibits adipocyte growth and differentiation. MCP-1 promotes atherosclerosis by attracting macrophages and favoring their accumulation in vessel walls (39).

PAI-1 has higher expression in visceral compared to subcutaneous adipose tissue (40). It is strongly associated with visceral obesity, IR and metabolic syndrome. PAI-1 is hypothesized to contribute to obesity and IR, and has a causal role in further development of cardiovascular disease for its prothrombotic activity (8). PAI-1 plasma levels decrease after weight loss (8) and therapy with insulin sensitizing substances (41).

Studies with IL-6 have suggested its causal role in IR, as plasma concentrations and adipose tissue expression, and polymorphisms of IL-6 correlate well with obesity and IR. IL-6 was shown to interfere with insulin signaling (42), and to inhibit adipogenesis and secretion of adiponectin (8). IL-6 also induces IR in the liver and adipocytes (43).

In the central nervous system IL-6 has opposite effects – suggesting that it favors energy expenditure. Administration of IL-6 to IL-6 gene knockout rodents reversed obesity (44).

Glucocorticoids

Glucocorticoids are well known insulin antagonists. They oppose the effects of insulin and thereby could induce IR. They act on both levels of IR: they enhance liver gluconeogenesis and glucose release, and impair glucose uptake by peripheral tissues. The mechanism for the latter are previously mentioned high levels of FFA, and there are at least three possible ways how lipolysis can occur:

1. glucocorticoids increase norepinephrine conversion to epinephrine (phenyl-ethanolamine N-methyltransferase in skeletal muscle), which acts on hormone sensitive lipase in adipose tissue and performs lipolysis (45);

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3. oni suzbijaju lipoprotein lipazu i time onemogućavaju preuzimanje FFA u masnom tkivu (47).

U skeletnim mišićima je pokazana poremećena translokacija GLUT4 kao posljedica djelovanja glukokortikoida (48). Pokazano je kako glukokortikoidi suzbijaju vazodilataciju (izazvanu inzulinom putem dušičnom oksida), pa su tada ciljna tkiva dobivala manje glukoze (49). Ove učinke glukokortikoida još pojačavaju FFA povećanim vezanjem glukokortikoida za njihove receptore (50).

Molekularni mehanizmi poremećenog inzulinskog signaliziranja

Normalno inzulinsko signaliziranje

Inzulinski receptor je heterotetramerni receptor koji je izražen na jetrenim, adipoznim i skeletno mišićnim stanicama. Vezanje inzulina pokreće oligomerizaciju i autofosforilaciju receptora na tirozinskim ostacima, te tirozinsku fosforilaciju IRS-1, -2, -3, -4, IRS5/DOK4, IRS6/DOK5. Ova fosforilacija čini osnovu za daljnje udruživanje s nizvodnim signalnim bjelančevinama koje se razilaze u tri različite putanje: putanju fosfoinozitid-3-kinazu (engl. *phosphoinositide-3-kinase*, PI3K), putanju CAP/Cbl/TC10 i putanju ovisnu o mitogenom aktiviranoj protein kinazi (engl. *mitogen-activated protein kinase*, MAP-kinase) (Slika 1.) (51, 52). PI3K uzajamno djeluje s fosforiliranim Tyr na molekule IRS te se nakon stvaranja fosfatidilinozitol-3,4,5-trifosfata (engl. *phosphatidylinositol-3,4,5-triphosphat*, PIP_3) aktiviraju različite protein kinaze (53). Posljedično tome dolazi do deaktiviranja glikogen sintaze kinaze 3 (engl. *glycogen synthase kinase 3*, GSK-3), što na koncu rezultira sintezom glikogena; gen sintaze masnih kiselina reguliran je naviše, dok je gen fosfoenolpiruvat karboksikinaze (engl. *phosphoenolpyruvate carboxykinase*, PEPCK) reguliran naniže. Bitan učinak puta PI3K je translociranje glavnog prijenosnika glukoze GLUT4 u plazmatsku membranu (51, 52). Sinteza bjelančevina nastupa aktiviranjem ciljnog enzima za rapamicin koji je svojstven sisavcima (engl. *mammalian target of rapamycin*, mTOR) (54).

Kako bi se preuzimanje glukoze odvijalo u potpunosti, prilagodbena bjelančevina CAP upošljava proto-onkogen Cbl u fosforilirani inzulinski receptor, što u konačnici dovodi do pojačane translokacije GLUT4 (51).

Treći put dovodi do aktiviranja MAP-kinaze te stanične proliferacije i diferencijacije putem regulacije genske transkripcije (52, 55).

Nedostatci u inzulinskom signaliziranju

Manji broj slučajeva inzulinske rezistencije obilježen je po jednom genetskom ili stečenom značajkom. Protuinzulinska autoantitijela nađena su kod šećerne bolesti tipa 1. (56). S druge strane, u genu inzulinskih receptora utvrđeno je više od 60 mutacija. Među njima je IR tip A udružen sa stanjem heterozigotne mutacije, koje čini osnovu

2. they mediate lipolysis *via* up-regulation of PPAR-γ (46); and

3. they inhibit lipoprotein lipase and thus disable the uptake of FFA by adipose tissue (47).

In skeletal muscle impaired translocation of GLUT4 was shown as a consequence of glucocorticoid action (48). Glucocorticoids were shown to inhibit vasodilatation (induced by insulin *via* nitrogen oxide) and less glucose was then delivered to target tissues (49). These effects of glucocorticoids are even potentiated by FFA increasing glucocorticoids binding to their receptors (50).

Molecular Mechanisms of Impaired Insulin Signaling

Normal insulin signaling

Insulin receptor is a heterotetramer receptor, which is expressed on the liver, adipose and skeletal muscle cells. Binding of insulin triggers oligomerization and receptor autophosphorylation on tyrosine residues and tyrosine phosphorylation of IRS-1, -2, -3, -4, IRS5/DOK4, IRS6/DOK5. This phosphorylation provides the base for following association with downstream signal proteins which diverge into three different pathways: phosphoinositide-3-kinase (PI3K) pathway, CAP/Cbl/TC10 pathway and mitogen-activated protein kinase (MAP-kinase) dependent pathway (Fig. 1) (51, 52). PI3K interacts with phosphorylated Tyr on IRS molecules and upon formation of phosphatidylinositol-3,4,5-triphosphate (PIP_3) various protein kinases are activated (53). As a consequence, glycogen synthase kinase 3 (GSK-3) is inactivated, which at the final stage results in glycogen synthesis; the fatty acid synthase gene is up-regulated and phosphoenolpyruvate carboxykinase (PEPCK) gene is down-regulated. An essential effect of PI3K pathway is translocation of the main glucose transporter GLUT4 to the plasma membrane (51, 52). Protein synthesis is activated *via* enzyme mammalian target of rapamycin (mTOR) activation (54). For glucose uptake to manifest fully, the adapter protein CAP recruits proto-oncogene Cbl to the phosphorylated insulin receptor, which finally results in reinforced GLUT4 translocation (51). The third pathway leads to MAP-kinase activation and cellular proliferation and differentiation *via* gene transcription regulation (52, 55).

