NEDOSTATAK HORMONA RASTA KOD ODRASLIH – DIJAGNOZA I LEČENJE

GROWTH HORMONE DEFICIENCY IN ADULTS – DIAGNOSIS AND TREATMENT

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Sažetak

Nedostatak hormona rasta kod odraslih je redak klinički sindrom sa incidencom 1,4-4,2 na 100.000 osoba godišnje i prevalencom od 350/milion. Karakteriše se nepovoljnim telesnim sastavom, smanjenom mišićnom i koštanom masom, slabijim kapacitetom podnošenja fizičkog napora, lošim lipidnim profilom, povećanim kardiovaskularnim rizikom i lošim kvalitetom života. I pored kliničkih manifestacija, ovaj entitet je često neprepoznat, pa postavljanje dijagnoze deficita hormona rasta često izostaje ili je odloženo. Razlog tome je nespecifična i suptilna klinička slika, što zahteva testiranje sekrecije hormona rasta stimulacionim testovima. Za procenu sekrecije ovog hormona koristi se test insulinske tolerancije i glukagonski test, koji zahtevaju iskustvo tima koji ih izvodi. Od nedavno je u upotrebi test oralnim sekretagogom hormona rasta (macimorelin), koji je jednostavan za izvođenje i bezbedan po pacijenta. Nedovoljna sekrecija hormona rasta kod odraslih se može manifestovati u izolovanoj formi ili u kombinaciji sa deficitima drugih hormona adenohipofize. Hormon rasta je najčešće detektovan hormonski deficit odraslih u sklopu hipopituitarizma. Uzroci njegovog nedostatka mogu biti urođeni i stečeni. Urođeni razlozi su posledica poremećaja embriogenog razvoja hipofize i hipotalamusa, a stečeni su najčešće komplikacija tumora selarne regije i traume glave. Pacijenti sa nedovoljnom sekrecijom ovog hormona imaju povećanu stopu mortaliteta u odnosu na opštu populaciju. Uzroci skraćenog životnog veka ovih bolesnika zavise od etiologije hipopituitarizma, primenjene terapije tumora selarne regije (operacija, radioterapija) i nadoknade drugih nedostajućih hormona adenohipofize. Tokom poslednje dve decenije, terapija hormonom rasta kod odraslih je ušla u rutinsku kliničku praksu. Povoljni efekti ove supstitucije se ogledaju na telesnom sastavu, skeletnom sistemu, metaboličkom statusu i poboljšanju kvaliteta života. Nadoknada hormona rasta kod odraslih vraća stopu mortaliteta na očekivanu za uzrast u opštoj populaciji. Zbog poznatih proliferativnih, angiogenih i antiapoptotskih svojstava hormona rasta, još uvek postoji određen oprez u vezi pojave recidiva tumora uzročnika hipopituitarizma ili pojave novih tumora tokom terapije ovim hormonom. Međutim, velike i dugotrajne studije praćenja odraslih na terapiji hormonom rasta su pokazale visok bezbednosni profil ovog tretmana. Dnevne injekcije hormona rasta su do sada bile jedini način njegove primene, a odnedavno su plasirane i dugodelujuće nedeljne forme, čime će se značajno poboljšati adherence ove terapije.

Ključne reči: nedostatak hormona rasta kod odraslih, terapija hormonom rasta kod odraslih, tranzicija

Uvod

Nedostatak hormona rasta (*Growth Hormone Deficiency,* GHD) odraslih je dobro definisan klinički fenomen, koji karakterišu nepovoljan telesni sastav, smanjena mineralna gustina kostiju (*Bone Mineral Denisty*, BMD), intolerancija glukoze, loš lipidni profil, povećan kardiovaskularni rizik i slab kvalitet života[1]. Pacijenti sa hipofunkcijom prednjeg režnja hipofize, odnosno hipopituitarizmom, u okviru koga je najčešće prisutan i GHD, imaju i do dva puta veću stopu smrtnosti u odnosu na opštu populaciju istog starosnog doba[2]. Odrasle osobe sa deficitom hormona (*Adult Growth Hormone Dificiency*, AGHD) rasta se mogu grupisati u dve grupe: 1) pacijenti kod kojih je GHD nastao u detinjstvu i perzistira i nakon završetka rasta (*Childhood Onset Growth Hormone Deficiency*, COGHD) i 2) pacijenti koji su stekli GHD u odraslom

dobu (*Adult Onset Growth Hormone Deficiency*, AOGHD). Uzroci nedostatka ili nedovoljne sekrecije hormona rasta (*Growth Hormone*, GH) mogu biti urođeni (kongenitalni) i stečeni[3, 4]. Urođeni GHD je posledica urođene strukturne ili funkcionalne anomalije hipotalamo/hipofizne regije, kao i dokazane mutacije gena, bitnih u embrionalnom razvoju ove regije. Obzirom na isto embrionalno poreklo, strukturne/razvojne anomalije hipofize i hipotalamusa mogu biti udružene sa poremećajima funkcije i anatomije mozga i oka[5]. Stečeni GHD je najčešće posledica tumora hipofize i hipotalamusa (nefunkcijski adenomi hipofize, kraniofaringeomi, germinomi, Kušingova bolest), kranijalno zračenje, povrede glave, infekcije mozga, vaskularne anomalije i perinatalna trauma. U slučajevima kada razlog GHD nije poznat, uz normalan snimak hipofizne regije na magnetnoj rezonanci (MR), radi se o idiopatskom GHD.

Lečenje hormonom rasta kod odraslih sa dokazanim GHD je odobreno u kliničkoj praksi 1996. godine[6]. Velike baze podataka su potvrdile brojne povoljne efekte ove terapije na telesni sastav, skeletni sistem, kardiovaskularni aparat, metabolički status i kvalitet života pacijenata, uz visok bezbednosni profil.

Do sada u domaćim časopisima nisu objavljivani radovi koji se tiču nedostataka GH kod odraslih i njegove nadoknade. Zbog kliničkog značaja ove teme, lekarima na svim nivoima zdravstvene zaštite potrebno je da budu upoznati sa ovim entitetom. U cilju toga je napisan ovaj revijalni rad, u kome je korišćena literatura objavljena tokom poslednjih 15 godina, pretraživanjem baza Pubmed, Scopus i Medline. Kriterijumi na osnovu kojih smo uključili studije u analizu su sledeći: originalni članci, revijalni radovi, randomizovana kontrolisana klinička ispitivanja, otvorene studije, neinterventne studije praćenja i podaci registara stvarne kliničke prakse.

Fiziološka uloga hormona rasta

Za razliku od drugih hormona prednjeg režnja hipofize, GH i prolaktin nemaju isključivo jedan ciljni organ ili žlezdu. Većinu svojih dejstava GH ostvaruje posredstvom molekula koji se naziva insulinu-sličan faktor rasta I (*Insulin Growth Factor I*, IGF-I). Ovaj biološki medijator hormona rasta se produkuje u jetri i potom ostvaruje endokrino dejstvo dospevajući krvotokom do pojedinih organa, ali se produkuje i lokalno u svim tkivima ostvarujući tako svoja parakrina i autokrina dejstva. IGF-I u značajnoj meri ispoljava suprotne efekte na metabolizam masti, ugljenih hidrata kao i insulinsku rezistenciju u odnosu na GH, dok su dejstva na mišiće i kosti veoma slična efektima hormona rasta. Hipofizna sekrecija GH je regulisana hipotalamusnim hormonima: stimulisana je oslobađajućim hormonom za hormon rasta (GHRH) i inhibirana somatostatinom[7]. Drugi stimulatorni egzogeni i endogeni faktori (L-DOPA, kinidin, arginin, grelin) mogu uticati na lučenje GH. Regulacija sekrecije GH je kontrolisana negativnom povratnom spregom preko IGF-I na nivou hipofize i hipotalamusa. GH se sekretuje u diskretnim pulsevima (sekretorne epizode) tokom 24 sata. Na njegovu sekreciju utiču različiti faktori kao što su: godine, pol, nutritivni status, stres, spavanje i neki farmakološki agensi. Kod zdravih osoba najveća sekrecija GH se odvija tokom dubokog sna. Koncentracija IGF-I ostaje relativno nepromenjena tokom 24 sata, ali njegov nivo varira u zavisnosti od godina i pola.

