Pregledni članak

TIMOČKI MEDICINSKI GLASNIK

Vol. 47 (2022) br. 1

UDK 616.441-008.64
COBISS.SR-ID 66103817

SUBKLINIČKI HIPOTIROIDIZAM

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SAŽETAK: Subklinički hipotiroidizam (SKH) je poremećaj štitaste žlezde u kom je normalan nivo tiroidnih hormona, tiroksina i trijodotironina u krvi, ali je povišen nivo tirotropina - TSH, hipofiznog hormona koji negativnom povratnom spregom reguliše rad štitaste žlezde. To je biohemijska dijagnoza jer su pacijenti tipično asimptomatski i bez znakova bolesti, te je otkrivanje SKH obično slučajno. Procenjena ukupna prevalenca SKH u opštoj populaciji je od 4-10% u zavisnosti od karakteristika ispitivane populacije tj. pola, životne dobi, rase, geografskog područja, jodnog statusa.U zavisnosti od stepena povišenja početnog nivoa TSH, godišnje 5-8% pacijenata sa SKH ima progresiju ka kliničkom hipotiroidizmu. Najčešći uzrok subkliničkog hipotiroidizma, kao i kliničkog, u područjima sa dovoljnim unosom joda je hronični autoimuni tiroiditis. Postojeći vodiči za lečenje SKH razlikuju se među sobom, s obzirom da postoje oprečni dokazi o koristi od dugoročne supstitucije levotiroksinom u ovom stanju. Iako postoje podaci iz više sveobuhvatnih pregleda o kliničkim ishodima lečenja SKH, još uvek se nije došlo do konačnog zaključka o koristi od ovakvog pristupa. Faktori koji opredeljuju za terapiju levotiroksinom su: klinička proba zbog simptoma hipotiroidizma, želja pacijenta, depresija, neplodnost/ovulatorna disfunkcija, progresivni porast TSH, trudnoća, ili planiranje trudnoće, deca, adolescenti. Podaci istraživanja pokazuju da je kod trudnica sa SKH povećan rizik od gestacijskog dijabetesa, spontanog pobačaja, gestacijske hipertenzije, preeklampsije, prevremenog porođaja, te se u trudnoći terapijski postupak razlikuje u odnosu na ostalu populaciju odraslih. Biće kratko pomenut pristup kod dece sa SKH, kod amiodaronom indukovanog SKH i mikronutritijentima.

Ključne reči: subklinički hipotiroidizam, levotiroksin, trudnoća, amiodaron

UVOD

Subklinički hipotiroidizam (SKH) je često kliničko stanje za koje postoje mnoge kontroverze. Sve do danas ne postoji definitivni konsenzus među tiroidolozima u pogledu nekoliko aspekata. Najpre, postavlja se pitanje da li je potrebno raditi skrining na SKH, tj. aktivno tragati za poremećajem u široj asimtomatskoj populaciji na rutinskim periodičnim/preventivnim pregledima, ili nalaziti slučajeve prema kliničkim indikacijama. Drugi aspekt problema je kako procenjivati značaj ovog kliničkog stanja, kao i moguće neželjene posledice na kardiovaskularni sistem, metaboličke parametre i mentalno zdravlje individualnog pacijenta. Iz prva dva pitanja proizlazi i treće, a to je: kakav terapijski pristup imati kod SKH – lečiti, ili ne?

ŠTA JE SUBKLINIČKI HIPOTIROIDIZAM

Subklinički hipotiroidizam je poremećaj štitaste žlezde u kom je normalan nivo tiroidnih hormona (TH), tiroksina (T4) i trijodotironina (T3) u krvi, ali je povišen nivo tirotropina (TSH), hipofiznog hormona, koji negativnom povratnom spregom reguliše rad štitaste žlezde. To je biohemijska dijagnoza jer su pacijenti tipično asimptomatski i bez znakova bolesti, te je otkrivanje SKH obično slučajno. Tokom vremena SKH može napredovati ka kliničkom hipotiroidizmu (KH). [1,2] SKH, u zavisnosti od dužine trajanja i stepena povišenja TSH, može biti udružen sa povećanim rizikom od kardiovaskularnih (KV) bolestii KV mortaliteta, negativnim uticajem na metaboličke parametre, kognitivnom disfunkcijom, anksioznošću i depresijom [2,3]. Predloženo je nekoliko alternativnih naziva koji opisuju stanje SKH kao što su: kompenzovani hipotiroidizam, preklinički hipotiroidizam, blagi hipotiroidizam, snižena tiroidna rezerva, blaga tiroidna slabost [4].

KOLIKA JE PREVALENCA SUBKLINIČKOG HIPOTIROIDIZMA?

Procenjena ukupna prevalenca SKH u opštoj populaciji je od 4-10% u zavisnosti od

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Rad primljen: 04.04.2022. Elektronska verzija objavljena: 19.05.2022.

karakteristika ispitivane populacije tj. pola, životne dobi, rase, geografskog područja, jodnog statusa [4]. SKH je češći kod žena i kod starijih osoba. Kod žena je prevalenca od 8-10%, a kod žena starijih od 60 godina objavljena je prevalenca čak do 20% [5,6]. Prevalenca je oko tri puta veća kod belaca nego kod crnaca [7]. Takođe, tokom povećanja unosa joda kod prethodno jod-deficitne populacije, može doći do lakog porasta prevalence SKH i tiroidne autoimunosti [8]. Postoje istraživanja u kojima je nađena skoro dva i po puta veća prevalenca SKH kod osoba sa metaboličkim sindromom (MetS) [9]. Osim toga, SKH je češći kod pacijenta sa Diabetes Melitus-om tip 2 (DM T2), nego kod zdrave populacije i iznosi oko 10%, prema nekim izveštajima [10]. SKH je relativno često stanje kod pacijenta sa hroničnom bubrežnom slabošću (HBI) i može se naći kod oko 18% pacijenta sa HBI koji nisu na dijalizi [11]. Objavljena incidenca SKH kod trudnica je 2-2.5%, a u nekim zemljama kao što je Kina, Belgija i severni deo Španija čak 4-13.7%. Kod dece je prevalenca manja od 2% [12].

Naravno, da bi se procenila prevalenca ovog stanja u populaciji/populacijama, neophodno je tačno registrovanje i adekvatna zdravstvena statistika. Procenjene prevalence se neretko baziraju na metaanalizama objavljenih članaka u dostupnim bazama stručnih i naučnih radova, u kojima se analiziraju podaci iz ograničenih uzoraka ispitanika. Na razlike u procenjenoj prevalenci mogu uticati i različiti dijagnostički kriterijumi za ovo stanje, npr. korišćenje ili nekorišćenje specifičnih referentnih opsega serumskog nivoa TSH (u ovom slučaju gornje granice referentnog opsega za pojedine populacione grupe). Istraživanja pokazuju da je neophodno odrediti distribuciju koncentracije i opseg normalnih vrednosti TSH, verovatno uslovljenim genetičkim faktorima, prema životnoj dobi i rasi, odnosno drugim specifičnim karakteristikama populacije koji bi se koristili za procenu prisustva tiroidne disfunkcije (TD) [13]. U vezi s ovim, neki autori smatraju da je prevalenca SKH kod starijih precenjena, pošto gornja granica referentnog opsega za TSH raste sa godinama starosti [14].

UZROCI SUBKLINIČKOG HIPOTIROIDIZMA

Najčešći uzrok subkliničkog hipotiroidizma, kao i kliničkog, u područjima sa dovoljnim unosom joda je hronični autoimuni tiroiditis: Hashimoto tiroiditis (HT), atrofični tiroiditis (AT), postpartalni tiroiditis (PPT) [3]. Autoimune tiroidne bolesti (AITB), u koje spadaju HT, AT i PPT, su 5 do 10 puta češće kod žena, nego kod muškaraca, prevalenca raste s godinama starosti, češće su kod osoba koje imaju i druge autoimune bolesti, kao i kod njihovih krvnih srodnika [3,15-17].

AITB se karakteriše patološkom infiltracijom štitaste žlezde senzibilisanim T limfocitima i prisustvom tiroidnih autoantitela u krvi – antimikrozomskih antitela/antitela na tiroidnu peroksidazu (TPOAb), antitiroglobuliskih antitela (TgAb) i antitela na TSH receptor (TRAb) [3,18,19]. Određivanje ovih antitela u serumu je jedna od ključnih dijagnostičkih metoda za dijagnozu AITB.

S druge strane, veoma čest uzrok SKH je nedostatak joda u ishrani jer je u svetskim razmerama još uvek izražen problem područja sa deficitom joda [20]. Jod je mikroelement neophodan za stvaranje tiroidnih hormona (TH), tirokisna (T4) i trijodotironina (T3) koji se mora uneti u organizam hranom, najmanje 150 μg dnevno.