Defects in insulin signaling

A minority of insulin resistant cases are characterized by a single genetic or acquired trait. Anti-insulin autoantibodies have been found in diabetes mellitus DM type 1 (DM1) (56). On the other hand, more than 60 mutations have been identified in the insulin receptor gene. Among them type A IR is associated with heterozygous mutation state which underlies decreased Tyr phosphorylation of the β-
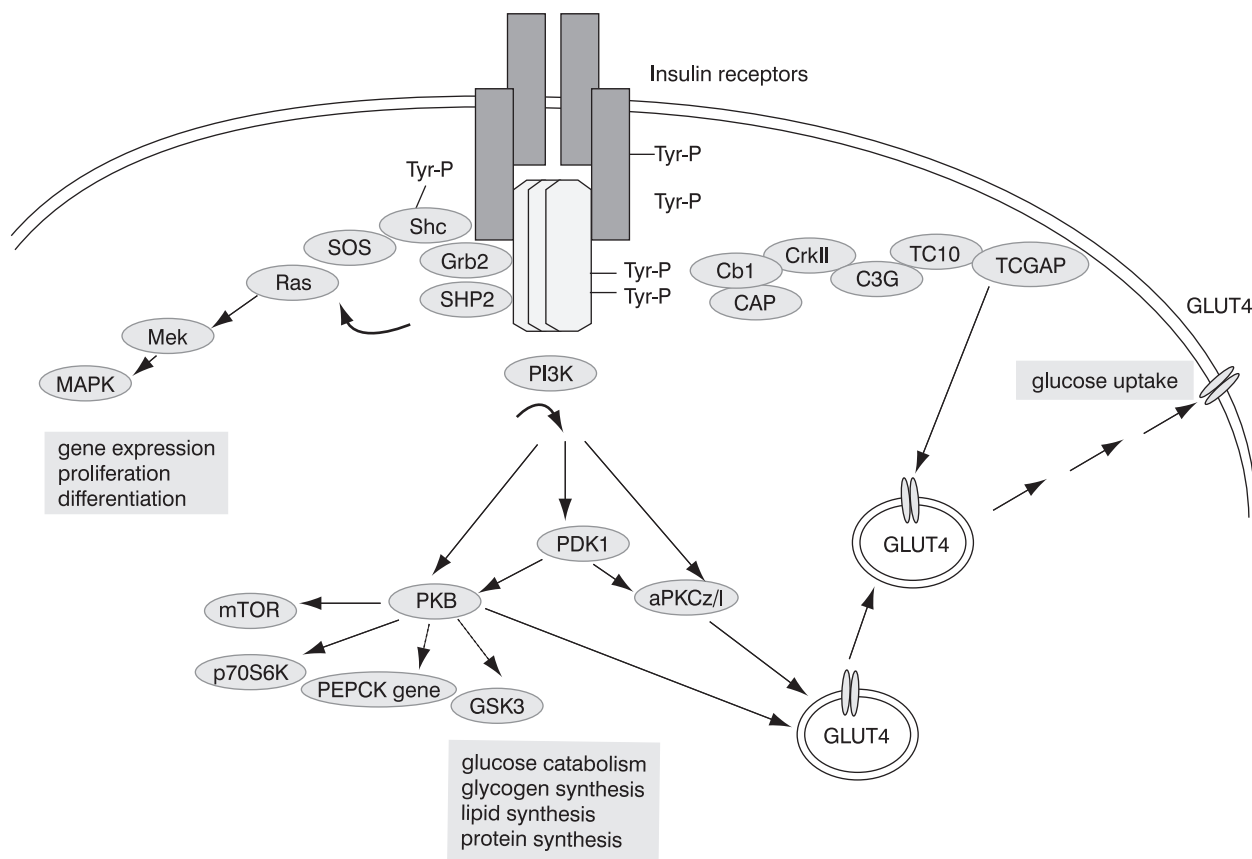
SLIKA 1. Pretvorba inzulinskih signala (51-55). Nakon Tyr autofosforilacije inzulinskih receptora dolazi do Tyr fosforilacije supstrata za inzulinke receptora 1 to 4 (IRS-1 do -4), a potom se signal pretvara trima različitim putovima: putom ovisnim o PI3K koji posreduje metaboličke odgovore uključujući metabolizam glukoze/lipida/bjelančevina inzulinom poticano preuzimanje glukoze, putom CAP/Cbl koje je dodatno potreban za translokaciju prijenosnika glukoze 4 (GLUT4) i putom mitogenom aktivirane protein kinaze (MAPK) koji rezultira staničnom proliferacijom i diferencijacijom. Puna crta: poticanje; isprekidana crta: suzbijanje. IRS, supstrat za inzulinske receptore; PI3K, fosfoinozitid-3-kinaza; PDK-1, kinaza 1 ovisna o fosfoinozitidu; PKB, protein kinaze B; aPKC, atipične protein kinaze C; mTOR, cilj za rapamicin u sisavaca; p70S6K, p70 ribosomna S6 kinaza; PEPCK, fosfoenolpiruvat karboksikinaza; GSK3, glikogen sintaza kinaza 3.

FIGURE 1. Insulin signal transduction (51-55). After insulin receptor Tyr autophosphorylation, insulin receptor substrates 1 to 4 (IRS-1 to 4) Tyr phorphorylation takes place and subsequently three different pathways transduce the signal: PI3K-dependent pathway mediating metabolic responses including glucose/lipid/protein metabolism and insulin-stimulated glucose uptake; CAP/Cbl pathway which is additionally required for glucose transporter-4 (GLUT4) translocation; and mitogen-activated protein kinase (MAPK) pathway resulting in cell proliferation and differentiation. Solid line: stimulation; dashed line: inhibition. IRS, insulin receptor substrate; PI3K, phosphoinositide-3-kinase; PDK-1, phosphoinositide-dependent kinase 1; PKB, protein kinase B; aPKC, atypical proteinkinases C; mTOR, mammalian target of rapamycin; p70S6K, p70 ribosomal S6 kinase; PEPCK, phosphoenolpyruvate carboxykinase; GSK3, glycogen synthase kinase 3.

za smanjenu fosforilaciju Tyr u β-podjedinici nakon vezanja inzulina (57). Pretpostavlja se da mutacije gena inzulinskih receptora kod Rabson-Mendenhallova sindroma i Donohueva sindroma remete vezanje inzulina za receptor (57). IR možda nastaje zbog nenormalne proizvodnje protutijela za protuinzulinske receptore (IR tip B) (58). Za mutacije PPAR-γ koje nisu udružene s lipodistrofijom također se izvještava da uzrokuju IR (59).

Neki autori izvještavaju o povećanoj razgradnji inzulinskih receptora (60). Uz to, pretpostavlja se kako bi fosforilacija serina/treonina raznim protein kinazama C (engl. *protein kinase C*, PKC) mogla biti dodatnim čimbenikom

subunit after insulin binding (57). In Rabson-Mendenhall syndrome and leprechaunism (Donohue syndrome) insulin receptor gene mutations are presumed to impair insulin binding to the receptor (57). IR may be due to abnormal production of anti-insulin-receptor antibodies (type B IR) (58). PPAR-γ mutations which are not associated with lipodystrophy are also reported to cause IR (59).