Dijagnoza nedostatka hormona rasta kod odraslih (AGHD)

Klinička dijagnoza AGHD

Dijagnoza GHD kod odraslih se razmatra kod svih bolesnika sa anamnezom hipotalamo-hipofizne bolesti (pre svega tumora), zračenja endokranijuma, deficita hormona rasta u detinjstvu, traume glave, subarahnoidne hemoragije, Sheehan-ovog sindroma, autoimunih bolesti hipofize, kod lečenih od maligniteta u detinjstvu i pacijenata sa nejasnom osteopenijom. Klinička dijagnoza AGHD nije uvek laka, jer ne postoji patognomoničan znak koji nedvosmisleno upućuje na ovo stanje, za razliku od dece gde je nizak rast ključna dijagnostička tačka ovog stanja[8]. Manifestacije GHD su nespecifične i suptilne. One su posledice izostanka anaboličkog i lipolitičkog efekta GH, pa pacijenti imaju povećano nagomilavanje masnog tkiva u abdominalnoj regiji, slabost mišića, sklonost frakturama kostiju, smanjen kapacitet fizičke aktivnosti, uz različite probleme mentalnog funkcionisanja u smislu depresivnog raspoloženja, nesanice i zaboravnosti (tabela 1). Za razliku od gojaznosti, gde su

Tabela 1. Klinički znaci i simptomi GHD kod odraslih osoba

Klinički znaci	Simptomi
Smanjena mišićna masa	Loš kvalitet života
Povećana masna masa	(depresija, zaboravnost, nesanica)
Ubrzana aterogeneza	Abdominalna gojaznost
Loš lipidni profil	Osteoporoza i frakture kostiju
Intolerancija glukoze	Slabo podnošenje fizičkog napora
Metabolički sindrom	Brzo zamaranje
Hiperkoagulabilnost	Tromboze
Koronarna bolest	Smanjeno znojenje

Tabela 2. Dijagnoza GHD kod odraslih osoba

	Preporuke
Pacijenti-kandidati za ispitivanje GHD	• hipotalamo-hipofizna bolest • anamneza zračenja kranijuma • anamneza COGHD • narušena struktura hipofize • urođene anomalije hipofize • genske mutacije • deficit drugih hormona hipofize • *Sheehan* sindrom • nejasna osteopenija
Broj provokativnih testova za procenu sekrecije GH	• jedan test kod onih sa hipotalamo-hipofiznom bolešću i deficitom jednog ili više hormona hipofize • dva testa kod onih sa izolovanim deficitom GH Provokacioni test nije potreban ukoliko nedostaju svi hormoni hipofize (kompletni hipopituitarizam) uz nizak IGF-I
Dinamski testovi za procenu sekrecije GH	• test insulinske tolerancije (ITT) • glukagonski test

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povećani depoi masti i mišićna mase, kod GHD je mišićna masa redukovana. Epidemiološke studije su pokazale da je koštana masa kod AGHD značajno manja čak i kada se uzmu u obzir mogući uticaji hipogonadizma i prekomerne supstitucije glukokortikoidima[9]. Svaka treća odrasla osoba sa GHD koji je nastao u detinjstvu ima osteoporozu. Bolesnici sa GHD imaju 2-5 puta veći rizik od koštanih preloma u odnosu na zdrave osobe. Histologija kostiju kod ovih bolesnika pokazuje povećanu resorpciju kostiju kao i povećanu debljinu osteoidnog matriksa što ukazuje na odloženu i smanjenu mineralizaciju[10].

Pacijenti sa AGHD imaju povećan morbiditet i mortalitet usled kardiovaskularnih bolesti. Direktni efekti na srcu se odnose na smanjenje mase i dijametra leve komore i komorskog septuma. Kod mladih osoba se radiografski opisuje „kapljičasto srce" obzirom da izostankom anaboličkog dejstva GH dolazi do redukcije ukupne mase miokarda. Smanjenje dijametra leve komore, dijastolne funkcije i ejekcione frakcije, vodi tzv. „hipokinetičkom sindromu" ovih osoba[11]. Posledica tih promena je redukovana fizička performansa i slabo podnošenje fizičkog napora. Kod AGHD postoje promene na krvnim sudovima, koje ubrzavaju aterogenezu, posebno na karotidnim arterijama i torakoabdominalnoj aorti. Naime, pacijenti sa niskim koncentracijama GH i IGF-I razvijaju zadebljanje zida arterija, što uz loš lipidni status sa povećanjem ukupnog i LDL holesterola, povećava njihov kardiovaskularni rizik.

Pokazano je da bolesnici sa GHD imaju lošiji kvalitet života (*Quality of Life*, QoL). U praksi se primenjuje nekoliko upitnika za procenu QoL kod ovih pacijenata. Kod nas je u upotrebi upitnik QoL-AGHDA (*Quality of Life of Adult GHD Assessment*), čija je verzija prošla ekspertsku validaciju i prevod na naš jezik. Ovaj upitnik je nastao zahvaljujući ispitivanju QoL bolesnika, koji su imali nadoknadu svih drugih hormona u hipopituitarizmu, ali ne i GH[12]. Sastoji se od 25 pitanja, sa odgovorima „DA" ili „NE", a veći broj pozitivnih odgovora ukazuje na slabiji kvalitet života. Iako je ovaj upitnik odlično sredstvo za ispitivanje QoL, ne postoji korelacija sa težinom deficita GH. Tokom terapije GH, ovaj upitnik se popunjava na 6 meseci, odgovori se upoređuju i formiraju zaključak o efektu supstitucije.

Biohemijska dijagnoza GHD

I pored navedenih kliničkih znakova, osnova za definisanje AGHD je biohemijska dijagnoza. Sekrecija GH je pulsatilna, njegov poluživot je svega 19 minuta, tako da je kod zdravih odraslih osoba koncentracija GH skoro nedetektabilna. Zbog toga merenje serumske koncentracije GH nije validno za dokazivanje GHD, već je potrebno sprovesti stimulacione testove za sekreciju GH. Lučenje GH zavisi od pola, godina i indeksa telesne mase. Izmerena niska koncentracija IGF-I, takođe nije dovoljna za postavljanje dijagnoze GHD, već samo sugeriše da je potrebno sprovesti dalje testiranje (tabela 2). Kako nivoi GH i IGF-I u serumu opadaju sa starenjem (somatopauza), važno je razlikovati fiziološko smanjenje nivoa GH i stvarni nedostatak AGHD, koji obično ima prepoznatljivu etiologiju. Nivo IGF-I u serumu može biti smanjen zbog neuhranjenosti, bubrežne insuficijencije i bolesti jetre[13]. Za većinu pacijenata su potrebni testovi za stimulaciju GH da bi se utvrdila dijagnoza GHD, sa izuzetkom pacijenata sa hipotalamo/hipofiznom bolešću koji imaju deficite ostalih hormona adenohipofize i nizak nivo serumskog IGF-I. Ako nedostaju 1 ili 2 hormona prednjeg režnja hipofize u 80% slučajeva postoji i nedostatak GH, dok ako nedostaju 3 ili 4 hormona hipofize u 98% slučajeva je prisutan i GHD.