Uzroci SKH mogu biti i jatrogeni, na primer stanje nakon radiojodne, ili operativne terapije benignih i malignih oboljenja štitaste žlezde tj. difuzne toksične strume, toksičnog adenoma, polinodozne toksične strume, benignih i malignih atoksičnih nodoznih struma. Takođe, do oštećenja tkiva štitaste žlezde može dovesti radijaciona terapija vrata zbog netiroidnih bolesti glave i vrata, uključujući i limfom.

Jatrogeni SKH može biti i farmakološki, uzrokovan primenom lekova za netiroidne bolesti, ili dijagnostiku, kao što su antiaritmik bogat jodom, Amiodaron, potom Litijum, koji se koristi u psihijatriji, kontrastna jodna stredstva, interferon-alfa i drugi citokini, inhibitori tirozin kinaze (TKI), antituberkulotik paraaminosalicilna kiselina (PAS), ređe aminoglutetimid. Oni dovode do SKH različitim mehanizmima npr. tiroidnom citotoksičnošću, blokadom stvaranja i oslobađanja TH viškom joda, smanjujući prokrvljenost tiroidnog tkiva, delovanjem na dejodinaze tipa 2 i 3, koje učestvuju u stvaranju TH i njihovih metabolita i drugo [21-26]. Naravno da i antitiroidni lekovi koji se daju u terapiji hipertiroidizma, tj. metimazol i propil tirouracil, mogu da dovedu do SKH.

Infiltracione bolesti, kao što su amiloidoza, sarkoidoza, hemohromatoza,

skleroderma, cistinoza, Ridlov tiroiditis, takođe mogu zahvatiti štitastu žlezdu i biti uzrok snižene funkcijske rezerve, tj. SKH [27, 28].
Kao što je već pomenuto, SKH kao posledica AITB, može često biti udržen sa drugim autoimunim bolestima, nrp. DM tip 1, Adisonova bolest, reumatodni artritis [29-31], ali i hromozomskim poremećajima kao što su Daunov, ili Tarnerov sindrom [32,33], što nalaže obavezno ispitivanje tiroidne funkcije kod pacijenata sa ovim bolestima i sindromima.

Konsumptivni, ili „potrošni“ SKH je retko stanje koji se dešava kod pacijenata sa hemangiomima i drugim tumorima u kojima je eksprimirana dejodinaza tip 3, što izaziva ubrzanu razgradnju T4 i T3 [34].
Na kraju, prolazni SKH se može naći kod pacijenata u fazi oporavka od neautoimunih tiroiditisa, subakutnog i bezbolnog tiroiditisa, kao i tokom oporavka od težih netiroidnih bolesti (NTB) [35].

TOK SUBKLINIČKOG HIPOTIROIDIZMA

Kod većine pacijenata SKH ostaje stabilan tokom vremena. U zavisnosti od stepena povišenja početnog nivoa TSH, godišnje 5-8% pacijenata sa SKH ima progresiju ka kliničkom hipotiroidizmu (KH) [36]. S druge strane, funkcija štitaste žlezde može se tokom vremena normalizovati kod 6-35% pacijenata, takođe u zavisnosti od početnog nivoa TSH, kao i nivoa tiroidnih autoantitela [37]. Kod pacijenata sa povišenim TPOAb, progresija SKH ka KH je 4.3% godišnje, a kod onih sa normalnim nivoom TPOAb, skoro duplo manja, 2.6% godišnje (38). Stoga se po dijagnozi SKH, testovi tiroidne funkcije (TFT) ponavljaju za 8-12 nedelja i dodatno se uradi merenje nivoa tiroidnih autoantitela. Ukoliko perzistira SKH, TFT se ponavljaju na 6 meseci tokom prve dve godine praćenja, a potom jedanput godišnje, ukoliko su nalazi stabilni. Nasuprot tome, ukoliko su TFT normalni po ponovljenom određivanju, a pacijent nema simptome, strumu i povišena tiroidna autoantitela, dalje praćenje nije neophodno [3].

POSTAVLJANJE DIJAGNOZE SUBKLINIČKOG HIPOTIROIDIZMA

Dijagnoza SKH se postavlja kada se kod pacijenta detektuju povišene vrednosti TSH (referentni opseg većine testova je od 0.4 – 4.0 do 5 m IU/L) uz normalne vrednosti FT4 u krvi [39]. Imajući u vidu da se dijagnoza SKH zasniva na rezultatima laboratorijskih analiza, treba uzeti u obzir specifičnost, senzitivnost i referentne vrednosti primenjenog testa, pa u skladu sa tim tumačiti nalaz [40]. Iako je povišena koncentracija TSH u serumu najčešće znak primarne hipotireoze, neophodno je znati da izmerene koncentracije mogu biti povišene (obično <8 mU/L) kod osoba starijih od 65 godina bez kliničkih i laboratorijskih dokaza bolesti štitaste žlezde [41]. Druga neka stanja, poput stanja nakon radioterapije vratne regije, insuficijencija nadbubrežne žlezde, trudnoće, upotreba pojedinih lekovi (litijum, AMD), ili prisustvo specifičnih antitela u krvi (HAMA, ili makro TSH) mogu da imitiraju SKH [42–44]. Osim toga, patološka gojaznost zbog efekta leptina na tireotropin oslobađajući hormon (TRH) dovodi do reverzibilnog povišenja TSH u krvi [45]. Fluktuacije u koncentraciji TSH su očekivane kod akutnih, naročito težih netiroidnih bolesti, kao i nakon operativnih zahvata – hemitiroidektomije, što treba uzeti u obzir kod tumačenja laboratorijskih nalaza [42,46]. Laboratorijsku dijagnostiku bi trebalo odložiti 2-3 meseca nakon oporavka od akutnih bolesti zbog efekata citokina na koncentraciju TSH, a suplementaciju biotinom koji ulazi u sastav brojnih multivitamina (naročito onih koji se preporučuju za zdravlje kose i noktiju) prekinuti najmanje 2 dana pre obavljanja laboratorijskih analiza zbog interferencije sa imunoesejima [42,47,48].

Postoje dve kategorije SKH prema stepenu povišenja TSH. Lako povišen TSH, od 4-10 m IU/L koji se nalazi kod 80-90% pacijenta i znatnije povišen TSH > 10 m IU/L [3]. Nakon postavljanja dijagnoze TSH, treba pristupiti utvrđivanju uzroka, tj. postavljanju etiološke dijagnoze. Dodatne laboratorijske analize u cilju postavljanja etiološke dijagnoze su merenje tiroidnih autoantitela (TAT). TPOAb uglavnom, zbog veće senzitivnosti i ređeTgAb, kao i ultrazvučni pregled štitaste žlezde kojim se mogu otkriti karakteristične parenhimske promene kod autoimunog tiroidita, koji je i najčešći uzrok SKH [49,50].
Nivo TSH kod zdrave osobe ima male varijacije tokom vremena, oko 1/3 referentnog opsega, što se naziva sopstvenim „TSH setpoint-om“ koji tokom napredovanja životne dobi ima tendenciju nalog porasta [51, 52]. Kod starijih osoba koristimo širi referentni opseg (4.0-7.0 m IU/L), tj, lako povišen nivo TSH kod starijih se smatra fiziološkom adaptacijom na starenje [41].

Kako kod zdravih, tako i kod osoba sa SKH, nivo TSH ima cirkadijalne flktuacije serumskih koncentracija – najniža koncentracija je rano popodne, sa oko 30% višim koncentracija uveče i preko noći.

Odloženi noćni pik TSH može se naći kod: radnika koji rade u noćnoj smeni; onih koji imaju poremećaj spavanja; nakon težih fizičih aktivnosti; kod poremećaja raspoloženja – depresije [3].

Biološki neaktivni oblici TSH mogu kod nekih osoba biti razlog izmerenih viših vrednosti TSH [53].

Nivo TSH korelira sa BMI i markerima insulinske rezistencije pa je nalaz TSH > 3.5 čest kod gojaznih [54].

KLINIČKE KARAKTERISTIKE SUBKLINIČKOG HIPOTIROIDIZMA

Simptomi

Po definiciji SKH je asimtomatsko stanje, bez kliničkih znakova hipotiroidizma (Tabela 1). Međutim, da li je SKH zaista bez simptoma? Neka istraživanja pokazuju da mali, ali statistički značajan broj pacijenta sa SKH ima češće simptoma hipotiroidizma u odnosu na zdrave i to: suvlju kožu, slabije pamćenje, sporije mišljenje, slabije mišiće, brže umaranje, češće mišićne grčeve, veću zimogrožljivost, dublji i promukliji glas, otečenije oči i češći zatvor [5]. S druge strane, s obzirom da su simptomi i znaci hipotiroidizma opšti i mogu se javiti i u drugim stanjima, neka istraživanja pokazuju da nema poboljšanja simptoma kod pacijenta sa SKH kada im se uvede supstitucije levotiroksinom [55]. Ipak, većina pacijenata sa SKH nema hipotiroidne simptome.