Some studies report an increased degradation of insulin receptor (60). Besides, it is hypothesized that serine/threonine phosphorylation by various protein kinases C (PKCs) could be an additional factor to regulate insulin receptor activity (61). Decreased Tyr phosphorylation state of IRS-1

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regulacije aktivnosti inzulinskih receptora (61). Stanje smanjene Tyr fosforilacije IRS-1, koje je zapaženo kod hiperinzulinemičnih ob/ob miševa, moglo bi biti posljedica smanjenje aktivnosti inzulinskih receptora (62).

Novija ispitivanja su uglavnom usredotočena na povećanu Ser/Thr fosforilaciju IRS-1, koja bi mogla biti posljedica povišenih koncentracija TNF-α i dalje se pogoršava hiperinzulinemijom koju uzrokuje IR. Smatra se da su PKC, PI3K-daljnje kinaze i MAP-kinaze odgovorne za Ser/Thr fosforilaciju, nakon čega slijedi pojačana proteazomna razgradnja IRS-1. Naime, smanjen sadržaj IRS-1 bjelančevine opisan je u ljudi, životinja i uzgojenim stanicama s IR (51).

Valja naglasiti kako je stanovito bazalno stanje Ser/Thr fosforilacije IRS-1 neophodno za uspješnu Tyr fosforilaciju i inzulinsko signaliziranje. Zato preostaje rasvijetliti koji je stupanj fosforilacije IRS-1 i na kojim Ser/Thr mjestima potreban da bi pokazao svoje raznovrsne učinke.

Uz to što posreduje razgradnju IRS-1, hiperinzulinemija može utjecati na koncentraciju bjelančevina u IRS-2 i izazvati neke promjene niže na putu inzulinske signalizacije (51). TNF-α, IL-6 i inzulin induciraju drugu važnu skupinu čimbenika IR – supresore citokinskog signaliziranja (engl. *suppressors of cytokine signalling-1-3*, SOCS-1-3), koji imaju najmanje tri različita mehanizma djelovanja: oni se natječu s IRS-1 za udruživanje s inzulinskom receptorom, suzbijaju Janus kinazu upletenu u inzulinsko signaliziranje i povećavaju proteazomnu razgradnju IRS-1 (63). Za hiperglikemiju je pokazano kako teško smanjuje aktivnost protein kinaze B (engl. *protein kinase B*, PKB), iako su bile aktivirane neke druge proksimalne sastavnice inzulinske signalizacije (inzulinski receptor, IRS-1, IRS-2, PI3K).

Pokazano je kako slobodne masne kiseline u visokim plazmatskim koncentracijama kroz pretvorbu u diacilglicerol i acil-CoA smanjuju aktivnosti IRS-1, -2, te aktivnosti PI3K i različitih izoforma PKB i PKC u mišiću štakora (51). Kod transgeničnih miševa FFA su povećale aktivnost bjelančevine Munc18c, negativnog regulatora translokacije GLUT4 u plazmatsku membranu (64). Ipak, nezasićene FFA su korisne utoliko što omogućavaju normalnu inzulinsku osjetljivost u nekim ciljnim tkivima (51).

Pokazano je kako glicirane bjelančevine, koje nastaju kao posljedica hiperglikemije, unutar stanice smanjuju aktivnost PI3K, PKB i GSK-3, te tako možda doprinose IR. Slično tome, glukozamin (UDP-N-acetil glukozamin), koji nastaje iz glukoze i predstdavlja glavni supstrat za staničnu glikozilaciju, pojačava glikozilaciju IRS-1 smanjujući tako njegovu aktivnost, te glikozilaciju glikogen sintaze, smanjujući tako njezinu sposobnost odgovora na inzulin (51).

Pretilost

Stanje uhranjenosti se najbolje opisuje pomoću indeksa tjelesne mase (engl. *body mass index*, BMI). BMI se izračunava tako da se težina osobe u kilogramima podijeli kvadratom visine u metrima. Uz neke iznimke BMI dobro kore-

that was found in hyperinsulinemic ob/ob mice could be a consequence of decreased insulin receptor activity (62). Recent studies focus mainly on increased Ser/Thr phosphorylation of IRS-1, which could be a consequence of increased TNF-α concentrations and further exacerbated by hyperinsulinemia which is secondary to IR. PKCs, PI3K-downstream kinases and MAP-kinases are thought to be responsible for Ser/Thr phosphorylation, which is followed by enhanced proteasomal degradation of IRS-1. Namely, decreased IRS-1 protein content has been reported in humans, animals and cultured cells with IR (51).

It is to emphasize that certain basal Ser/Thr phosphorylation state of IRS-1 is necessary for successful Tyr phosphorylation and insulin signaling. Therefore, it remains to be elucidated to which degree and on which Ser/Thr sites IRS-1 must be phosphorylated to display its diverse effects.

Besides mediating IRS-1 degradation, hyperinsulinemia might affect protein concentration of IRS-2 and provoke some downstream changes in insulin signaling (51).

TNF-α, IL-6 and insulin induce another important group of IR factors – suppressors of cytokine signaling (SOCS-1 and -3), which have at least three different mechanisms of action: they compete with IRS-1 for association with insulin receptor, they inhibit Janus kinase, involved in insulin signaling, and they augment proteasomal IRS-1 degradation (63).

Hyperglycemia was shown to severely decrease protein kinase B (PKB) activity, although some other proximal components of insulin signaling (insulin receptor, IRS-1, IRS-2, PI3K) were activated.

FFA in high plasma concentrations were shown, by transformation to diacylglycerol and acyl-CoA, to diminish the activities of IRS-1, -2 and activities of PI3K and various isoforms of PKB and PKC in rat muscle (51). In transgenic mice, FFA increased the activity of Munc18c protein, a negative regulator of GLUT-4 translocation to plasma membrane (64). Nevertheless, unsaturated FFA have benefit to allow normal insulin sensitivity in some target tissues (51).

Glycated proteins, emerging as a consequence of hyperglycemia were shown intracellularly to diminish the PI3K, PKB, and GSK-3 activity, thus possibly contributing to IR. Similarly, glucosamine (UDP-N-acetyl glucosamine), produced from glucose and being the main substrate for cellular glycosylation, enhances IRS-1 glycosylation thereby decreasing its activity, and glycogen-synthase glycosylation, which reduces its insulin responsiveness (51).

Obesity

The state of nutrition is best described by body mass index (BMI). BMI is calculated by dividing a person's weight in kilograms by the square of his height in meters. BMI is, with some exceptions, in good correlation with the amount of total body fat. According to BMI, the following

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lira s količinom ukupne tjelesne masti. Prema BMI utvrđene su slijedeće kategorije prekomjerne tjelesne mase ili uhranjenosti (65):

    BMI 25-30 kg/m^2 prekomjerna težina
    BMI 30-40 kg/m^2 pretilost
    BMI 40-50 kg/m^2 bolesna pretilost
    BMI >50 kg/m^2 krajnja pretilost

Inzulinska i leptinska rezistencija kod pretilosti

Visceralna pretilost predisponira razvoj hipertenzije, šećerne bolesti tipa 2, kardiovaskularne bolesti i određenih vrsta raka (66). Povećan rizik za zdravlje postoji već i u skupini prekomjerne težine. Uz ukupnu tjelesnu masu masti, za moguće metaboličke komplikacije bitna je i raspodjela masti. Visceralno i potkožno masno tkivo razlikuju se prema njihovim endokrinim aktivnostima. Specifični receptori kao što su receptori tipa 1 angiotenzina II. (AT1), β_1-, β_2- i β_3-adrenergični receptori, receptori glukokortikoida i androgena zastupljeni su u većoj mjeri u visceralnom masnom tkivu, gdje promiču lipolizu (8, 67, 68). S druge strane, antilipolitični inzulinski receptori, α-2A adrenergični receptori i estrogenski receptori prevladavaju u potkožnom masnom tkivu (67, 68). Uz to, visceralno masno tkivo luči svoje proizvode u portalnu cirkulaciju i tako dovodi oslobođene FFA izravno u jetru gdje one onda pogoduju glukoneogenezi, sintezi VLDL, smanjuju preuzimanje glukoze i uzrokuju sveopću IR.