U standardnoj kliničkoj praksi su dva testa procene sekretorne rezerve hipofize za GH kod odraslih: test insulinske tolerancije (*Insulin Tolerance Test*, ITT) i glukagonski test (*Glucose Tolerance*, GT). ITT se smatra „zlatnim standardom" za dijagnozu GHD, pod uslovom da se njime postigne adekvatna hipoglikemija, tj. glikemija < 2,2 mmol/L. Ovaj test se izvodi u prisustvu lekara u tercijarnim ustanovama zdravstvene zaštite. Kontraindikovan je kod pacijenata starijih od 65 godina, kod onih sa promenama EKG, srčanom insuficijencijom, cerebrovaskularnom bolešću, epilepsijom i anamnezom kriza svesti. Alternativni stimulacioni test koji se koristi u dijagnostici AGHD je glukagonski test[14]. Kada se glukagon koristi kao stimulator GH moguće je zakasnelo oslobađanje ovog hormona, pa se preporučuje izvođenje testa, tj. praćenje GH u periodu od najmanje tri sata. Glavni nedostaci GT-a su dugo trajanje testa (3 do 4 sata), potreba za intramuskularnom administracijom i relativno česta pojava mučnine i povraćanja. Ovaj test je manje specifičan od ITT. U oba ova testa diskriminatorna vrednost za dijagnozu GHD je 3 ng/mL za osobe starije od 25 godina, a za osobe u periodu tranzicije (18-25 godina) ta vrednost je 5-7 ng/mL (15-20 mU/L). Pre sprovođenja ovih testova, treba adekvatno nadoknaditi ostale hormone (tiroksin, kortizol). Krajem 2017. godine u Sjedinjenim Američkim Državama i 2019. godine u Evropi, FDA i EMA odobrile su macimorelin test za postavljanje dijagnoze AGHD. Macimorelin je oralno aktivni agonista grelina, koji se dobro apsorbuje u gastrointestinalnom traktu i efikasno stimuliše endogeno lučenje GH. Macimorelin je upoređen sa ITT u multicentričnoj randomizovanoj studiji, koja je pokazala da je to jednostavan, reproducibilan i siguran test, sa diskriminatornom vrednošću hormona rasta od 2,8 ng/mL za odrasle[15].

Terapija hormonom rasta kod odraslih

Primena GH je indikovana kod svih odraslih osoba sa potpunim nedostatkom ovog hormona i kliničkim posledicama tog deficita, ako nema kontraindikacija (tabela 3). U dečjem uzrastu se leče svi pacijenti sa GHD, bilo da je on potpun ili parcijalan, zbog postizanja zadovoljavajuće telesne visine. Sa druge strane u odraslom periodu supstituciju GH dobijaju samo oni sa potpunim GHD. Cilj terapije GH kod odraslih osoba je normalizacija nivoa IGF-I, čime će se smanjiti morbiditet i mortalitet osoba sa GHD[16]. Zbog svog anaboličkog i lipolitičkog dejstva, nadoknada hormona rasta povećava količinu mišićne mase i smanjenje količine

Tabela 3. Ciljevi nadoknade hormona rasta kod odraslih

Normalizovati koncentraciju IGF-I
Ispraviti abnormalnosti uzrokovane deficitom GH
- popraviti telesni sastav (smanjiti depoe abdominalnog masnog tkiva, povećati mišićnu masu)
- poboljšati metaboličke parametre (lipidni profil, insulinsku senzitivnost)
- poboljšati mišićnu funkciju (uključujući i srčanu) i povećati fizičku izdržljivost
- povećati koštanu masu
- poboljšati funkciju srca (povećati ejekcionu frakciju i masu leve komore, poboljšati dijastolnu funkciju)
- poboljšati kvalitet života (QoL)

masnog tkiva prevashodno u regiji abdomena[17]. Terapija GH ispoljava povoljan uticaj i na koštani sistem, ali su efekti bifazični jer GH stimuliše i formiranje i razgradnju kostiju, te prvih 12 meseci lečenja može doći do smanjenja koštane mase, ali nakon 18-24 meseca postoji povećanje BMD prevashodno u predelu kičme. Zbog toga se merenje gustine kostiju (*Dual X-ray Absorptiometry,* DXA) sprovodi najranije 12 meseci nakon početka terapije GH. Povoljni efekti terapije GH na telesni sastav i kosti održavaju se tokom više od decenije lečenja ovim hormonom. Naime, studija Elbornsson i sar. je pokazala tendenciju porasta mišićne mase tokom 15 godina, i smanjenju masne mase u prvih 7 godina terapije. Posle sedme godine, dolazi do postepenog povećavanja masne mase, što može biti povezano sa starenjem[18]. Pretpostavlja se da su porast indeksa telesne mase i povećanje obima struka uzrokovani fiziološkim starenjem jedinke, bez obzira na nivo GH. Sa druge strane, istraživanje holandske grupe je pokazalo da dugoročni efekti terapije GH na telesni sastav nisu konzistentni, da među studijama u zavisnosti od dizajna postoje neslaganja u smislu efekata na telesni sastav[19]. Efekti supstitucije GH se ogledaju i na kardiovaskularni sistem, povećava se ejekciona frakcija, debljina zida leve komore i dijastolna funkcija leve komore. Poboljšanje metabolizma lipoproteina je verovatno posledica indukcije hepatičkog LDL receptora, što dovodi do smanjenja nivoa LDL holesterola u serumu[20]. Promena u lipoproteinskom statusu je evidentna posle godinu dana terapije sa GH. Poboljšanje QoL na terapiji hormonom rasta je evidentno već nakon tri meseca, sa maksimalnim efektom posle 12 meseci terapije i tendencijom održavanja i do 15 godina lečenja[12].

Efekti terapije GH zavise od pola i uzrasta pacijenta, kao i od toga kada je nastao nedostatak ovog hormona. Poboljšanje BMD je izraženije kod muškaraca u odnosu na žene, kao i kod bolesnika sa nedostatkom COGHD u odnosu na one kod kojih je GHD nastao u odraslom dobu[21]. Suprotno tome, bolesnici sa AOGHD imaju značajnije poboljšanje QoL u odnosu na COGHD. Žene, stariji i osobe sa većom telesnom težinom, imaju slabiji odgovor na terapiju hormonom rasta[22].

Doziranje hormona rasta kod odraslih

U pogledu određivanja doze GH za odrasle osobe, uzima se u obzir pol i starost pacijenta, kao i terapija estrogenom kod žena. Počinje se nižom dozom, a potom se ona individualno titrira do doze održavanja prema kliničkom odgovoru, neželjenim efektima i nivou serumskog IGF-I. Zbog supresivnog dejstva estrogena na hepatičku produkciju IGF-I žene zahtevaju veće doze GH od muškaraca da bi normalizovale IGF-I. Žene sa GHD koje su na oralnoj terapiji estrogenom zahtevaju veće doze GH od onih koje su na transdermalnim estrogenima[23].