Poremećaj raspoloženja i mentalnog zdravlja

Na osnovu mnogih istraživanja, čini se da mogu postojati blagi poremećaji deklarativnog pamćenja (poznavanje činjenica), proceduralnog pamćenja (veštine koje se obavljaju automatski) i raspoloženja kod mlađih osoba sa SKH koji se poboljšavaju supstitucijom levotiroksinom [56]. Međutim, takvi dokazi uglavnom nisu nađeni u populaciji osoba starijih od 65 godina. [57].

Tabela 1. Simtomi i znaci hipotiroidizma

SIMPTOMI	ZNACI
Zamor, slabost, gušenje	Bradikardija
Suva koža	Suva, hrapava koža
Osećaj hladnoće/zimogrožljivost	Hladni ekstremiteti
Opadanje kose	Difuzna alopecija
Dodavanje u težini uz normalan, ili slabiji apetit	Otoci lica, šaka, stopala, miksedem
Konstipacija (zatvor)	Produženo vreme relaksacije tetiva
Promuklost	Dublji, promukao glas
Oslabljena koncentracija, oslabljeno pamćenje	Efuzije u serozne duplje
Oslabljen sluh, parestezije	Sindrom karpalnog tunela
Menoragija, oligomenoreja, amenoreja	

Gojaznost, glikoregulacija, insulinska rezistencija, dijabetes melitus, dislipidemija

Nivo serumskog TSH u pozitivnoj je korelaciji sa telesnom težinom [58] i pokazano je da za svaku jedinicu porasta log TSH, telesna težina je za 2.3 kg veća kod žena i 1.1 kg kod muškaraca [59]. Nasuprot tome, znatan pad telesne težine je udružen sa padom nivoa TSH [60]. Ipak, uzorčna veza između SKH i gojaznosti nije pokazana.

SKH bi mogao uticati na smanjenje insulinske senzitivnosti delovanjem na pad broja glukoznih transportera u plazma membrani (membrani ćelijskih organela) i direktnim dejstvom na lučenje i klirens insulina, kao što je poznato da se dešava u hipotiroidizmu u značajnom obimu [61]. Kod pacijenata sa utvrđenim diabetes melitusom (DM) tip 2, promena glikemjske kontrole može da ukaže na SKH i druge tiroidne poremećaje, dok je prevalenca SKH sa povišenim TAT kod pacijenta sa DM tip 1 čak do 30% [62].

Velike epidemiološke studije su pokazale pozitivnu korelaciju između nivoa TSH i dislipidemije što ukazuje na potencijalan uticaj SKH na lipidni profil [5]. Slično tome, još jedno veliko istraživanje pokazalo je npr. da je porast nivoa TSH za 1.0 m IU/L udružen s prosečnim porastom nivoa ukupnog holesterola kod žena

za 0.09 mmol, što ukazuje na razlike uslovljene polom u odnosu između SKH i lipidnog profila. Takođe, veza između nivoa TSH i lipidnog profila je naglašenija sa napredovanjem životne dobi [63].

Kardiovaskularni sistem, srčana slabost i ishemijska bolest srca

SKH je udružena sa funkcijskim srčanim poremećajima, kao što su dijastolna disfunkcija leve komore i snižena sistolna funkcija u miru i fizičkom naporu [64]. Takođe su pokazane i vaskularne abnormalnosti u ovom stanju, kao što su povećana vaskularna rezistencija, krutost arterija, endotelna disfunkcija i ateroskleroza [65]. Mnoga istraživanja ukazuju na SKH kao nezavisan faktor rizika za razvoj srčane slabost, kao i za pogoršanje postojeće [64].

Neki od rezultata istraživanja o uticaju na ishemijsku bolest srca nisu pokazali udruženost AITB i ishemijske bolesti srca, ali ponovnom analizom populacione Whickham studije [66], došlo se do rezultata da je kod pacijenata sa SKH nađena značajno veća učestalost srčanih ishemijskih događaja i mortaliteta usled ishemijske bolesti srca. Slične rezultate je pokazala i metaanaliza nekoliko relevantnih prospektivnih studija [67].

Stepen povišenja TSH

Rezultati studija pokazuju da nije beznačajno koliko je povišen TSH u SKH. Postoje dve kategorije SKH prema stepenu povišenja TSH: lako povšen TSH, od 4-10 m IU/L i znatnije povišen. TSH> 10 m IU/L. Simptomi, manifestacije i potencijalne komplikacije, uključivši poremećaje endotela, lipida i kardiovaskularne poremećaje, u vezi su sa stepenom povišenja TSH, ali zavise i od pola i životne dobi [68]. Rezultati brojnih završenih kao i studija koje su u toku, biće korisni da se utvrdi, kako prag TSH, tako i prag životne dobi za razmatranje terapijske intervencije tj. supstitucije levotiroksinom.

TERAPIJSKI PRISTUP KOD SUBKLINIČKOG HIPOTIROIDIZMA

SKH se, kao i KH, leči supstitucijom levotiroksinom. Cilj lečenja, kao i kod KH, treba da bude otklanjanje simtoma hipotiroidizma postizanjem normalizacije TSH [69].

Međutim, s obzirom da se po definiciji radi o asimtomatskom poremećaju kod većine pacijenata, poremećaju samo na nivou krvi, pri donošenju odluke o lečenju treba da imamo na umu dva pitanja:

-kakav je uticaj lečenja levotiroksinom na dugoročne kliničke ishode kod pacijenata sa SKH?

-kakav je ishod praćenja bez lečenja levotiroksinom na dugoročne ishode kod pacijenata sa SKH [70]? Postojeći vodiči za lečenje SKH razlikuju se među sobom, s obzirom da postoje oprečni dokazi o koristi od dugoročne supstitucije levotiroksinom u ovom stanju. Iako postoje podaci iz više sveobuhvatnih pregleda o kliničkim ishodima lečenja SKH, još uvek se nije došlo do konačnog zaključka o koristi od ovakvog pristupa [1]. Svakako, kao što je naglašeno u prethodnom tekstu, pre započinjanja supstitucije treba za 3 meseca od postavljanja dijagnoze SKH, ponoviti testiranje TSH. Ovo je važno jer se kod oko 60% pacijenata TSH normalizuje unutar 3 meseca, a kod oko 62% tokom 5 godina [71,44]. S druge strane, kod pacijenata sa SKH i hipotirodinim simptomima, treba najpre razmotriti druge moguće uzroke za postojeće simptome.

Prema većini vodiča, supstituciju levotiroksinom kod SKH treba započeti kada je TSH >10 mIU/L, bez obzira na odsustvo simtpoma. Supstituciju levotiroksinom treba razmotiriti u slučajevima u kojima je TSH između 5–10 mIU/L u ponovljenim merenjima i postoje simptomi slični hipotiroidizmu. Međutim, ukoliko se simptomi ne povuku nakon 3-4 meseca supstitucije levotiroksinom i normalizacije TSH, trebalo bi prekinuti lečenje [70, 1]. U ostalim slučajevima, odluku o lečenju SKH, kada je TSH između 5–10 mIU/L u ponovljenim merenjima, treba prilagoditi individualno u zavisnosti od starosti, komorbiditeta, stepena povišenja TSH, perzistentnosti i progresije povišenja TSH, prisustva TAT i prisustva strume. Smisao supstitucije bi se zasnivao na smanjenju rizika neželjenih KV događaja i eventualnom sprečavanju progresije ka KH. Pri tome treba imati na umu da supstitucija levotiroksinom može dovesti do jatrogene subkliničke/kliničke tirotoksikoze, pogotovo kod starijih pacijenata, što samo po sebi može biti rizik pogoršanja KV stanja i nema dokaza da je supstitucija korisna kod osoba sa 65 godina i starijih [42]. Faktori koji opredeljuju za terapiju levotiroksinom su dakle: klinička proba zbog simptoma hipotiroidizma, želja pacijenta, bipolarni poremećaj, depresija, neplodnost/ovulatorna

disfunkcija, prisustvo TAT, progresivni porast TSH, trudnoća, ili planiranje trudnoće, deca, adolescenti.