Visceralno masno tkivo je obilježeno relativno visokim lučenjem IL-1 i PAI-1, dok je lučenje leptina i adiponektina veće u potkožnom masnom tkivu (8). To je odgovorno za odnos između visceralne pretilosti i upalnih/trombotskih događaja, te objašnjava učinkovitost TZD u poboljšanju inzulinske osjetljivosti kroz preraspodjelu lipida u potkožno masno tkivo (69).

Kod pretilih osoba su koncentracije leptina u plazmi povišene pa egzogeno davanje leptina nema učinka na tjelesnu težinu (8). Ova se pojava objašnjava leptinskom rezistencijom ili desenzibilizacijom (23). Uz to, kod pretilosti su koncentracije topljivog leptinskog receptora niske, a time i koncentracije frakcije vezanog leptina. Ovo obilježje je neovisno udruženo s abdominalnom pretilošću i IR. Smatra se kako topljivi leptinski receptori imaju važnu ulogu u prijenosu u i kroz krvno-moždanu barijeru, pa bi zasićenost ovoga prijenosa ili poremećaj u pretvaranju signala leptinskog receptora mogli biti uzrokom leptinske rezistencije. Koncentracije leptina u cerebrospinalnoj tekućini pretilih bolesnika tek su blago povišene (23).

Patofiziologija pretilosti

Svaka osoba ima genetski određenu težinsku strukturu kojom se tjelesna težina strogo regulira energetskim homeostatskim mehanizmom (Slika 2.) (6, 66, 71). Adipociti luče leptin, a β-stanice luče inzulin, oboje razmjerno sadržaju tjelesne masti. Ova dva hormona ulaze u mozak; ve-

categories of excessive body mass or nutrition are postulated (65):

    BMI 25-30 kg/m^2 overweight
    BMI 30-40 kg/m^2 obesity
    BMI 40-50 kg/m^2 morbid obesity
    BMI >50 kg/m^2 extreme obesity

Insulin and leptin resistance in obesity

Visceral obesity predisposes to the development of hypertension, diabetes mellitus type 2 (DM2), cardiovascular disease, and certain types of cancer (66). An increased risk for health exists already in the overweight group. Besides total body fat mass, distribution of fat is essential for eventual metabolic complications. Visceral and subcutaneous adipose tissues differ in their endocrine activities. Specific receptors such as angiotensin II receptors type-1 (AT1), β_1-, β_2-, β_3-adrenergic receptors, glucocorticoid and androgen receptors are represented to a larger degree in visceral adipose tissue where they promote lipolysis (8, 67, 68). On the other hand, antipolytic insulin receptors, α-2A adrenergic receptors, and estrogen receptors are predominantly expressed in subcutaneous adipose tissue (67, 68). Additionally, visceral adipose secretes its products to the portal circulation, which brings the released FFA directly to the liver where they promote gluconeogenesis, VLDL synthesis, decrease glucose uptake and cause overall IR.

Visceral adipose tissue is characterized by a relatively higher secretion of IL-1 and PAI-1, whereas leptin and adiponectin secretion is greater in subcutaneous adipose tissue (8). This accounts for the relationship between visceral obesity and inflammatory/thrombotic events, and explains the effectivity of TZD to improve insulin sensitivity by redistribution of lipids to subcutaneous adipose tissue (69).

In obese individuals there are increased plasma leptin concentrations and exogenous administration of leptin has no effect on body weight (8). The phenomenon has been explained as leptin resistance or desensitization (23). Besides, soluble leptin receptor concentrations are low in obesity and hence the fraction of bound leptin concentrations. This feature is independently associated with abdominal obesity and IR. Soluble leptin receptors are thought to be important for transport to or over the blood – brain barrier and it is the saturation of this transport or impairment of leptin receptor signal transduction that may be the cause of leptin resistance. Leptin concentrations in the cerebrospinal fluid of obese patients are only modestly increased (23).

The pathophysiology of obesity

Each individual has a genetically determined weight setpoint and hence body weight is tightly regulated by an energy homeostatic mechanism (Figure 2) (6, 66, 71). Adi-

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žu se na svoje središnje receptore na neuronima hipotalamusa i djeluju tako da smanjuju tjelesnu težinu. Neuroni hipotalamusa izražavaju peptide i njihove receptore, koji se mogu svrstati kao oreksigeni: neuropeptid Y, agouti-povezan protein (engl. *agouti-related protein*, AgRP), hormon za koncentriranje melanina (engl. *melanin-concentrating hormone*, MCH), oreksini A i B; ili anoreksigeni: melanokortini (tj. hormon koji potiče melanocite; engl. *melanocyte-stimulating hormone*, α-MSH) i transkript povezan s kokainom i amfetaminom (engl. *cocaine and amphetamine related transcript*, CART). U stanju preobilja leptina ili inzulina prevladavaju anoreksigeni putovi: porast potrošnje energije, porast termogeneze, smanjen unos hrane. Smanjene serumske koncentracije leptina i inzulina dovo-