Za pacijente od 30 do 60 godina, startna doza je 0,2-0,3 mg dnevno, pa se onda prema nivou IGF-I povećava ili smanjuje za 0,1-0,2 mg svakih 1-2 meseca, dok se ne postigne normalan IGF-I za starost pacijenta. Za osobe mlađe od 30 godina i osobe u tranzicionom periodu početna doza je veća i iznosi 0,4-0,5 mg dnevno, takođe se titrira individualno prema IGF-I. Osobe starije od 60 godina, počinju lečenje malim dnevnim dozama od 0,1-0,2 mg. Način doziranja je isti za one koji su stekli deficit GH u detinjstvu i kod onih koji su ga dobili u odraslom dobu. Da bi se što bolje imitirala fiziološka noćna sekrecija GH, doza hormona rasta se daje uveče, supkutanim putem[24]. Dnevne injekcije hormona rasta su do sada bile jedini način njegove primene, a od nedavno su plasirane i dugodelujuće nedeljne forme, čime će se značajno poboljšati adherenca ove terapije[25].

Praćenje efekata terapije hormonom rasta

Podešavanje doze GH treba vršiti na 1-2 meseca u početnim mesecima njegove primene, a po postizanju doze održavanja, praćenje se vrši na 6 meseci. Pošto je doza održavanja GH uspostavljena, praćenje efikasnosti i bezbednosti terapije treba nastaviti sve vreme lečenja. Najbolji način praćenja biohemijskog dejstva GH je IGF-I. On je esencijalni marker monitoringa sigurnosti primene GH terapije. Promene koncentracije IGF-I su merljive brzo nakon promene doze GH, što omogućava rano prepoznavanje prekoračenja doze[24]. Osim biohemijskog praćenja, veoma su bitni klinički znaci u praćenju efikasnosti lečenja hormonom rata. Telesni sastav (obim kuk/struk, debljina potkožnog masnog tkiva, gustina kostiju i količina masnog tkiva putem DXA metode) i QoL se prate u određenim vremenskim intervalima. Pošto je stabilna doza GH uspostavljena, bolesnika treba kontrolisati svakih 3 do 6 meseci tokom prve godine terapije, a kasnije na 6 do 12 meseci. Vreme kasnijih kontrola se određuje u zavisnosti od primarne hipofizne patologije i drugih faktora kao što je zračna terapija hipofize ili mozga. Prate se neželjeni efekti terapije GH (retencija tečnosti, poremećaj glikoregulacije, eventualno pojava tumora *de novo* ili porast ostatka tumora hipofize uzročnika GHD), kao i potencijalnih interakcija GH sa drugim hormonima. Hormon rasta stimuliše perifernu konverziju T4 u T3, što može dovesti do smanjenja nivoa slobodnog tiroksina (FT4). Merenja koncentracija FT4

u serumu su neophodna tokom supstitucije GH, radi korekcije doze tiroksina ako je prisutan u terapiji ili da se u slučaju demaskiranja sekundarne hipotireoze započne supstitucija tiroksinom[26]. Hormon rasta ubrzava metabolizam kortizola, pa može doći do potrebe za povećanjem doze hidrokortizona ako je deo terapije ili uvođenja hidrokortizona zbog ispoljavanja sekundarnog hipokorticizma. Ako je terapija GH efikasna nema razloga da bude prekinuta do duboke starosti.

Pre uvođenja terapije GH poseban oprez treba imati kod pacijenata operisanih ili zračenih zbog tumora endokranijuma ili anamneze nekog maligniteta. Zbog mitogenog efekta GH, praktično od početka njegove primene kod pacijenata sa GHD, polemiše se o riziku recidiva primarnog tumora ili nastanka sekundarne neoplazme[27]. Zbirni podaci velikih studija i dugotrajnog praćenja osoba sa AGHD na terapiji GH, pokazali su da nema povećanog rizika od razvoja recidiva tumora uzročnika GHD, ni pojave *de novo* tumora[28]. Pravi izbor pacijenata za supstituciju sa GH i optimalna doza ovog hormona obezbeđuju veliku sigurnost primene terapije. Za mlade odrasle osobe u periodu tranzicije (18-25 godina starosti), treba da prođe najmanje dve godine od remisije osnovne bolesti (stabilna veličina tumorskog ostatka na MR) da bi se započela terapija GH. Kod starijih od 25 godina, taj period može biti i duži, a ako je osoba imala malignitet odraslog doba, čeka se najmanje pet godina od remisije bolesti za početak terapije GH[29]. Kliničko iskustvo govori da je bezbednost uvođenja GH veća što je duži vremenski period praćenja stabilne veličine ostatka tumora selarne regije. Tokom prve godine terapije sa GH, preporuka je da se vrši MR hipofizne regije na 6 meseci, a potom na jednu do tri godine od početka terapije u zavisnosti od same osnovne patologije i tretmana (operacija, radioterapija).

Neželjeni efekti i kontraindikacije terapije hormonom rasta

Neželjeni efekti primene GH su obično zavisni od doze i prolazni su, rešavaju se redukcijom doze GH. Niža početna doza GH i pažljivo titriranje do doze održavanja, može prevenirati neželjene efekte. Najčešći neželjeni efekti su oticanje i artralgije (usled zadržavanja tečnosti zbog antinatriuretskog dejstva GH). Zbog antiinsulinskog efekta hormona rasta, postoji trend porasta glikemije i insulina. Međutim, te promene su blage i vezane za prve mesece terapije, posle se ti parametri vraćaju na bazalne vrednosti i dolazi do poboljšanja dugoročne glikoregulacije zahvaljujući poboljšanju telesnog sastava (redukcija abdominalnog masnog tkiva). Višegodišnje studije praćenja efekata terapije GH na preko 15.000 pacijenata, pokazuju da je rizik od razvoja dijabetes melitusa (*Diabetes Mellitus*, DM) blago povećan i da sklonost za DM imaju starije osobe i osobe sa većim BMI i lošim lipidnim profilom[23, 30]. Kontraindikacije za primenu GH su: aktivna maligna bolest, manifestna šećerna bolest, teška oboljenja jetre i bubrega, benigna intrakranijalna hipertenzija, teška psihička oboljenja.

Primena hormona rasta u periodu tranzicije

Period tranzicije (*Transition Period*, TP) predstavlja etapu u životu jedinke koji počinje u kasnom pubertetu i završava se potpunim fizičkim i psihosocijalnim sazrevanjem u odraslu osobu[26]. Tranzicija traje šest do sedam godina nakon završetka rasta, odnosno postizanja konačne telesne visine. U tom periodu je neophodno razmotriti potrebu za nastavkom terapije GH kod osoba koje su tokom detinjstva imale nedostatak ovog hormona (COGHD). Pacijenti sa drugim razlozima niskog rasta tokom detinjstva ne treba da budu lečeni hormonom rasta u odraslom dobu (idiopatski GHD, Turner-ov sindrom, Noon-anov sindrom, Prader-Willi sindrom, hronična bubrežna insuficijencija, mali rast za gestaciono doba). Zbog telesnih, metaboličkih, psiholoških i socijalnih specifičnosti koje generalno prate prelazak iz adolescencije u odraslo doba, kod pacijenata sa COGHD, potrebna je posebna pažnja i saradnja između pedijatra i endokrinologa, nekada psihologa i ginekologa, kao i roditelja/staratelja pacijenta radi što boljeg praćenja i lečenja ovih osoba[31].

Postizanje zadovoljavajuće telesne visine je samo preduslov za postizanje normalnog telesnog sastava. Kod zdravih osoba upravo je TP period kada se postiže maksimum u mišićnoj masi i gustini kostiju. Kada u tom periodu nedostaje GH, dolazi do pogoršanja telesnog sastava na račun redukcije mišićne mase i mase kostiju, povećanja masnog tkiva uz povećan kardiovaskularni rizik. Cilj terapije GH u tranziciji je postizanje normalnog telesnog sastava, smanjenje učestalosti fraktura kostiju i poboljšanje funkcije miokarda[32]. Ne treba zanemariti i poboljšanje kvaliteta života u ovom osetljivom psihosocijalnom periodu svake jedinke tokom terapije, kada se osamostaljuju i odvajaju od roditelja, bilo da nastavljaju dalje školovanje ili se zapošljavaju.