PREPORUKE [3]

- Postoje dve kategorije SKH prema nivou TSH: Lako povišen TSH – 4-10 m IU/L koji se nalazi kod 90% osoba sa SKH; i TSH> 10 m IU/L
- Nalaz povišenog TSH uz normalan FT4 u prvom merenju, treba ponoviti za 2-3 meseca, ponovnim merenjem TSH, T4 i TPOAb
- Osobama sa povišenim TPOAb/TgAb i/ili ultrazvučnim nalazom koji ukazuje na AIT, treba uraditi merenje TSH i FT4
- Za postavljanje dijagnoze SKH u starijoj populaciji treba koristiti za životnu dob specifične referentne opsege.
- Kod pacijenata mlađih od 65 godina i TSH > 10 m IU/L, čak i u odsustvu simptoma hipotiroidizma, preporučuje se uvođenje supstitucije L-tiroksinom.
- Kod pacijenata mlađih od 65 godina koji imaju simptome hipotiroidizma i TSH < 10 m IU/L, razmotriti kliničku probu uvođenjem supstitucije L-tiroksinom.
- Nakon hemitiroidektomije, perzistentni SKH treba lečiti L-tiroksinom u cilju normalizacije TSH.
- Pacijente sa difuznom, ili nodoznom strumom i perzistentnim SKH, treba lečiti L-tiroksinom u cilju normalizacija TSH.
- Kod pacijenta sa DM tip 1, nivo TSH treba pratiti jedanput godišnje.
- Kod pacijenata sa DM tip 2 i neobjašnjivim pogoršanjem glikemijske kontrole, treba uraditi TSH i FT4.
- Ograničeni su dokazi da supstitucija L-tiroksinom kod mlađih osoba sa SKH dovodi do poboljšanja mentalne funkcije.
- Nema dokaza za korisne efekte terapije L-tiroksinom kod gojaznh osoba sa TSH < 10 m IU/L i normalnim FT4 na smanjenje telesne težine.
- Terapija L-tiroksinom kod SKH može sniziti i ukupni i LDL holesterol, ali se normalizacija lipida retko postiže.
- Efekat supstitucije L-tiroksinom na koncentracije serumskih lipida je najizraženiji kod pacijenta sa nivoima TSH > 10 m IU/L pre lečenja.
- Osobe preko 80 godina starosti, sa nivoom TSH ≤ 10 m IU/L, pažljivo pratiti, izbegavajući uvođenje supstitucije L-tiroksinom.
- Ako su u kontrolnom testiranju hormoni normalni, uz normalan nivo TAT i odsustvo strume – nije potrebno dalje testiranje.
- Ako perzistira SKH i nije započeta terapija L-tiroksinom, hormone testirati na 6 meseci najmanje tokom prve 2 godine, a potom jedanput godišnje.

TRUDNOĆA I SUBKLINIČKI HIPOTIROIDIZAM

SKH u trudnoći definiše se kao stanje u kome je serumski TSH viši od gornje granice referentnog opsega specifičnog za trimestar trudnoće, dok su serumski T4 i T3u referentnim opsezima [72,73,14,74]. Javlja se kod otprilike 2-2.5% trudnica, s tim što u je u pojedinim državama taj broj znatno veći (u severnoj Španiji čak 13.7%) [75].

Izolovana hipotiroksinemija se definiše kao koncentracija FT4 u serumu ispod 2.5 percentila od referentnog opsega (0.80 ng/dL; 10.30pmol/L), uz normalnu koncentraciju TSH [72,12].

Dijagnoza SKH u trudnoći postavlja se jedino na osnovu laboratorijskih analiza, pošto su simptomi i znaci nespecifični i veoma slični tegobama koje mogu biti povezane sa varijacijama u načinu života, ili tegobama koje su posledica mnogih drugih stanja kao i same trudnoće [72,12,74]. Referentni opseg TFT kod trudnica se razlikuje od referntnog opsega opšte populacije, a takođe se razlikuje i po trimestrima trudnoće.Na osnovu objavljenih studija, uglavnom zapadnih zemalja, predložen je sledeći referentni opseg za TSH u trudnoći: prvi trimester 0.1 - 2.5 mU/L; drugi trimestar 0.2 – 3.0 mU/L; treći trimestar 0.3–3.5 mU/L [76-78]. Međutim, savetuje se određivanje ovih vrednosti za svaku državu, odnosno region ponaosob. Treba napomenuti da tokom trudnoće dolazi do povećanja koncentracije T4 koja je najviša tokom prvog trimestra trudnoće, dok je to povećanje znatno manje tokom drugog i trećeg trimestra. Uprkos povećanom vezivanju hormona za transportne protein, koji su takođe povećani u trudnoći, mnogi autori smatraju da je pouzdanost određivanja slobodnog tiroksina (FT4) standardnim imunoesejom za FT4 zadovoljavajuća [72,12].

Kako se definicija SKH zasniva na povišenom nivou TSH u kombinaciji sa normalnim vrednostima FT4, bilo bi od ključnog značaja odrediti refernetni opseg TH specifičnih za trimester. Dostupni podaci iz literature ukazuju da je u prvom trimestru trudnoće donja granica FT4 2.5-ti percentil referentnog opsega detektovan imunoesejom iznosi oko 0.80 ng/Dl (10.30pmol/L) [72,12]. Kako bi dobili referentnu vrednost specifičnu za prvi trimester trudnoće, neki autori predlažu da se normalne vrednosti ukupnog, za transportne proteine vezanog T4 (TT4), koje iznose 5–12 mg/dL, ili 50–150 nmol/L za žene koje nisu trudne, pomnože sa 1.5 i tako dobijene vrednosti koriste kao referentne vrednosti specifične za prvi trimester [72,12].

Antitela na tiroidnu peroksidazu (TPOAb) prisutna su kod oko 50% trudnica sa SKH, a čak i do 80% kod trudnica sa kliničkim hipotiroidizmom. Kod trudnica sa SKH određivanje TPOAb se preporučuje u cilju utvrđivanja AITB. Antitela na tireoglobulin (TgAb) ne treba zanemariti. Kod 5% žena sa SKH i normalnim TPOAb, pronađena su povišena TgAb. Žene sa povišenim TgAb, a normalnim TPOAb, imale su značajno viši nivo TSH u serumu u poređenju sa ženama bez AITB tako da kod trudnica sa negativnim TPOAb treba odrediti i TgAb. Nakon prvog trimestral TAT mogu biti negativna zbog imunosupresije tokom trudnoće, te u prisustvu povišenih vrednosti TSH i negativnih antitela, treba uraditi i ultrazvuk štitaste žlezde [72,12].

Neželjeni efekti SKH tokom trudnoće

Ispoljeni, klinički hipotiroidizam tokom trudnoće jasno je povezan sa neželjenim događajima kao što su preeklampsija, eklampsija, gestacijska hipertenzija, kretenizam, smrt fetusa i spontani pobačaji. Međutim, manje je dokaza o komplikacijama tokom trudnoće i SKH. Studije koje se bave ovim problemom pokazuju oprečne rezultate. Većina studija ukazuje na povećan rizik od gestacijskog dijabetesa (GD), sa pozitivnom korelacijom između nivoa TSH i rizika od GD.

Nekoliko studija je potvrdilo povezanost SKH sa spontanim pobačajima, veoma ranim gubitkom embriona, gestacijskom hipertenzijom i preeklampsijom. Rizik od prevremenog porođaja, takođe je prisutan kod trudnica sa SKH. Ostale komplikacije koje se pominju kao moguće, ali dosta retke jesu: abrupcija placente, povišen perinatalni mortalitet, nizak Apgar rezultat i niska porođajna težina. Međutim, povezanost između SKH u trudnoći i poremećaja psihomotornog razvoja potomstva nije u potpunosti dokazana [72,12].

Efekti lečenja SKH tokom trudnoće

Smatra se da lečenje SKH levotiroksinom ima potencijalne koristi koje su veće od potencijalnih rizika. SKH koja nastaje pre začeća, ili tokom gestacije, treba lečiti levotiroksinom. Nasuprot tome, nema studija koje pokazuju korist od lečenja izolovane hipotiroksinemije tokom trudnoće u pogledu akušerskih komplikacija majke. Međutim, terapija levotiroksinom može se razmotriti kod izolovane hipotiroksinemije otkrivene u prvom trimestru trudnoće, zbog povezanosti sa povoljnijim neuropsihološkim razvojem kod dece. Terapija levotiroksinom se ne preporučuje u izolovanim slučajevima hipotiroksinemije otkrivene u drugom i trećem trimestru.

Kod pacijntkinja kod kojih je u prvom trimestru TSH > 10 mU/l, nezavisno od prisustva TPOAb, treba započeti terapiju levotiroksinom. Isto tako, terapiju treba započeti i kod trudnica kod kojih je TSH > 4 mU/L i kod kojih su pozitivna TPOAb. Terapiju treba razmotriti kod trudnica kod kojih je TSH od 2.5-4mU/L sa pozitivnim TPOAb i kod trudnica sa vrednostima TSH od 2.5-10mU/L sa negativnim TPOAb. Kod pacijentkinja koje se pripremaju za trudnoću asistiranom reproduktivnom tehnikom, TSH treba da je < 2,5mU/L. Kod ovih pacijentkinja TSH treba određivati dve nedelje pre i dve nedelje nakon inseminacije i vantelesne oplodnje (VTO) [79].