pocytes secrete leptin and β-cells secrete insulin, both in proportion to the body-fat content. The two hormones enter the brain. They bind to their central receptors on the hypothalamic neurons exerting effects to reduce body weight. Hypothalamic neurons express peptides and their receptors that could be categorized as orexigenic: neuropeptide Y, agouti-related protein (AgRP), melanin-concentrating hormone (MCH), orexins A and B; or anorexigenic: melanocortins (i.e. melanocyte-stimulating hormone, α-MSH) and cocaine and amphetamine related transcript (CART). In leptin or insulin abundance the anorexigenic pathways prevail: increase of energy expenditure, increase of thermogenesis, diminished food intake. Decreased leptin and insulin serum concentrations
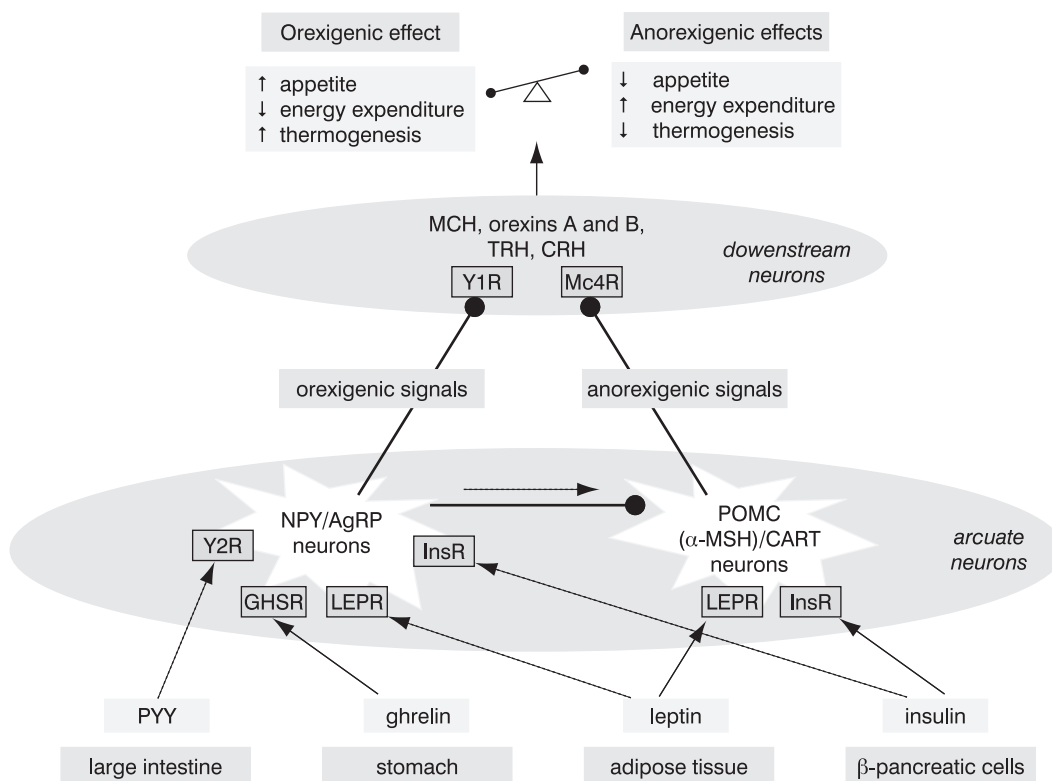
SLIKA 2. Energetska homeostaza. Neuroni neuropeptida Y (NPY)/proteina povezanog s agouti (AgRP) te neuroni proopiomelanokortina (POMC)/transkripta povezanog s kokainom i amfetaminom (CART) u lučnoj jezgri hipotalamusa primaju signale iz periferije. Oni prenose oreksigene i anoreksigene signale do nizvodnih neurona koji osiguravaju ravnotežu između unosa i potrošnje energije (6, 66, 71).
Puna crta: poticanje; isprekidana crta: suzbijanje. PYY, peptid YY3-36; Y1R i Y2R, podtipovi receptora neuropeptida Y; a-MSH, hormon za poticanje a-melanocita, izveden cijepanjem POMC; Mc4R, receptor melanokortina 4; GHSR, sekretagogni receptor hormona rasta (receptor za grelin); InsR, inzulinski receptor; MCH, hormon za koncentriranje melanina; TRH, hormon za otpuštanje tirotropina; CRH, hormon za otpuštanje kortikotropina.

FIGURE 2. Energy homeostasis. NeuropeptideY (NPY)/agouti related protein (AgRP) neurons and proopiomelanocortin (POMC)/cocaine and amphetamine related transcript (CART) neurons in the arcuate nucleus in the hypothalamus receive signals from the periphery. They relay orexigenic and anorexigenic signals to the downstream neurons, which provide balance between the food intake and energy expenditure (6,66,71).
Solid line: stimulation; dashed line: inhibition. PYY, peptide YY3-36; Y1R and Y2R, subtypes of neuropeptide Y receptor; a-MSH, a-melanocyte stimulating hormone derived by cleavage of POMC; Mc4R, melanocortin 4 receptor; GHSR, growth hormone secretagogue receptor (receptor for ghrelin); InsR, insulin receptor; MCH, melanin concentrating hormone; TRH, thyrotropin-releasing hormone; CRH, corticotropin-releasing hormone.

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de do aktiviranja oreksigenih putova, što dovodi do niske stope metabolizma i pojačanog apetita (6).

Leptin i inzulin posreduju dugoročnu regulaciju tjelesne mase. Oni su isto tako djelatni u kratkoročnim signalima kojima se pojedini obrok započinje ili završava. Uz to, unos hrane praćen je nekim drugim kratkodjelujućim hormonima/čimbenicima: grelin, motilin, neuromedin U, neurotenzin (70), kolecistokinin, peptid YY_{3-36} (engl. *peptide* YY_{3-36}, PYY) (71) i glukagonu sličan peptid-1 (72), od kojih se svi luče u probavnom sustavu, te vagalnim aferentnim signaliziranjem (72). Grelin se luči u bazi želuca i pojačava osjećaj gladi te potiče pražnjenje želuca (70), dok PYY signalizira sitost i suzbija crijevnu pokretljivost (71). Grelin potiče neuropeptid Y i ArRP neurone, dok PYY suzbija te iste neurone kod životinja (71). Nedavno je otkriven peptid izveden iz istoga prohormona kao grelin. Nazvali su ga obestatin, a on se suprotstavlja učincima grelina (73).

Izgleda kako je leptinsko-melanokortinski put anoreksigenog signaliziranja osobito očuvan među vrstama i mutacije gena koji kodiraju sastavnice ovoga puta, odnosno leptin, leptinski receptor, pro-opiomelanokortin (engl. *pro-opiomelanocortin*, POMC), prohormon-konvertazu 1 (engl. *prohormone-convertase 1*, PC1) i receptor melanokortina 4 (engl. *melanocortin 4 receptor*, Mc4R), uzrokuju rijetke oblike bolesne monogene pretilosti te dovode do nekih prirodno nastalih modela pretilosti kod miševa i štakora (ob, db, Ay i mg) (6). Suprotno tome, uklanjanje gena (*knockout*) za oreksigene putove kod miševa ne dovodi do stvaranja krtih fenotipova, ukazujući na iznimno snažne uzajamne učinke sastavnica u sustavu anabolizma i porasta težine (71).

Današnja visoka incidencija pretilosti mogla bi se objasniti hipotezom o "štedljivom genotipu": kroz duža vremenska razdoblja birali su se aleli koji pogoduju porastu težine i pohrani masti kako bi se osigurali dostatni nutrijenti za vrijeme nedostatka hrane. U današnje vrijeme dostupnosti hrane i smanjenje tjelesne aktivnosti takvi genotipovi uzrokuju pretilost (74).

Sposobnost tijela da precizno održava tjelesnu težinu odražava se u neuspjehu intervencija kojima je cilj smanjenje tjelesne težine. Dijete ograničenih kalorija dovode do kompenzacijskog porasta razina grelina, čime se potiče uzimanje hrane (71). Smanjenje tjelesne težine rezultira padom razina leptina, što opet potiče porast težine (71). Kirurško uklanjanje masnog tkiva dovodi do obnavljanja masti na novim lokacijama, dok poticanje termogeneze adrenergičnim β_3-agonistima izaziva kompenzacijski odgovor središnjega živčanog sustava (6). Tek se je krajnjom intervencijom u miševa s opsežnom prekomjernom ekspresijom nevezujućeg proteina-3 (UCP-3), koji je signalna bjelančevina u termogenezi, uspjelo prevladati središnje prilagodbene mehanizme i miševi su ostali mršavi (75). Kod ljudi je uspješan operacijski zahvat želučanog premoštenja, koji dovodi do sniženja plazmatske koncen-

lead to the activation of orexigenic pathways resulting in low metabolic rate and enhanced appetite (6).