Smatra se da 30-70% osoba sa izolovanim idiopatskim GHD u detinjstvu, prilikom retestiranja u tranziciji ima normalnu sekreciju GH. Verovatnoća da GHD perzistira i u odraslom dobu je velika kod osoba sa anamnezom tumora selarne regije, strukturnih anomalija hipotalamusa/hipofize ili mutacijom gena uključenih u embrionalno sazrevanje hipofize. Sa druge strane, osobe sa izolovanim idiopatskim GHD treba da budu ispitane sa dva stimulaciona testa radi potvrde ili odbacivanja dijagnoze GHD. Završetak rasta nastaje kada je brzina rasta < 2,0 cm godišnje na adekvatnoj terapiji GH i kada zrelost kostiju odgovara uzrastu od 14,5 godina kod devojčica, odnosno 16,5 godina kod dečaka. Tada je jedinka dostigla 99% svoje konačne telesne visine. Preporuka je da se tada obustavi terapija GH na jedan do tri meseca i da se potom pristupi retestiranju[31]. Doze GH u tranziciji su bliže onima koje se primenjuju kod odraslih sa GHD, obično se izražavaju u mg i ne izračunavaju se na kilogram telesne težine. Cilj je da IGF-I bude u normalnom opsegu za godine starosti, više ka gornjoj granici normale. Doza kod dečaka u tranziciji je manja u odnosu na onu kod devojčica[33]. Pre početka terapije sa GH jednom godišnje treba sprovesti antropološka merenja (telesna težina, telesna

visina, obim kuka i struka), merenje krvnog pritiska, lipidnog profila, insulinske senzitivnosti (glikemija našte, insulin, HbA1c), reproduktivne funkcije, nivoa tiroidnih hormona i kortizola i određivanje QoL pomoću adekvatnog upitnika. Merenje telesnog sastava i gustine kostiju metodom DXA, potrebno je sprovesti bazno i svakih dve do pet godina terapije hormonom rasta[10].

Zaključak

Nedostatak hormona rasta kod odraslih osoba je sindrom koji se karakteriše nepovoljnim fenotipskim profilom, metaboličkim poremećajima i lošim kvalitetom života. Tokom poslednje dve decenije, brojne studije su potvrdile poboljšanje ovih parametara na terapiji hormonom rasta (GH). Iako je generalno bezbedna, nadoknada GH zahteva pažljivo titriranje doze i praćenje u cilju postizanja veće efikasnosti i tolerancije lečenja. I pored svih pogodnosti ovog tretmana, klinička praksa ukazuje da je sindrom GHD često neprepoznat i da se supstitucija GH ne koristi dovoljno, iako naš zdravstveni fond pokriva troškove lečenja. Razlog leži u nedovoljnoj informisanosti lekara o značaju i rizicima ove terapije, što nameće potrebu za njihovom intenzivnijom edukacijom o ranom prepoznavanju GHD sindroma odraslih i optimizaciji lečenja.

Abstract

Growth hormone deficiency (GHD) in adults is a rare clinical syndrome with an incidence of 1.4–4.2 per 100,000 persons per year and a prevalence of 350/million. It is characterized by unfavorable body composition, reduced muscle, and bone mass, lower capacity to endure physical effort, abnormal lipid profile, increased cardiovascular risk and poor quality of life. Despite these clinical manifestations, GHD is often unrecognized, so its diagnosis is often missed or delayed. The reason is the non-specific and subtle clinical characteristics, which require the testing of growth hormone (GH) secretion with stimulation tests. Two tests are in use, the insulin tolerance test and the glucagon test, which require the experience of the team performing them. Recently, an oral secretagogue of growth hormone - macimorelin has been used, which is simple test to perform and is safe for the patient. Insufficient secretion of GH in adults can be manifested as isolated or in combination with deficits of other pituitary hormones. However, GH is the most frequently detected hormonal deficit in adults as part of hypopituitarism. Causes of GHD can be congenital or acquired. Congenital reasons are the result of disorders of the embryogenic development of the pituitary gland and hypothalamus, and acquired are the most common complications of tumors of the sellar region and head trauma. Patients with GHD have an increased mortality rate compared to the general population. The causes of the shortened life span of these patients depend on the etiology of hypopituitarism, the applied therapy of tumors of the hypothalamus/pituitary region (surgery, radiotherapy), and the replacement of other missing pituitary hormones. During the last two decades, growth hormone therapy in adults has entered routine clinical practice. The beneficial effects of this substitution are reflected in the body composition, skeletal system, metabolic status, and improvement of the quality of life. GH replacement in adults returns the mortality rate to that expected for age in the general population. Due to the known proliferative, angiogenic, and anti-apoptotic properties of GH, there is still some caution regarding the recurrence of hypopituitarism-causing tumors or the appearance of new tumors during GH replacement. However, large and long-term follow-up studies of adults on GH therapy have shown a high safety profile of this treatment. Daily injections of GH were until recently the only way of its application, and now long-acting weekly forms have been marketed, which will significantly improve adherence to this therapy.

Keywords: growth hormone deficiency in adults, growth hormone replacement in adults, transition

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GROWTH HORMONE DEFICIENCY IN ADULTS – DIAGNOSIS AND TREATMENT

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Abstract

Growth hormone deficiency (GHD) in adults is a rare clinical syndrome with an incidence of 1.4–4.2 per 100,000 persons per year and a prevalence of 350/million. It is characterized by unfavorable body composition, reduced muscle, and bone mass, lower capacity to endure physical effort, abnormal lipid profile, increased cardiovascular risk and poor quality of life. Despite these clinical manifestations, GHD is often unrecognized, so its diagnosis is often missed or delayed. The reason is the non-specific and subtle clinical characteristics, which require the testing of growth hormone (GH) secretion with stimulation tests. Two tests are in use, the insulin tolerance test and the glucagon test, which require the experience of the team performing them. Recently, an oral secretagogue of growth hormone - macimorelin has been used, which is a simple test to perform and is safe for the patient. Insufficient secretion of GH in adults can be manifested as isolated or in combination with deficits of other pituitary hormones. However, GH is the most frequently detected hormonal deficit in adults as part of hypopituitarism. Causes of GHD can be congenital or acquired. Congenital reasons are the result of disorders of the embryogenic development of the pituitary gland and hypothalamus, and acquired are the most common complications of tumors of the sellar region and head trauma. Patients with GHD have an increased mortality rate compared to the general population. The causes of the shortened life span of these patients depend on the etiology of hypopituitarism, the applied therapy of tumors of the hypothalamus/pituitary region (surgery, radiotherapy), and the replacement of other missing pituitary hormones. During the last two decades, growth hormone therapy in adults has entered routine clinical practice. The beneficial effects of this substitution are reflected in the body composition, skeletal system, metabolic status, and improvement of the quality of life. GH replacement in adults returns the mortality rate to that expected for age in the general population. Due to the known proliferative, angiogenic, and anti-apoptotic properties of GH, there is still some caution regarding the recurrence of hypopituitarism-causing tumors or the appearance of new tumors during GH replacement. However, large and long-term follow-up studies of adults on GH therapy have shown a high safety profile of this treatment. Daily injections of GH were until recently the only way of its application, and now long-acting weekly forms have been marketed, which will significantly improve adherence to this therapy.