Ako se donese odluka o uvođenju supstitucije kod trudnica sa SKH, predložene doze levotiroksina su: 1.20 μg/kg/dan za TSH ≤ 4.2 mU/L; 1.42 μg/kg/dan za TSH >4.2–10 m IU/L i 2.33 μg/kg/dan za TSH > 10 mU/L. Vrednosti TSH treba proveravati svakih 4-6 nedelja tokom prvog trimestra i jednom tokom drugog i trećeg trimestra.

Kod pacijentkinja sa jutarnjom mučninom, primena levotiroksina kasno uveče može biti legitimna opcija. Cilj lečenja levotiroksinom tokom trudnoće je normalizacija vrednosti TSH u serumu majke unutar referntnih vrednosti specifičnih za trimestar trudnoće.

Većina slučajeva SKH u trudnoći je prolazna i oporavlja se nakon trudnoće. Međutim, kod trudnica sa pozitivnim TPOAb i TSH > 5 mU/L, velika je verovatnoća da će imati

stalno povišen TSH, odnosno da će se hipotireoidizam zadržati i nakon trudnoće. Nakon porođaja doza levotiroksina treba da bude smanjena na dozu pre začeća. Kod žena sa dijagnozom SKH tokom trudnoće, kod kojih je TSH < 5 mU/L i koje imaju negativna TPOAb, kao i kod žena čija je supstituciona doza bila manja od 50 μg levotiroksina, može se pokušati prekid supstitucije nakon porođaja, s tim što treba proveriti tiroidini status 6 nedelja nakon porođaja, potom na 6 i 12 meseci. Kod ostalih žena sa dijagnozom SKH nakon trudnoće, treba proveriti tiroidni status 6 meseci i godinu dana po porođaju i utvrditi potrebu za supstitucijom. Terapija levotiroksinom za eutiroidne žene sa pozitivnim antitelima se ne savetuje [72,12]. Dokazi za skrining na SKH u trudnoći su dvosmisleni. Iako još uvek nema dobro kontrolisanih studija da bi se opravdao opšti skrining, veliki broj autora preporučuje skrining. Takođe, veliki broj autora zagovara skrinig samo kod trudnica koje su u posebnom riziku tj. žene sa anamnezom o tiroidnim bolestima, žene sa porodičnom anamnezom o tiroidnim bolestima, žene sa strumom, žene DM tip 1, žene sa drugim autoimunim bolestima, žene s infertilitetom nepoznatog uzroka, žene s anamnezom o radioterapiji glave i vrata, žene s anamnezom o ranijem pobačaju i preranom porođaju [72,12,74,80].

SUBKLINIČKI HIPOTIROIDIZAM KOD DECE

Predmet razmatranja je prevashodno SKH kod odrasle populacije, ali uključiće se i nekoliko napomena o ovom stanju kod dece. Kada se radi o mogućem prenatalnom uticaju, rezultati mnogobrojnih istraživanja o vezi između SKH majke i oštećenog neurofiziološkog razvoja deteta nisu konzistentni, kao što je to veoma jasno kod KH [12], te su neophodna dalja istraživanja kako bi se tačan uticaj odredio. Kod novorođenčadi i u periodu ranog detinjstva, posebno u prve 3 godine života, TH imaju nezamenjivu ulogu u procesu sazrevanja i ravoja mozga, a uticaj na linearni rast perzistira do zatvaranja epifiza u adolescenciji [81]. Po porođaju se dešavaju velike promene u tirodinoj funkciji kod novorođenčeta, a nivo TSH > 5 mU/L, može se smatrati povišenim nakon 1 meseca života. Stoga je neophodno, kao i kod starije populacije, za tumačenje dijagnostičkih biohemijskih nalaza koristiti za uzrast specifične referentne vrednosti [82]. U opštoj dečijoj i adolescentnoj populaciji sa SKH, hormoni se normalizuju kod preko 70% njih, ili perzistiraju nepromenjeni kod većine preostalih, tokom narednih 5 godina od postavljanja dijagnoze [12]. SKH je 10 puta češći kod dece sa Daunovim sindromom nego u opštoj populaciji [83]. Kod gojazne dece, nivo TSH od 5-7 m IU/L je verovatno posledica, a ne uzrok gojaznosti [84]. U područjima sa dovoljnim unosom joda, SKH kod mlađe dece je najčešće idiopatski (tzv. perzistentna „Hypertirotropinemija“ i „Ne-autoimuni“ idipopatski SKH), ili izazvan različitim perinatalnim i genetskim uzrocima. Kod starije dece i adolescenata, najčešći uzrok je AITB [12]. Za sada nema dovoljno dokaza da bi se kod većine dece sa SKH i TSH <10 mU/L preporučila supstitucija levotiroksinom [85].

AMIODARONOM INDUKOVAN SUBKLINIČKI HIPOTIROIDIZAM

Hronična terapija amiodaronom (AMD), antiaritmikom bogatim jodom, udružena je sa pojavom predvidljivih promena u TFT, kao i pojavom tirodinih disfunkcija, za čiji nastanak je odgovorno, kako opterećenje jodom, tako i cititoksičnost samog antiaritmika [86]. Prema istraživanjima autora ovog rada, amiodaronom indukovani subklinički hipotiroidizam (AISKH) se na području sa dovoljnim unosom joda, nalazi kod 10% kardioloških pacijenata lečenih ovim antiarimikom, češće kod žena, pacijenata sa uvećanom štitastom žlezdom i pacijenata sa povišenim TPOAb [87]. Kod većine pacijenata sa AISKH, stanje ne progedira ka KH, a kod velikog broja dolazi do spontane normalizacije tiroidnog statusa, čak i uz nastavak terapije amiodaronom [88]. Opisan je i slučaj amiodaronom indukovane tirotoksikoze (AIT) nakon AISKH kod pacijenta tokom nastavka terapije amiodaronom [89]. Takođe, tokom oporavka od AIT može se razviti SKH, prolazna, ali i trajna [87,89]. Preporuka je da pre uvođenja terapije amiodaronom treba utvrditi tiroidni status i redovno ga kontrolisati (najčešće na 6 meseci) tokom terapije ovim antiaritmikom. Kod pacijenata sa povećanim rizikom za tiroidnu disfunkciju, to jest kod žena, pacijenata sa strumom i sa povišenim TAT, treba razmotriti mogućnost primene drugog antiaritmika, ili češće kontrolisati tiroidni status. Smatramo da kod AISKH nije neophodno ukidati terapiju amiodaronom, već nastaviti redovno praćenje tiroidnog statusa [90,91].

MIKRONUTRIJENTI I SUBKLINIČKI HIPOTIROIDIZAM

Životne navike uključujući san, pušenje, ishranu i fizičku aktivnost su značajni faktori koji utiču na normalnu funkciju štitne žlezde u SKH [92]. Jod, selen i gvožđe su neophodni za sintezu hormona štitne žlezde. Hem-vezano gvožđe ulazi u sastav tiroidne peroksidaze (TPO) koja omogućava ugradnju atoma joda u molekule tirozina u procesu sineteze hormona štitne žlezde [93]. Mio-inozitol, kao sekundarni glasnik fosfolipaze C, takođe stimuliše organifikaciju joda i njegovu ugradnju u hormone štitne žlezde kroz inozitol fosfat/Ca2+/diacilglicerol signalni put [94].. Selen (dnevne potrebe su 55 μg, a u trudnoći i tokom laktacije 60-70 μg) kao integralni deo enzima dejodinaze, omogućava sintezu trijodtironina, ili inaktivaciju tiroksina prevođenjem u reverzni T3. Dodatno, selenoproteini, glutation peroksidaza i tioredoksin reduktaza, kroz efekte na koncentraciju reaktivnih vrsta kiseonika, naročito H2O2, utiču na organifikaciju joda [93].

Adekvatan unos joda (oko 150 μg dnevno), kao i adekvatna sinteza TSH su osnovni preduslovi za sintezu hormona štitne žlezde. Nedostatak joda u ishrani dovodi do smanjene sinteze hormona štitne žlezde, ali isti efekat ima i njegov preteran unos, zbog Wolff-Chaikoff-ljevog efekta [94]. Zbog efekta na organifikaciju joda, nedostatak gvožđa (dnevne potrebe su oko 9 mg za muškarce i oko 15 mg za žene koje menstruiraju) utiče na tiroidni status kao i nedostatak mio-inozitola, koji se za razliku od gvožđa, selena i joda, ipak može sintetisati u organizmu iz glukoze, pa su deficiti retki [94,95]. Kod kombinovanog deficita joda i selena u cilju normalizacije funkcije štitne žlezde neophodno je najpre nadoknaditi deficit joda, pa tek nakon toga deficit selena [94,96].