Leptin and insulin mediate long-term body mass regulation. They are also active in short-term signals that effect single meal to be initiated and terminated. In addition, there are some other short-acting hormones/factors which accompany food intake: ghrelin, motilin, neuromedin U, neurotensin (70), cholecystokinin, peptide YY_{3-36} (PYY) (72) and glucagon-like peptide-1 (72), all secreted by the gastrointestinal tract, and vagal afferent signaling (71). Ghrelin is secreted by the stomach fundus and increases the sense of hunger and stimulates gastric emptying (70), whereas PYY signals satiety and inhibits gut motility (71). Ghrelin stimulates neuropeptide Y and AgRP neurons, while PYY exerts inhibition of the same neurons in animals (71). Recently, a peptide derived from the same prohormone as ghrelin, was discovered. It has been named obestatin and it opposes the effects of ghrelin (73).

Particularly the leptin-melanocortin anorexigenic signaling pathway appears to be very conserved among species, and mutations in genes encoding for components of this pathway: leptin, leptin receptor, pro-opiomelanocortin (POMC), prohormone-convertase 1 (PC1), and melanocortin 4 receptor (Mc4R), cause rare forms of morbid monogenic obesity and lead to some naturally occurring murine models of obesity (ob, db, Ay and mg) (6). On the contrary, knockouts in genes for orexigenic pathways in mice fail to produce lean phenotypes, demonstrating the extremely powerful mutual effects of anabolism and weight gain system components (71).

Today's high incidence of obesity could be explained by the "thrifty genotype" hypothesis: over periods of time the alleles were selected which favored weight gain and fat storage in order to provide enough nutrients for times of food deprivation. In today's times of food availability and decreased physical activity such genotypes cause obesity (74).

The potential of the body to precisely maintain body weight is reflected in the failure of interventions aimed at body weight reduction. Calorie-restricted diet results in compensatory increase in ghrelin levels thereby stimulating eating (71). Reduction of body weight results in the fall of leptin levels, which again stimulates weight gain (71). Surgical removal of adipose tissue results in restoration of fat at new locations, and stimulation of thermogenesis by adrenergic β_3-agonists elicits a compensatory central nerve system response (6). Only extreme intervention in mice with gross overexpression of uncoupling protein-3 (UCP-3), which is a signal protein in thermogenesis, was successful to override central adaptive mechanisms, and mice remained lean (75). In humans, gastric bypass surgery is successful as it results in ghrelin plasma concentration decrease and PYY increase, which suppresses hunger and maintains reduced body weight (71).

tracije grelina i porasta PYY koji zatomljuje glad i održava smanjenu tjelesnu težinu (71).

Razvoj mršavog životinjskog modela suzbijanjem razvoja masnog tkiva rezultirao je hiperfagičnim miševima s teškim dijabetesom otpornim na inzulin (76). Pretpostavljeni mehanizam koji je uzrokovao IR bio je nedostatak leptina i adiponektina zbog odsutnosti masnog tkiva. Naime, davanje ovih hormona zajedno preokrenulo je stanje IR (77). Tako se čini da su ova dva hormona potrebna za normalnu inzulinsku osjetljivost.

Uz monogene oblike pretilosti postoji barem 20 rijetkih sindroma s očitom genetskom osnovom koji izgledaju složenijima, jer se povezuju s većim brojem disfunkcija (mentalna retardacija, višestruki znaci poremećaja hipotalamusa) (66).

Obična pretilost u ljudi smatra se oligogenim stanjem i njezinu izraženost mijenjaju mnogobrojni modificirajući geni i čimbenici okoline: unos hrane, tjelesna aktivnost i pušenje (6). Procjenjuje se kako genetska osnova sudjeluje s 40–80% u patofiziologiji pretilosti (66). Identificirana su najmanje 204 navodna genska lokusa udružena s pretilošću, a oni koji su potvrđeni u više studija prikazani su u tablici 1. (78).

Metabolički sindrom

Grupiranje hipertenzije, hiperglikemije i gihta prvobitno je prepoznato još dvadesetih godina 20. stoljeća (1). Reaven je 1988. godine identificirao sindrom X koji potječe iz IR. Godine 2004. je III. panel o liječenju odraslih Nacionalnog obrazovnog programa o kolesterolu (engl. *National Cholesterol Education Program's Adult Treatment Panel* III, ATPIII) definirao metabolički sindrom pod alternativnim

Development of lean animal model by suppression of adipose tissue development resulted in hyperphagic mice with severe insulin resistant diabetes (76). The hypothesized mechanism causing IR was leptin and adiponectin deficiency due to the absence of adipose tissue. Namely, the administration of these hormones together reversed IR (77). Thus, these two hormones appear to be required for normal insulin sensitivity.

Besides monogenic forms of obesity there are at least 20 rare syndromes with obvious genetic basis, which appears to be more complex as it predisposes more dysfunctions (mental retardation, multiple signs of hypothalamic disorder) (66).

The common human obesity is thought to be an oligogenic state and its expression is modulated by multiple modifier genes and by environmental factors: food intake, physical activity, and smoking (6). The genetic basis in the pathophysiology of obesity is estimated to be 40%-80% (66). At least 204 putative gene loci associated with obesity have been identified, and those which have been confirmed by multiple studies are presented in Table 1 (78).

Metabolic Syndrome

The first recognition of clustering of hypertension, hyperglycemia and gout came already in the twenties of 20th century (1). In 1988, Reaven identified syndrome X originating from IR. In 2004, the National Cholesterol Education Program's Adult Treatment Panel III (ATPIII) defined the metabolic syndrome with alternative names: IR syndrome, Reaven syndrome, characterized by the following components (G52):

Tablica 1. Popis gena udruženih s pretilošću potvrđenih u 5 ili više studija

Table 1. The list of genes associated with obesity confirmed by 5 or more studies

Gene name*	Protein name	Gene name*	Protein name
ADIPOQ	Adiponectin	LEPR	Leptin receptor
ADRA2A	Adrenergic receptor α-2A	NR3C1	Nuclear receptor subfamily 3, group C
ADRA2B	Adrenergic receptor α-2B	PPARG	PPAR-γ
ADRB1	Adrenergic receptor β-1	UCP1	Uncoupling protein 1
ADRB2	Adrenergic receptor β-2	UCP2	Uncoupling protein 2
ADRB3	Adrenergic receptor β-3	UCP3	Uncoupling protein 3
DRD2	Dopamine receptor D2	TNF	TNF-α
LEP	Leptin	LIPE	Hormone sensitive lipase

* according to HUGO Nomenclature Committee

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imenima: sindrom IR i Reavenov sindrom, obilježen slijedećim sastavnicama (G52):

- abdominalna pretilost
- aterogena dislipidemija
- hipertenzija
- IR
- proupalno stanje
- protrombotsko stanje

Ova klinička obilježja su snažni čimbenici rizika za šećernu bolest tipa 2 i kardiovaskularnu bolest s mogućim dodatnim komplikacijama uključujući kolesterolne žučne kamence, apneju u snu, sindrom policističnog jajnika kod žena, masnu jetru i neke vrste raka (7).