Keywords: growth hormone deficiency in adults, growth hormone replacement in adults, transition

Introduction

Adult growth hormone deficiency (GHD) is a well-defined clinical phenomenon characterized by unfavorable body composition, reduced bone mineral density (BMD), glucose intolerance, poor lipid profile, increased cardiovascular risk, and diminished quality of life[1]. Patients with hypofunction of the anterior pituitary lobe, also known as hypopituitarism, which often includes GHD, have up to twice the mortality rate compared to the general population of the same age group[2]. Adults with Growth Hormone Deficiency (AGHD) can be grouped into two categories: 1) patients in whom GHD originated in childhood and persists after growth completion (Childhood Onset Growth Hormone Deficiency, COGHD), and 2) patients who acquire GHD in adulthood (Adult Onset Growth Hormone Deficiency, AOGHD). Causes of inadequate secretion or deficiency of growth hormone (GH) can be congenital (inherited) or acquired[3, 4].

Congenital GHD is the result of congenital structural or functional anomalies in the hypothalamic/pituitary region, as well as documented mutations in genes crucial to the embryonic development of this region. Given their common embryonic origin, structural/developmental anomalies

of the pituitary and hypothalamus can be associated with disruptions in brain and eye function and anatomy[5]. Acquired GHD is most commonly a result of pituitary and hypothalamic tumors (non-functioning pituitary adenomas, craniopharyngiomas, germinomas, Cushing's disease), cranial irradiation, head injuries, brain infections, vascular anomalies, and perinatal trauma. In cases where the cause of GHD is unknown, with a normal magnetic resonance imaging (MRI) scan of the pituitary region, it is referred to as idiopathic GHD.

The treatment with growth hormone in adults with confirmed GHD was approved in clinical practice in 1996[6]. Large databases have confirmed numerous beneficial effects of this therapy on body composition, skeletal system, cardiovascular system, metabolic status, and quality of life of patients, with a high safety profile.

To date, articles addressing adult GH deficiency and its supplementation have not been published in domestic journals. Due to the clinical significance of this topic, it is essential for healthcare professionals at all levels to be familiar with this entity. To achieve this goal, this review paper was written, utilizing literature published over the past 15 years searched through databases such as PubMed, Scopus, and Medline. The criteria for including studies in the analysis were as follows: original articles, review papers, randomized controlled clinical trials, open-label studies, non-interventional follow-up studies, and data from registries of actual clinical practice.

Physiological role of growth hormone

Unlike other hormones of the anterior pituitary, GH and prolactin do not have exclusively one target organ or gland. Most of GH's actions are mediated through a molecule called Insulin-like Growth Factor I (IGF-I). This biological mediator of growth hormone is produced in the liver and then exerts endocrine effects by entering the bloodstream and reaching various organs. However, it is also locally produced in all tissues, exerting its paracrine and autocrine effects. IGF-I significantly opposes the effects of GH on fat metabolism, carbohydrate metabolism, and insulin resistance, while its effects on muscles and bones are very similar to those of growth hormone. Pituitary GH secretion is regulated by hypothalamic hormones: it is stimulated by Growth Hormone Releasing Hormone (GHRH) and inhibited by somatostatin[7]. Other stimulatory exogenous and endogenous factors (such as L-DOPA, kinidin, arginine, and ghrelin) can influence GH secretion. The regulation of GH secretion is controlled by negative feedback via IGF-I at the level of the pituitary and hypothalamus. GH is secreted in discrete pulses (secretory episodes) throughout a 24 hours. Its secretion is influenced by various factors such as age, gender, nutritional status, stress, sleep, and certain pharmacological agents. In healthy individuals, the highest GH secretion occurs during deep sleep. The concentration of IGF-I remains relatively unchanged throughout the day, but its level varies depending on age and gender.

Diagnosis of adult growth hormone deficiency (AGHD)

Clinical diagnosis of AGHD

Diagnosis of GHD in adults is considered in all patients with a history of hypothalamic-pituitary disease (primarily tumors), cranial irradiation, childhood growth hormone deficiency, head trauma, subarachnoid hemorrhage, Sheehan's syndrome, autoimmune pituitary diseases, those treated for childhood malignancies, and patients with unclear osteopenia. Clinical diagnosis of AGHD is not always straightforward because there is no pathognomonic sign that unequivocally indicates this condition, unlike in children where short stature is a key diagnostic indicator of this condition[8]. The manifestations of GHD are nonspecific and subtle. They result from the lack of the anabolic and lipolytic effects of GH, so patients have increased accumulation of adipose tissue in the abdominal region, muscle weakness, susceptibility to bone fractures, decreased physical activity capacity, along various mental functioning problems such as depressive mood, insomnia, and forgetfulness (Table 1). Unlike obesity, where there is an increase in fat deposits and muscle mass, in GHD, muscle mass is reduced. Epidemiological studies have shown that bone mass in AGHD is significantly lower even when considering possible influences of hypogonadism and excessive glucocorticoid substitution[9].

Table 1. Clinical signs and symptoms of GHD in adults

Clinical signs	Symptoms
Reduced muscle mass	Poor quality of life
Increased fat mass	(depression, forgetfulness, insomnia)
Accelerated atherogenesis	Abdominal obesity
Poor lipid profile	Osteoporosis and bone fractures
Glucose intolerance	Poor tolerance to physical exertion
Metabolic syndrome	Rapid fatigue
Hypercoagulability	Thromboses
Coronary disease	Reduced sweating

Table 2. Diagnosis of GHD in adults

	Recommendations
Patients-candidates for GHD testing	• hypothalamic-pituitary disease • history of cranial radiation • anamnesis of COGHD • disrupted structure of the pituitary gland • congenital anomalies of the pituitary gland • genetic mutations • deficiency of other pituitary hormones • *Sheehan* syndrome • unclear osteopenia
The number of provocative tests for assessing GH secretion	• one test in those with hypothalamic-pituitary disease and deficiency of one or more pituitary hormones • two tests in those with isolated growth hormone deficiency. A provocative test is not necessary if all pituitary hormones are missing (complete hypopituitarism) with low IGF-I levels
Dynamic tests for assessing GH secretion	• insulin tolerance test (ITT) • glucagon stimulation test

Every third adult with childhood-onset GHD has osteoporosis. Patients with GHD have a 2-5 times greater risk of bone fractures compared to healthy individuals. Histology of bones in these patients shows increased bone resorption as well as increased thickness of the osteoid matrix, indicating delayed and reduced mineralization[10].

Patients with AGHD have increased morbidity and mortality due to cardiovascular diseases. Direct effects on the heart involve the reduction in mass and diameter of the left ventricle and interventricular septum. In young individuals, a "droplet-shaped heart" is radiographically described, as the lack of the anabolic effects of GH leads to a reduction in total myocardial mass. Reduction in the diameter of the left ventricle, diastolic function, and ejection fraction leads to the so-called "hypokinetic syndrome" in these individuals[11]. The consequence of these changes is reduced physical performance and poor tolerance to physical exertion. In AGHD, there are changes in blood vessels that accelerate atherogenesis, particularly in the carotid arteries and thoracoabdominal aorta. Specifically, patients with low concentrations of GH and IGF-I develop thickening of arterial walls, which, combined with poor lipid status characterized by increased total and LDL cholesterol, increases their cardiovascular risk.

It has been shown that patients with GHD have a poorer Quality of Life (QoL). Several questionnaires are used in practice to assess QoL in these patients. In our practice, the QoL-AGHDA (Quality of Life of Adult GHD Assessment) questionnaire is used, which has undergone expert validation and translation into our language. This questionnaire originated from the examination of the QoL of patients who had replacement of all other hormones in hypopituitarism except for GH[12]. It consists of 25 questions with "YES" or "NO" answers, and a higher number of positive responses indicate poorer quality of life. Although this questionnaire is an excellent tool for assessing QoL, there is no correlation with the severity of GH deficiency. During GH therapy, this questionnaire is completed every 6 months, the responses are compared, and conclusions about the substitution effect are formed.