ZAKLJUČAK

SKH je često stanje i kod većine ne zahteva lečenje, već samo praćenje. Postoji konsenzus da supstituciju levotiroksinom treba indikovati kod odraslih pacijenata sa SKH čiji je TSH ≥ 10 m IU/L. U svim ostalim slučajevima, procena je individualna. Preporuke u pogledu skrininga na SKH veoma se razlikuju među stručnim udruženjima i ekspertskim grupama. Ukupno gledano, ne preporučuje se skrining u opštoj populaciji i treba ga ograničiti na osobe sa visokim rizikom za postojanje ovog stanja, kao što su pacijenti sa autoimunim bolestima, pozitivna lična, ili porodična anamneza na tiroidna oboljenja, te na one sa simptomima slIčinim hipotiroidizmu. Čak i kod asimtomatskih trudnica, mišljenja o potrebi univerzalnog skrininga su podeljena. Najveći broj stručnih udruženja predlaže ciljani skrining samo određenih grupa pacijenata.

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Vol. 47 (2022) No. 1 TIMOK MEDICAL GAZETTE Review article

SUBCLINICAL HYPOTHYROIDISM

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ABSTRACT: Subclinical hypothyroidism (SKH) is a thyroid disorder in which the level of thyroid hormones, thyroskin and triiodothyronine in the blood is normal, but the level of thyrotropin - TSH, pituitary hormone, which regulates the work of the thyroid gland with negative feedback, is elevated. This is a biochemical diagnosis, because patients are typically asymptomatic and without signs of disease and the detection of SCC is usually accidental. Gender, age, race, geographical area, iodine status. Depending on the degree of increase in baseline TSH levels, 5-8% of patients with SCH annually have progression to clinical hypothyroidism. Iodine is chronic autoimmune thyroiditis. Existing guidelines for the treatment of SKH differ from each other, as there is conflicting evidence on the benefits of long-term levothyroxine substitution in this condition. Although there are data from several comprehensive reviews of the clinical outcomes of SKH treatment, no definitive conclusion has yet been reached on the benefits of this approach. Factors that support application of levothyroxine therapy are: clinical trial due to symptoms of hypothyroidism, patient's desire, depression, infertility / ovulatory dysfunction, progressive increase in TSH, pregnancy, or pregnancy planning, children, adolescents. Research data show that pregnant women with SCC have an increased risk of gestational diabetes, miscarriage, gestational hypertension, preeclampsia, premature birth, and the therapeutic procedure in pregnancy differs from the rest of the adult population. The approach in children with SKH, amiodarone-induced SKH and micronutrients will be briefly mentioned.

Key words: subclinical hypothyroidism, levothyroxine, pregnancy, amiodarone

INTRODUCTION

Subclinical hypothyroidism (SKH) is a common clinical condition about which there is much controversy. To date, there has been no definite consensus among thyroidologists on several aspects. First of all, the question arises whether it is necessary to do screening at SKH, ie. actively search for disorder in a wider asymptomatic population at routine periodic / preventive examinations, or find cases according to clinical indications. Another aspect of the problem is how to assess the significance of this clinical condition, as well as possible adverse effects on the cardiovascular system, metabolic parameters and mental health of the individual patient. From the first two questions the third one arises, and that is what kind of therapeutic approach to have in SKH - to treat it or not.

WHAT IS SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism is a thyroid disorder in which the level of thyroid hormones (TH), thyroskin (T4) and triiodothyronine (T3) in the blood is normal, but the level of thyrotropin (TSH), a pituitary hormone that regulates thyroid function, is elevated. This is a biochemical diagnosis, because patients are typically asymptomatic and without signs of disease and the detection of SCH is usually accidental. Over time, SKH may progress to clinical hypothyroidism (KH). [1,2] SKH, depending on the duration and degree of TSH elevation, may be associated with an increased risk of cardiovascular (CV) disease and CV mortality, adverse effects on metabolic parameters, cognitive dysfunction, anxiety and depression [2,3]. Several alternative names describing the condition of SKH have been suggested such as: compensated hypothyroidism, preclinical hypothyroidism, mild hypothyroidism, decreased thyroid reserve, mild thyroid weakness [4].

WHAT IS THE PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM

The estimated total prevalence of SKH in the general population is 4-10% depending on the characteristics of the examined population,

ie. gender, age, race, geographical area, iodine status [4]. SKH is more common in women and the elderly. In women, the prevalence is 8-10%, and in women older than 60, the published prevalence is up to 20% [5,6]. The prevalence is about three times higher in whites than in blacks [7]. Also, during an increase in iodine intake in a previously iodine-deficient population, there may be a slight increase in the prevalence of SKH and thyroid autoimmunity [8]. There are studies in which the prevalence of SKH in people with metabolic syndrome (MetS) is almost two and a half times higher [9]. In addition, SKH is more common in patients with Type 2 Diabetes Mellitus (DM T2) than in the healthy population and is about 10% according to some reports [10]. SKH is a relatively common condition in patients with chronic renal failure (HBI) and can be found in about 18% of patients with HBI who are not on dialysis [11]. The reported incidence of SCH in pregnant women is 2-2.5%, in some countries such as China, Belgium and northern Spain even 4-13.7%, and in children the prevalence is less than 2% [12].

Of course, in order to assess the prevalence of this condition in the population / populations, accurate registration and adequate health statistics are necessary. Estimated prevalences are often based on meta-analyzes of published articles in available databases of professional and scientific papers, in which data from limited samples of respondents are analyzed. However, differences in the estimated prevalence may also be influenced by different diagnostic criteria for this condition, e.g. use, or not, of specific serum TSH reference ranges, in this case upper limits of the reference range for individual population groups. Research shows that it is necessary to determine the distribution of concentration and range of normal TSH values, probably due to genetic factors, according to age and race, or other specific characteristics of the population, which would be used to assess the presence of thyroid dysfunction (TD) [13]. In this regard, some authors believe that the prevalence of SKH in the elderly is overestimated, because the upper limit of the reference range for TSH increases with age [14].

CAUSES OF SUBCLINICAL HYPOTHYROIDISM

The most common cause of subclinical hypothyroidism, as well as clinical, in areas with sufficient iodine intake, is chronic autoimmune thyroiditis - Hashimoto's thyroiditis (HT), atrophic thyroiditis (AT), postpartum thyroiditis (PPT) [3]. Autoimmune thyroid diseases (AITB), which include HT, AT and PPT, are 5 to 10 times more common in women than in men, the prevalence increases with age, they are more common in people with other autoimmune diseases, as well as in their blood relatives [3, 15-17].

AITB is characterized by pathological infiltration of the thyroid gland by sensitized T lymphocytes and the presence of thyroid autoantibodies in the blood - antimicrosomal antibodies / antibodies to thyroid peroxidase (TPOAb), antithyroglobulin antibodies (TgAb), prescription (TgAb) and 3 antibodies, [18], TSA [19], TSA antibodies. Determination of these antibodies in serum is one of the key diagnostic methods for the diagnosis of AITB.

On the other hand, a very common cause of SCC is iodine deficiency in the diet, because the problem of iodine deficiency areas is still pronounced worldwide [20]. Iodine is a microelement necessary for the production of thyroid hormones (TH), thyroxine (T4) and triiodothyronine (T3), which must be taken into the body through food, at least 150 μg per day.

Causes of SKH can also be iatrogenic, for example the condition after radioiodine, or surgical therapy of benign and malignant diseases of the thyroid gland, ie. diffuse toxic goiter, toxic adenoma, polynodose toxic goiter, benign and malignant atoxic nodular goiter. Also, radiation therapy to the thyroid gland can lead to radiation therapy of the neck due to non-thyroid diseases of the head and neck, including lymphoma.

Iatrogenic SKH can also be pharmacological, caused by the use of drugs for non-thyroid diseases, or diagnostics, such as iodine-rich antiarrhythmics, amiodarone, then lithium, used in psychiatry, iodine contrast agents, interferon alpha and other cytokines, tyrosine kinase inhibitors (TKI), antituberculotic Paraaminosalicylic acid (pAS), less often aminoglutethimide, which lead to SKH by various mechanisms e.g. thyroid cytotoxicity, blockade of TH production and release of excess iodine, reducing blood supply to thyroid tissue, action on type 2 and 3 deiodinases, which participate in the production of TH and their metabolites, and others [21-26]. Of course, there are also antithyroid drugs that are given in the

treatment of hyperthyroidism, ie. methimazole and propyl thyrouracil, may lead to SKH.

Infiltrative diseases, such as amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis, Riddle's thyroiditis, can also affect the thyroid gland and be the cause of reduced functional reserves, ie. SKH [27,28].