Pretpostavljene su tri moguće etiologije za metabolički sindrom: utvrđeno je kako je pretilost odgovorna za prekomjerno otpuštanje slobodnih masnih kiselina, citokina i drugih proupalnih proizvoda koji su upleteni u razvoj IR, hipertenzije i dislipidemije. IR kao drugi mogući uzrok metaboličkog sindroma postavlja pitanje je li moguće razdvojiti pretilost i IR. Zapravo, IR u različitim stupnjevima postoji u svim kategorijama indeksa tjelesne mase, ukazujući na njen neovisan nasljedni doprinos, barem do neke mjere. Neke populacije (iz južne Azije) s blago prekomjernom tjelesnom težinom pokazuju IR i to se smatra primarnom IR. S tog stajališta se IR može svrstati kao zaseban etiološki čimbenik za metabolički sindrom. Hiperinzulinemija kao posljedica IR može povećati lučenje VLDL iz jetre i uzrokovati hipertenziju. Mišićna IR može uzrokovati hiperglikemiju koja se pojačava glukoneogenezom kod jetre rezistentne na inzulin (7). Smatra se da treća etiologija uključuje neovisne čimbenike: imune, vaskularne, jetrene itd., na koje utječe specifična genetska osnova pojedine osobe, kao i čimbenici okoline (7).

Kliničke pojavnosti i kriteriji za dijagnosticiranje metaboličkog sindroma

Razine glukoze i FFA u plazmi

Hiperinzulinemija se razvija kao posljedica IR. U ovom stanju su koncentracije FFA u plazmi tek umjereno povišene, dok koncentracija glukoze može biti normalna ili povišena. Ova potonja ukazuje na poremećenu toleranciju glukoze, koja se dokazuje vrijednostima oralnoga testa tolerancije glukoze (OGTT) višim od normalnih, ali još uvijek ne toliko povišenim da bi označavale šećernu bolest (79). Drugo moguće obilježje metaboličkog sindroma je poremećena glukoza natašte (7). Kad se koncentracije inzulin u plazmi snize kao rezultat razgradnje β-stanica, razine FFA se znatno povisuju uz popratnu hiperglikemiju i stanje metaboličkog sindroma prerasta u šećernu bolest (79).

Aterogena dislipidemija

Hipertrigliceridemija nastaje kao posljedica povećane sinteze VLDL u jetri. HDL u plazmi je snižen, uz veću zastup-

- abdominal obesity
- atherogenic dyslipidemia
- hypertension
- IR
- proinflammatory state
- prothrombotic state

These clinical features are strong risk factors for DM2 and cardiovascular disease with additional possible complications including cholesterol gallstones, sleep apnea, polycystic ovary syndrome in women, fatty liver and some types of cancer (7).

Three possible etiologies for the metabolic syndrome have been postulated: obesity was found to be responsible for excess release of FFA, cytokines and other proinflammatory products which are implicated in the development of IR, hypertension and dyslipidemia. IR as the second possible cause of metabolic syndrome rises a question of whether it is possible to dissociate between obesity and IR. Indeed, IR exists to various degrees in all particular classes of body mass index, suggesting an independent inheritable contribution of it to at least some extent. Some populations (South Asians) with mild overweight display IR and this is said to be primary IR. From this point of view IR can be classified as a separate etiological factor for metabolic syndrome. Hyperinsulinemia as a consequence of IR is capable to increase VLDL secretion from the liver and to cause hypertension. IR of muscle can cause hyperglycemia, exaggerated by gluconeogenesis in insulin-resistant liver (7).

The third etiology is thought to include independent factors: immune, vascular, hepatic, etc., which are influenced by specific genetic background of an individual, and by environmental factors (7).

Clinical manifestations and criteria for the diagnosis of metabolic syndrome

Glucose and FFA plasma level

As a consequence of IR, hyperinsulinemia develops. In this condition plasma FFA concentrations are only moderately elevated, but glucose concentration can be normal or increased, the latter denoting impaired glucose tolerance which is demonstrated by oral glucose tolerance test (OGTT) values above normal, yet not elevated enough to define DM (79). Another possible feature in the metabolic syndrome is impaired fasting glucose (7). When plasma insulin concentrations decline, as a result of β-cell degeneration, FFA levels increase considerably with accompaning hyperglycemia and the condition of metabolic syndrome grows to DM2 (79).

Atherogenic dyslipidemia

As a consequence of increased liver VLDL synthesis hypertriglyceridemia occurs. Plasma HDL is decreased with

ljenost malog gustog HDL. Slično tome, sastav LDL se pomiče prema prevlasti malog gustog LDL. Ovaj potonji se smatra aterogenijim od običnog LDL. Isto tako dolazi do promjena u apolipoproteinima (1).

Hipertenzija

Kod zdravih osoba inzulin potiče simpatički živčani sustav i djeluje na krvne žile uzrokujući vazodilataciju. Inzulin isto tako potiče ponovnu apsorpciju natrija u bubregu. U stanju inzulinske rezistencije vazodilatacija se može izgubiti, ali se učinak na bubrege i simpatička stimulacija održavaju i čak povećavaju. To oboje doprinosi hipertenziji, koji dodatno pogoršavaju FFA koje pogoduju vazokonstrikciji. Pa ipak, čini se kako događaji povezani izravno s IR imaju tek umjerenu ulogu u razvoju hipertenzije (1). Uz to, leptin bi mogao u stanovitoj mjeri doprinositi hipertenziji, jer plazmatske koncentracije leptina vezanog uz bjelančevine kod normotenzivnih muškaraca koreliraju sa simpatičkom živčanom aktivnošću (26).

Ostala klinička obilježja

Proupalno stanje je obilježeno porastom C-reaktivnog proteina u plazmi, a protrombotsko stanje povišenjem PAI-1 i fibrinogena (7).

Dodatne pojavnosti metaboličkog sindroma su: masna jetra i steatohepatitis zbog povećane jetrene proizvodnje VLDL u stanju IR, hiperuricemija, povišeni homocistein i vaskularne nenormalnosti s mikroalbuminurijom (1). Osobito je zanimljiva hiperuricemija, koja je najvjerojatnije posljedica hiperinzulinemije: bubreg koji održava normalnu osjetljivost za inzulin prilagođava se na visoke koncentracije inzulina smanjenim lučenjem mokraćne kiseline, čime se povećava njegova razina u plazmi (79).

Drugi važan klinički biljeg IR je crnkasta akantoza (2) koja se očituje kao hiperpigmentirane kožne promjene zasnovane na epidermnoj hiperplaziji. Smatra se kako je ovo obilježje povezano s hiperinzulinemičnim stanjem, jer se je pokazalo da inzulin ubrzava rast epidermnih stanica u kulturi (80).