Biochemical diagnosis of GHD

Despite the mentioned clinical signs, the basis for defining AGHD is biochemical diagnosis. GH secretion is pulsatile, with a half-life of only 19 minutes, so in healthy adults, GH concentration is almost undetectable. Therefore, measuring serum GH concentration is not valid for proving GHD; instead, stimulation tests for GH secretion are required. GH secretion depends on gender, age, and body mass index. Additionally, a measured low concentration of IGF-I is also not sufficient for diagnosing GHD; it only suggests the need for further testing (Table 2). As serum levels of GH and IGF-I decline with aging (somatopause), it is important to differentiate physiological decreases in GH levels from actual AGHD, which typically has a recognizable etiology. Serum levels of IGF-I can be reduced due to malnutrition, renal insufficiency, and liver disease[13]. For most patients, stimulation tests for GH are required to establish a diagnosis of GHD, except for patients with hypothalamic/pituitary disease who have deficiencies in other pituitary hormones and low serum IGF-I levels. If one or two hormones of the anterior pituitary lobe are deficient, GHD is present in 80% of cases, while if three or four pituitary hormones are deficient, GHD is present in 98% of cases.

In standard clinical practice, two tests are commonly used to assess pituitary secretory reserve for GH in adults: the Insulin Tolerance Test (ITT) and the Glucose Tolerance (GT) test. ITT is considered the "gold standard" for diagnosing GHD, provided that adequate hypoglycemia (blood glucose < 2.2 mmol/L) is achieved. This test is performed under the supervision of a physician in tertiary healthcare institutions. It is contraindicated in patients older than 65 years, those with ECG changes, heart failure, cerebrovascular disease, epilepsy, and a history of loss of consciousness. An alternative stimulation test used in the diagnosis of AGHD is the glucagon test[14].

When glucagon is used as a GH stimulator, delayed release of this hormone is possible, so it is recommended to perform the test, i.e., monitoring GH for at least three hours. The main drawbacks of the GT include the long duration of the test (3 to 4 hours), the need for intramuscular administration, and relatively common occurrences of nausea and vomiting. This test is less specific than the ITT. In both of these tests, the discriminatory value for diagnosing GHD is 3 ng/mL for individuals older than 25 years, while for individuals in the transitional period (18-25 years), this value is 5-7 ng/mL (15-20 mU/L). Before conducting these tests, it is necessary to adequately replace other hormones (thyroxine, cortisol). At the end of 2017 in the United States and 2019 in Europe, the FDA and EMA approved the macimorelin test for diagnosing AGHD. Macimorelin is an orally active ghrelin agonist that is well absorbed in the gastrointestinal tract and effectively stimulates endogenous GH secretion. Macimorelin has been compared to ITT in a multicenter randomized study, which demonstrated that it is a simple, reproducible, and safe test, with a GH discriminatory value of 2.8 ng/mL for adults[15].

Growth hormone therapy in adults

The use of GH is indicated in all adult individuals with a complete deficiency of this hormone and the clinical consequences of that deficit, if there are no contraindications (see Table 3). In childhood, all patients with GHD, whether it is complete or partial, are treated to achieve satisfactory height. On the other hand, in adulthood, GH substitution is only given to those with complete GHD. The goal of GH therapy in adults is to normalize IGF-I levels, thereby reducing morbidity and mortality in individuals with GHD[16]. Due to its anabolic and lipolytic effects, growth hormone replacement

Table 3. Goals of growth hormone replacement therapy in adults

To normalize the concentration of IGF-I
To correct abnormalities caused by growth hormone deficiency
- To improve body composition (reduce abdominal fat, increase muscle mass)
- To improve metabolic parameters (lipid profile, insulin sensitivity)
- To improve muscle function (including cardiac) and increase physical endurance
- To increase bone mass
- To improve heart function (increase ejection fraction and left ventricular mass, improve diastolic function)
- To improve quality of life (QoL)

increases muscle mass and decreases fat mass primarily in the abdominal region[17]. GH therapy has a beneficial impact on the skeletal system, but its effects are biphasic because GH stimulates both bone formation and bone resorption. Therefore, in the first 12 months of treatment, there may be a decrease in bone mass, but after 18-24 months, there is an increase in BMD primarily in the spine. Hence, bone density measurement (Dual X-ray Absorptiometry, DXA) is conducted at least 12 months after starting GH therapy. The favorable effects of GH therapy on body composition and bones are sustained for more than a decade of treatment with this hormone. A study by Elbornsson et al. showed a tendency for an increase in muscle mass over 15 years and a reduction in fat mass in the first 7 years of therapy. After the seventh year, there is a gradual increase in fat mass, which may be associated with aging[18]. It is assumed that the increase in body mass index and waist circumference is caused by the physiological aging of the individual, regardless of GH levels. On the other hand, a study by a Dutch group has shown that the long-term effects of GH therapy on body composition are not consistent. There are discrepancies among studies depending on their design regarding the effects on body composition[19]. The effects of GH replacement therapy also manifest in the cardiovascular system. It increases ejection fraction, thickness of the left ventricular wall, and diastolic function of the left ventricle. Improvement in lipoprotein metabolism is likely due to the induction of hepatic LDL receptors, leading to a decrease in serum LDL cholesterol levels[20]. Changes in the lipoprotein status become evident after one year of GH therapy. Improvement in Quality of Life (QoL) on growth hormone therapy is apparent as early as three months, with maximal effect after 12 months of therapy and a tendency to maintain for up to 15 years of treatment[12].

The effects of GH therapy depend on the gender and age of the patient, as well as when the deficiency of this hormone occurrs. Improvement in bone mineral density (BMD) is more pronounced in men compared to women, as well as in patients with childhood-onset growth hormone deficiency (COGHD) compared to those with adult-onset growth hormone deficiency[21].

Contrary to that, patients with adult-onset growth hormone deficiency (AOGHD) experience significant improvement in Quality of Life (QoL) compared to childhood-onset growth hormone deficiency (COGHD). Women, older individuals, and those with higher body weight show a weaker response to growth hormone therapy[22].

Dosage of growth hormone in adults

When determining the dose of GH for adult individuals, factors such as gender and age of the patient are taken into account, as well as estrogen therapy in women. Treatment typically starts with a lower dose, which is then individually titrated based on the clinical response, adverse effects, and serum IGF-I levels. Due to the suppressive effect of estrogen on hepatic production of IGF-I, women require higher doses of GH than men to normalize IGF-I levels. Women with GHD who are on oral estrogen therapy require higher doses of GH compared to those on transdermal estrogen therapy[23].

For patients aged 30 to 60 years, the initial dose is typically 0.2-0.3 mg daily, which is then adjusted based on the IGF-I levels by increasing or decreasing by 0.1-0.2 mg every 1-2 months until a normal IGF-I level is achieved for the patient's age. For individuals younger than 30 years and those in the transitional period, the initial dose is higher, ranging from 0.4-0.5 mg daily, and similarly titrated individually based on IGF-I levels. For individuals older than 60 years, treatment usually starts with smaller daily doses of 0.1-0.2 mg. The dosing regimen is the same for those who acquired GH deficiency in childhood and those who developed it in adulthood. To better mimic physiological nocturnal GH secretion, the GH dose is administered subcutaneously in the evening[24]. Until now, daily injections of growth hormone have been the only method of administration, but recently, long-acting weekly formulations have also been introduced. This will significantly improve adherence to this therapy[25].