As already mentioned, SKH as a consequence of AITB can often be associated with other autoimmune diseases, e.g. DM type 1, Addison's disease, rheumatoid arthritis [29-31], but also chromosomal disorders such as Down's or Turner's syndrome [32,33], which requires mandatory examination of thyroid function in patients with these diseases and syndromes.

Consumptive, or "expendable" SKH is a rare condition that occurs in patients with hemangiomas and other tumors in which type 3 deiodinase is expressed, causing accelerated degradation of T4 and T3 [34].

Finally, transient SCH can be found in patients in the recovery phase from non-autoimmune thyroiditis, subacute and painless thyroiditis, as well as during recovery from severe non-thyroid disease (NTB) [35].

THE COURSE OF SUBCLINICAL HYPOTHYROIDISM

In most patients, SKH remains stable over time. Depending on the degree of increase in the initial level of TSH, annually 5-8% of patients with SKH have a progression to clinical hypothyroidism (KH) [36]. On the other hand, thyroid function may return to normal over time in 6-35% of patients, also depending on baseline TSH levels as well as thyroid autoantibody levels [37]. In patients with elevated TPOAb, the progression of SKH to KH is 4.3% per year, and in those with normal TPOAb levels, almost twice as low, 2.6% per year [38]. Therefore, after the diagnosis of SCH, thyroid function tests (TFT) are repeated in 8-12 weeks and additional measurement of thyroid autoantibody levels is performed. If SKH persists, TFTs are repeated for 6 months during the first two years of follow-up, and then once a year if the findings are stable. In contrast, if TFTs are normal after repeated determinations and the patient has no symptoms, goiter, and elevated thyroid autoantibodies, further monitoring is not necessary [3].

DIAGNOSIS OF SUBCLINICAL HYPOTHYROIDISM

The diagnosis of SKH is made when elevated TSH values are detected in the patient (the reference range of most tests is 0.4 - 4.0 to 5 m IU/L) with normal FT4 values in the blood [39] . Bearing in mind that the diagnosis of SKH is based on the results of laboratory analyses, the specificity, sensitivity and reference values of the applied test should be taken into account, and the finding should be interpreted accordingly [40]. Although elevated serum TSH is most often a sign of primary hypothyroidism, it is important to know that measured concentrations may be elevated (usually <8 mU/L) in individuals over 65 years of age without clinical and laboratory evidence of thyroid disease [41]. Other conditions, such as post-radiotherapy of the neck, adrenal insufficiency, pregnancy, use of certain drugs (lithium, AMD), or the presence of specific antibodies in the blood (HAMA, or macro TSH) may mimic SKH [42-44]. In addition, pathological obesity due to the effect of leptin on thyrotropin releasing hormone (TRH) leads to a reversible increase in blood TSH [45]. Fluctuations in TSH concentration are expected in acute, especially severe netiroid diseases, as well as after surgical procedures - hemithyroidectomy, which should be taken into account when interpreting laboratory findings [42,46]. Laboratory diagnosis should be postponed for 2-3 months after recovery from acute diseases, due to the effects of cytokines on TSH concentration, and supplementation with biotin, which is a part of many multivitamins (especially those recommended for hair and nail health) should be stopped at least 2 days before laboratory tests, Analysis, due to interference with immunoassays [42,47,48].

There are two categories of SKH according to the degree of TSH increase. Slightly elevated TSH, of 4–10 m IU/L, found in 80–90% of patients, and significantly elevated TSH,> 10 m IU/L [3]. After the diagnosis of TSH, the cause should be determined, ie. an etiological diagnosis should be made. Additional laboratory analyses in order to establish the etiological diagnosis are measurement of thyroid autoantibodies (TAT), TPOAb mainly due to higher sensitivity and less often TgAb, as well as ultrasound examination of the thyroid gland which can detect characteristic parenchymal changes in autoimmune thyroiditis, which is the most common cause of SKH [50].

The level of TSH in a healthy person has small variations over time, about 1/3 of the reference range, which is called its own "TSH

setpoint", which tends to increase with age [51,52]. Thus, as mentioned, in the elderly we use a wider reference range (4.0-7.0 m IU/L), i.e., a slightly elevated TSH level in the elderly is considered a physiological adaptation to aging [41].

In both healthy and SKH, TSH levels have circadian fluctuations in serum concentrations - the lowest concentration is in the early afternoon, with about 30% higher concentrations in the evening and overnight.

Delayed night peak TSH can be found in: night shift workers; those with sleep disorders; after strenuous physical activity; in mood disorders - depression [3].

Biologically inactive forms of TSH may be the reason for measured higher TSH values in some individuals [53].

Let us repeat that the level of TSH correlates with BMI and markers of insulin resistance, so the finding of TSH> 3.5 is common in obese [54].

CLINICAL CHARACTERISTICS OF SUBCLINICAL HYPOTHYROIDISM

Symptoms

By definition, SKH is an asymptomatic condition, with no clinical signs of hypothyroidism (Table 1). However, is SKH really asymptomatic? Some studies show that a small but statistically significant number of patients with SKH have more frequent symptoms of hypothyroidism than healthy ones: drier skin, poorer memory, slower thinking, weaker muscles, faster fatigue, more frequent muscle cramps, greater winter fever, deeper and hoarse voice, swollen eyes and more frequent constipation [5]. On the other hand, since the symptoms and signs of hypothyroidism are general and can occur in other conditions, some studies show that there is no improvement in symptoms in patients with SCI when levothyroxine substitution is introduced [55]. However, most patients with SCH do not have hypothyroid symptoms.

Mood and mental health disorders

Based on many studies, it seems that there may be mild disorders of declarative memory (knowledge of facts), procedural memory (skills that are performed automatically) and mood in younger people with SCC, which are improved by levothyroxine substitution [56]. However, such evidence is generally not found in the population over 65 years of age [57].

Table 1. Symptoms and signs of hypothyroidism

SYMPTOMS	SIGNS
Fatigue, weakness, suffocation	Bradycardia
Dry goat	Dry, rough skin
Feeling cold / cold	Cold extremities
Hair loss	Diffuse alopecia
Weight gain with normal, or poor appetite	Swelling of the face, hands, feet, myxedema
Constipation	Prolonged tendon relaxation time
Hoarseness	A deeper, hoarse voice
Impaired concentration, impaired memory	Efusions into serous cavities
Impaired hearing, paresthesias	Carpal tunnel syndrome
Menorrhagia, oligomenorrhea, amenorrhea	

Obesity, glycoregulation, insulin resistance, diabetes mellitus, dyslipidemia

Serum TSH levels are positively correlated with body weight [58] and it has been shown that for each unit of increase in log TSH, body weight is 2.3 kg higher in women and 1.1 kg in men [59]. In contrast, a significant decrease in body weight is associated with a decrease in TSH levels [60]. However, a sample relationship between SKH and obesity has not been shown.

SKH could reduce insulin sensitivity by reducing the number of glucose transporters in plasma membranes (cell organelle membranes) and by directly affecting insulin secretion and clearance, as is known to occur to a significant extent in hypothyroidism [61]. In patients with established diabetes mellitus (DM) type 2, a change in glycemic control may indicate SKH and long-term thyroid disorders, while the prevalence of SKH with elevated TAT in a patient with type 1 DM is up to 30% [62].

Large epidemiological studies have shown a positive correlation between TSH levels and dyslipidemia, indicating a potential impact of SKH on the lipid profile [5]. Similarly, another large study showed e.g. that an increase in TSH

levels of 1.0 m IU / L was associated with an average increase in total cholesterol levels in women of 0.09 mmol, indicating gender differences in the relationship between SCH and lipid profile. Also, the relationship between TSH levels and lipid profile is more pronounced with advancing age [63].

Cardiovascular system, heart failure and ischemic heart disease

SKH is associated with functional cardiac disorders, such as left ventricular diastolic dysfunction and decreased systolic function at rest and physical exertion [64]. Vascular abnormalities in this condition have also been shown, such as increased vascular resistance, arterial stiffness, endothelial dysfunction, and atherosclerosis [65]. Many studies point to SKH as an independent risk factor for the development of heart failure, as well as for the worsening of existing ones [64].

Some of the results of research on the impact on ischemic heart disease did not show an association between AITB and ischemic heart disease, but by re-analyzing a population-based Whickham study (66), it was found that in patients with SKH a significantly higher frequency of cardiac ischemic events and mortality due to ischemic heart disease was found. A meta-analysis of several relevant prospective studies has shown similar results [67].

Degree of TSH increase

It is not insignificant, as the results of the study show, how much TSH is elevated in SKH. We said that there are two categories of SKH according to the degree of TSH increase: slightly elevated TSH, from 4-10 m IU/L and significantly elevated. TSH> 10 m IU/L. Symptoms, manifestations, and potential complications, including endothelial, lipid, and cardiovascular disorders, are related to the degree of TSH elevation but depend, as has been said, on gender and age [68]. The results of numerous completed, as well as ongoing studies will be useful to determine both the TSH threshold and the age threshold for considering therapeutic intervention, levothyroxine substitution.