Dijagnostički kriteriji što su ih prihvatili ATPIII i *International Diabetes Federation* (engl. *International Diabetes Federation*, IDF) prikazani su u tablici 2. Prema dogovoru pri ATPIII, dijagnoza metaboličkog sindroma može se postaviti u bolesnika koji imaju najmanje 3 od 5 slijedećih obilježja: abdominalnu pretilost, povišene trigliceride, snižen HDL-kolesterol, povišen krvni tlak ili povišenu glukozu u plazmi natašte (7). Kriteriji koje je postavio IDF uglavnom su sukladni onima iz ATPIII (81). Manje razlike odnose se na središnju pretilost kao glavno obilježje i ispunjavanje dviju od četiri druga pojavnosti. Granična koncentracija glukoze niža je u kriterijima IDF, pričem se preporuča napraviti OGTT kad je vrijednost viša.

a greater proportion of small dense HDL. Similarly, the composition of LDL is shifted towards predominance of small dense LDL. The latter is thought to be more atherogenic than ordinary LDL. Changes of apolipoproteins also occur (1).

Hypertension

In healthy subjects insulin stimulates sympathetic nervous system and acts on blood vessels causing vasodilatation. Insulin also stimulates sodium reabsorption in the kidney. In insulin resistant state the vasodilatation can be lost but the renal effect and sympathetic stimulation are maintained and even increased. Both contribute to hypertension, which is further exacerbated by FFA favoring vasoconstriction. Nevertheless, it appears that the events linked directly to IR play only a moderate role in the development of hypertension (1). Additionally, leptin might have some contribution to hypertension as protein-bound leptin plasma concentrations in normotensive men correlate with sympathetic nerve activity (26).

Other clinical features

Proinflammatory state is characterized by a rise in plasma C-reactive protein, and prothrombotic state by elevation of PAI-1 and fibrinogen (7). Additional manifestations of the metabolic syndrome are fatty liver and steatohepatitis because of increased liver VLDL production in the state of IR, hyperuricemia, increased homocystein, and vascular abnormalities with microalbuminuria (1). Particularly interesting is hyperuricemia which is most likely a consequence of hyperinsulinemia: the kidney which maintains normal sensitivity to insulin, adapts to high insulin concentrations by decreased uric acid secretion, thereby elevating its plasma level (79).

Another important clinical marker of IR is acanthosis nigricans (2), which manifests as hyperpigmented skin changes based on epidermal hyperplasia. The feature is thought to be related to the hyperinsulinemic state, as insulin was shown to accelerate epidermal cell growth in culture (80).

Diagnostic criteria accepted by ATPIII and International Diabetes Federation (IDF) are presented in Table 2. According to ATPIII agreement, patients having at least 3 of 5 characteristics can be diagnosed as having the metabolic syndrome: abdominal obesity, elevated triglycerides, decreased HDL-cholesterol, increased blood pressure or increased fasting plasma glucose (7). IDF declares criteria fairly consistent with ATPIII (82). Slight differences include central obesity as the major feature and fulfilled two of four other manifestations. The borderline glucose concentration is lower in IDP criteria, with a strong recommendation for OGTT when exceeded.

TABLICA 2. Dijagnostički kriteriji za metabolički sindrom prema ATPIII (7) i IDF (81)

TABLE 2. Diagnostic criteria for metabolic syndrome according to ATPIII (7) and IDF (81)

Clinical feature	ATPIII	Defining level	IDF	Defining level
Central obesity – waist circumference	men	>102 cm	men (European)	≥94 cm (or specific values for other ethnic groups)
	women	>88 cm	women (European)	≥80 cm
Plus any 2 of the following:				
Triglycerides		≥1.7 mmol/L		≥1.7 mmol/L or specific treatment
HDL-cholesterol	men	≤1.03 mmol/L	men	≤1.03 mmol/L or specific treatment
	women	≤1.29 mmol/L	women	≤1.29 mmol/L
Blood pressure		≥130/≥85 mm Hg		≥130/≥85 mm Hg or treatment of previously diagnosed hypertension
Fasting plasma glucose		≥6.1 mmol/L		≥5.6 mmol/L or previously diagnosed DM2

Zaključak

Glavni osnovni uzrok IR je visceralna pretilost, jer je visceralno masno tkivo sklonije lipolizi od potkožnog masnog tkiva. Smatra se kako su najvažniji mehanizmi za razvoj IR povećano lučenje FFA, snižene koncentracije adiponektina, leptina, IL-6 i drugih adipokina. Uz to što je IR prisutna zajedno s pretilošću i drugim obilježima poznatim kao metabolički sindrom, smatra se da ima važnu ulogu i u razvoju sindroma policističnih jajnika kod žena (82) te da je glavno obilježje kod lipodistrofija (83). Ove potonje su obilježene selektivnim gubitkom masnog tkiva, što ukazuje na to da je određena količina masnog tkiva neophodna za normalnu inzulinsku osjetljivost, vjerojatno tako što osigurava mjesto za pohranu triglicerida, te što luči dovoljno adiponektina i leptina (77).

Međutim, tek valja u potpunosti razjasniti etiologiju bolesti udruženih s IR. Postoje prigovori definiranju pretilosti i s njom povezanih kardiovaskularnih rizičnih čimbenika kao "metabolički sindrom" zbog nesigurnosti njihova zajedničkog podrijetla (84). S druge pak strane, pojavljuju se nova važna saznanja o novootkrivenom inzulin-mimetičnom adipokinu podrijetlom iz masnog tkiva. Nazvan je visfatin, jer je u znatno većim koncentracijama otkriven u visceralnom nego u potkožnom masnom tkivu. Za visfatin je pokazano kako snižava koncentraciju glukoze u plazmi i djeluje neovisno od inzulina, vjerojatno vežući se za različita vezna mjesta istoga receptora (85).

Bolje razumijevanje mehanizama koji dovode do IR i udruženih bolesti te otkrivanje dodatnih terapijskih ciljeva kao što je visfatin biti će korisno u liječenju najozbiljnijih komplikacija IR – šećerne bolesti tipa 2 i kardiovaskularne bolesti.

Conclusion

The main underlying cause of IR is visceral obesity, as visceral adipose tissue is more prone to lipolysis than subcutaneous adipose tissue. The most important mechanisms for the development of IR are thought to be increased secretion of FFA, and decreased adiponectin, leptin, IL-6 and other adipokine concentrations. Besides the coexistence of IR with obesity and other features known as metabolic syndrome, IR is thought to play an important role in the development of polycystic ovary syndrome in women (82) and is the main feature of lipodystrophies (83). The latter are characterized by selective loss of adipose tissue, which indicates that a certain amount of adipose tissue is necessary for normal insulin sensitivity, presumably by providing the place for triglyceride storage and by secreting sufficient adiponectin and leptin (77).

However, the etiology of IR-associated disorders remains to be fully elucidated. There are some objections to defining obesity and related cardiovascular risk factors as the metabolic "syndrome" for the uncertainty about their common origin (84). On the other hand, some important knowledge is arising such as about a newly discovered insulin-mimetic adipokine derived from adipose tissue. It has been named visfatin for being detected in a much higher concentration in visceral than in subcutaneous adipose tissue. It has been shown to lower plasma glucose concentration and to act independently of insulin, presumably by binding to a different binding site of the same receptor (85).

Better understanding of the mechanisms leading to IR and associated diseases, and discovery of additional therapy targets such as visfatin would prove beneficial in the management of the most serious complications of IR, DM2 and cardiovascular disease.

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