Monitoring the effects of growth hormone therapy

Adjustment of growth hormone (GH) dosage should be done every 1-2 months during the initial months of its administration. Once the maintenance dose of GH is achieved, monitoring is conducted every 6 months. After the maintenance dose of GH is established, monitoring of the effectiveness and safety of the therapy should continue throughout the treatment period. The best way to monitor the biochemical effects of GH is through IGF-I levels.

IGF-I is an essential marker for monitoring the safety of GH therapy. Changes in IGF-I concentration can be measured rapidly after adjusting the GH dose, enabling early detection of dose excess[24]. Besides biochemical monitoring, clinical signs are also crucial in assessing the effectiveness of growth hormone treatment. Body composition (waist/

hip circumference, subcutaneous fat thickness, bone density, and fat quantity measured by the DXA method) and QoL are monitored at specific intervals. Once a stable GH dose is established, patients should be monitored every 3 to 6 months during the first year of therapy, and later on every 6 to 12 months. The timing of subsequent follow-ups is determined based on the primary pituitary pathology and other factors such as pituitary or brain radiation therapy. Adverse effects of GH therapy are monitored, including fluid retention, glycemic dysregulation, and the potential for *de novo* tumor occurrence or growth of the residual pituitary tumor causing GHD. Potential interactions of GH with other hormones are also assessed. Growth hormone stimulates the peripheral conversion of T4 to T3, which may lead to decreased levels of free thyroxine (FT4). Measurements of serum FT4 concentrations are necessary during GH substitution therapy to adjust the dose of thyroxine if it is part of the therapy or to initiate thyroxine substitution in case of unmasked secondary hypothyroidism[26]. Growth hormone accelerates cortisol metabolism, which may necessitate an increase in hydrocortisone dose if it is part of the therapy or the introduction of hydrocortisone due to the manifestation of secondary hypocortisolism. If GH therapy is effective, there is no reason for it to be discontinued until advanced age.

Before initiating GH therapy, special caution should be exercised in patients who have undergone surgery or radiation therapy for endocrine tumors or have a history of malignancy. Due to the mitogenic effect of GH, there has been ongoing debate about the risk of primary tumor recurrence or the development of secondary neoplasms practically since the beginning of its use in patients with GHD[27]. Aggregate data from large studies and long-term follow-up of individuals with AGHD on GH therapy have shown that there is no increased risk of tumor recurrence or *de novo* tumor development associated with GHD causative tumors[28]. The appropriate selection of patients for GH replacement therapy and the optimal dose of this hormone ensure the safety of treatment. For young adults in the transition period (18-25 years of age), at least two years of remission of the underlying disease (stable size of the tumor residue on MRI) should pass before starting GH therapy. For those older than 25 years, this period may be longer, and if the individual had adult-onset malignancy, at least five years of disease remission are required before initiating GH therapy[29]. Clinical experience indicates that the safety of introducing GH therapy is higher with a longer period of monitoring the stable size of the pituitary tumor residue. During the first year of GH therapy, it is recommended to perform an MRI of the pituitary region every 6 months, and then annually to every three years depending on the underlying pathology and treatment (surgery, radiotherapy).

Adverse effects and contraindications of growth hormone therapy

The adverse effects of GH administration are usually dose-dependent and transient, resolving with a reduction in GH dose. Lower initial GH doses and careful titration to maintenance doses can prevent adverse effects. The most common adverse effects are edema and arthralgia (due to fluid retention from the antinatriuretic effect of GH). Due to the anti-insulin effect of growth hormone, there is a trend towards increased blood glucose and insulin levels. However, these changes are mild and are related to the first months of therapy; afterward, these parameters return to baseline values and there is an improvement in long-term glycemic control due to changes in body composition (reduction in abdominal fat). Long-term studies monitoring the effects of GH therapy on over 15,000 patients show that the risk of developing diabetes mellitus (DM) is slightly increased, with older individuals and those with higher BMI and poor lipid profiles being more predisposed[23, 30]. Contraindications for GH therapy include: active malignant disease, manifest diabetes mellitus, severe liver and kidney diseases, benign intracranial hypertension, and severe psychiatric disorders.

Use of growth hormone during the transition period

The transition period (TP) represents a stage in an individual's life that begins in late puberty and ends with complete physical and psychosocial maturation into adulthood[26]. The transition lasts for six to seven years after the completion of growth or reaching final adult height. During this period, it is necessary to consider the need for continuing GH therapy in individuals who had growth hormone deficiency (COGHD) during childhood. Patients with other reasons for short stature during childhood should not be treated with growth hormone in adulthood (idiopathic GHD, Turner syndrome, Noonan syndrome, Prader-Willi syndrome, chronic renal insufficiency, small for gestational age). Due to the physical, metabolic, psychological, and social specificities generally associated with the transition from adolescence to adulthood, patients with COGHD require special attention and collaboration between pediatricians and endocrinologists, sometimes psychologists and gynecologists, as well as parents/guardians for better monitoring and treatment of these individuals[31].

Achieving satisfactory height is only a prerequisite for achieving normal body composition. In healthy individuals, the TP period is precisely when there is a peak in muscle mass and bone density. When GH is deficient during this period, it leads to a deterioration in body composition, characterized by a reduction in muscle mass and bone density, increased fat tissue, and heightened cardiovascular risk. The goal of GH therapy during the transition is to achieve

normal body composition, reduce the frequency of bone fractures, and improve myocardial function[32].

We should not overlook the improvement in quality of life during this sensitive psychosocial period of each individual during therapy, when they become independent and separate from their parents, whether they continue their education or they get a job.

It is considered that 30-70% of individuals with isolated idiopathic GHD in childhood, upon retesting during transition, have normal GH secretion. The likelihood of GHD persisting into adulthood is high in individuals with a history of sellar region tumors, structural anomalies of the hypothalamus/pituitary, or mutations in genes involved in pituitary embryonic development. On the other hand, individuals with isolated idiopathic GHD should undergo testing with two stimulation tests to confirm or reject the diagnosis of GHD. Growth cessation occurs when the growth rate is < 2.0 cm per year on adequate GH therapy and when bone maturity corresponds to an age of 14.5 years in girls or 16.5 years in boys. At that point, the individual has reached 99% of their final adult height. It is recommended to then discontinue GH therapy for one to three months and subsequently proceed with retesting[31]. GH doses during transition are closer to those used in adults with GHD, typically expressed in milligrams and not calculated based on body weight. The goal is to achieve IGF-I levels within the normal range for age, preferably towards the upper limit of normal. The dose for boys during transition is lower compared to that for girls[33].

Before starting GH therapy, annual anthropometric measurements (body weight, height, hip and waist circumference), blood pressure measurement, lipid profile, insulin sensitivity assessment (fasting glucose, insulin, HbA1c), reproductive function evaluation, thyroid hormone and cortisol levels determination, and assessment of QoL using an appropriate questionnaire should be conducted. Baseline measurement of body composition and bone density by the DXA method is necessary and should be repeated every two to five years during GH therapy[10].

Conclusion

Adult growth hormone deficiency (AGHD) is a syndrome characterized by an unfavorable phenotypic profile, metabolic disorders, and poor quality of life. Over the last two decades, numerous studies have confirmed improvements in these parameters with growth hormone (GH) therapy. Although generally safe, GH replacement requires careful dose titration and monitoring to achieve greater efficacy and treatment tolerance. Despite the benefits of this treatment, clinical practice suggests that AGHD is often unrecognized, and GH substitution is underutilized, even though our healthcare system covers the costs of treatment. The reason lies in physicians' insufficient awareness of the significance and risks of this therapy, underscoring the need for more intensive education on early recognition of GHD in adults and treatment optimization.

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