THERAPEUTIC APPROACH IN SUBCLINICAL HYPOTHYROIDISM

SKH, like KH, is treated with levothyroxine substitution. The goal of the treatment, as with KH, should be to eliminate the symptoms of hypothyroidism by achieving normalization of TSH [69].

However, since it is by definition an asymptomatic disorder in most patients, a disorder only at the blood level, two questions should be kept in mind when deciding on the treatment: what is the effect of levothyroxine treatment on long-term clinical outcomes in patients with SLE and what is the outcome of follow-up without levothyroxine treatment, on long-term outcomes in patients with SCV [70]. Existing guidelines for the treatment of SKH differ from each other, as there is conflicting evidence on the benefits of long-term levothyroxine substitution in this condition. Although there are data from several comprehensive reviews of the clinical outcomes of SKH treatment, no definitive conclusion has yet been reached on the benefits of this approach. (1). Certainly, as it was emphasized in the previous text, before starting the substitution, the TSH test should be repeated within 3 months from the diagnosis of SKH. This is important because in about 60% of patients TSH normalizes within 3 months, and in about 62% over 5 years [71,44]. On the other hand, in patients with SCC and hypothyroid symptoms, other possible causes for existing symptoms should be considered first.

According to most guides, levothyroxine substitution in SKH should be started when TSH is> 10 mIU/L, regardless of the absence of symptoms. Levothyroxine substitution should be considered in cases where TSH is between 5-10 mIU/L in repeated measurements and there are symptoms similar to hypothyroidism. However, if symptoms do not resolve after 3-4 months of levothyroxine substitution and TSH normalization, the treatment should be discontinued [70,1]. In other cases, the decision to treat SCH, when the TSH is between 5-10 mIU/L in repeated measurements, should be adjusted individually depending on age, comorbidity, degree of TSH elevation, persistence and progression of TSH elevation, TAT presence and goiter. The meaning of substitution would be based on reducing the risk of adverse CV events and possibly preventing progression to CH. It should be borne in mind that levothyroxine substitution can lead to iatrogenic subclinical / clinical thyrotoxicosis, especially in elderly patients, which in itself may be a risk of worsening CV condition and there is no evidence that substitution is useful in people

65 years of age and older [42]. Factors that support the application of left thyroxine therapy are: clinical trial due to symptoms of hypothyroidism, patient's desire, bipolar disorder, depression, infertility / ovulatory dysfunction, presence of TAT, progressive increase in TSH, pregnancy, or pregnancy planning, children, adolescents.

RECOMMENDATIONS [3]

There are two categories of SKH according to TSH level: Slightly elevated TSH - 4-10 m IU / L found in 90% of people with SKH; and TSH> 10 m IU / L

The finding of elevated TSH with normal FT4 in the first measurement should be repeated in 2-3 months, by re-measuring TSH, T4 and TPOAb

TSH and FT4 should be measured in individuals with elevated TPOAb / TgAb and / or ultrasound indicating AIT

Age-specific reference ranges should be used to diagnose SKH in the elderly population.

In patients younger than 65 years and with TSH> 10 m IU/L, even in the absence of symptoms of hypothyroidism, the introduction of L-thyroxine substitution is recommended.

In patients younger than 65 years with symptoms of hypothyroidism and TSH <10 m IU/L, a clinical trial by introducing L-thyroxine substitution should be considered.

After hemithyroidectomy, persistent SKH should be treated with L-thyroxine in order to normalize TSH.

Patients with diffuse or nodular goiter and persistent SKH should be treated with L-thyroxine in order to normalize TSH.

In patients with type 1 DM, TSH levels should be monitored once a year.

In patients with DM type 2 and unexplained deterioration of glycemic control, TSH and FT4 should be performed.

There is limited evidence that L-thyroxine substitution in younger people with SKH leads to improved mental function.

There is no evidence of beneficial effects of L-thyroxine therapy in obese individuals with TSH <10 m IU/L and normal FT4 on weight loss.

L-thyroxine therapy in SKH can lower both total and LDL cholesterol, but lipid normalization is rarely achieved.

The effect of L-thyroxine substitution on serum lipid concentrations is most pronounced in patients with TSH levels> 10 mIU/L before treatment.

The oldest elderly people, over 80 years of age, with a TSH level ≤ 10 m IU / L, should be carefully monitored, avoiding the introduction of L-thyroxine substitution.

If the hormones in the control test are normal, with a normal TAT level and the absence of goiter - no further testing is needed.

If SCH persists and L-thyroxine therapy is not started, hormones should be tested for 6 months for at least first 2 years, and then once a year.

PREGNANCY AND SUBCLINICAL HYPOTHYROIDISM

SKH in pregnancy is defined as a condition in which serum TSH is higher than the upper limit of the reference range specific to the trimester of pregnancy, while serum T4 and T3 are in the reference ranges [72,73,14,74]. It occurs in approximately 2-2.5% of pregnant women, with the number being significantly higher in some countries and as high as 13.7% in northern Spain [75].

Isolated hypothyroxinemia is defined as a serum FT4 concentration below the 2.5 percentile of the reference range (0.80 ng/dL; 10.30pmol/L), with a normal TSH concentration [72,12].

The diagnosis of SCH in pregnancy is made only on the basis of laboratory analyses, as the symptoms and signs are non-specific and very similar to problems that may be associated with lifestyle variations, or problems that result from many other conditions and pregnancy itself [72,12,74]. The reference range of TFT in pregnant women differs from the reference range of the general population, and also differs by trimesters of pregnancy. Based on published studies, mainly in Western countries, the following reference range for TSH in pregnancy is proposed: first trimester 0.1 - 2.5 mU/L; second trimester 0.2 - 3.0 mU/L, third trimester 0.3–3.5 mU/L [76-78]. However, it is advisable to determine these values for each country or region individually. It should be noted that during pregnancy there is an increase in the concentration of T4, which is highest during the first trimester of pregnancy, while this increase is significantly less during the second and third trimesters. Despite the increased binding of hormones to transport proteins, which are also increased in pregnancy, many authors believe that the reliability of the determination of free thyroxine (FT4) by standard immunoassay for FT4 is satisfactory [72,12].

As the definition of SKH is based on elevated TSH levels in combination with normal FT4 values, it would be crucial to determine the trimester-specific TH reference range. Available data from the literature indicate that in the first trimester of pregnancy the lower limit of FT4 2.5th percentile of the reference range detected by immunoassays is about (0.80 ng/dL; 10.30pmol/L) [72,12]. In order to obtain a reference value specific for the first trimester of pregnancy, some authors suggest that the normal values of total, for transport protein bound T4 (TT4), which are 5–12 mg / dL, or 50–150 nmol/L for non-pregnant women, be multiplied by 1.5 and the values thus obtained used as reference values specific to the first trimester [72,12].

Antibodies to thyroid peroxidase (TPOAb) are present in about 50% of pregnant women with SCC, and up to 80% in pregnant women with clinical hypothyroidism. In pregnant women with SCI, the determination of TPOAb is recommended in order to determine the AITB. Antibodies to thyroglobulin (TgAb) should not be neglected either. Elevated TgAbs were found in 5% of women with SKH and normal TPOAb. Women with elevated TgAb, and normal TPOAb, had significantly higher serum TSH levels compared with women without AITB. Thus, TgAb should be determined in pregnant women with negative TPOAb. After the first trimester, TAT may be negative due to immunosuppression during pregnancy, and in the presence of elevated TSH values and negative antibodies, thyroid ultrasound should be performed [72,12].

Side effects of SKH during pregnancy

Manifested clinical hypothyroidism during pregnancy is clearly associated with adverse events such as preeclampsia, eclampsia, gestational hypertension, cretinism, fetal death, and miscarriage. However, there is less evidence of complications during pregnancy and SCI. Studies dealing with this problem show conflicting results. Most studies indicate an increased risk of gestational diabetes (GD), with a positive correlation between TSH levels and the risk of GD.

Several studies have confirmed the association of SKH with miscarriages, very early embryo loss, gestational hypertension and preeclampsia. The risk of preterm birth is also present in pregnant women with SCI. Other complications that are mentioned as possible, but also quite rare, are: placental abruption, increased perinatal mortality, low Apgar score and low birth weight. However, the association between SKH in pregnancy and offspring developmental disorders has not been fully demonstrated [72,12].

Effects of SKH treatment during pregnancy

Treatment of SKH with levothyroxine is thought to outweigh the potential benefits. SKH that occurs before conception, or during gestation, should be treated with levothyroxine. In contrast, there are no studies that show the benefit of treating isolated hypothyroxinemia during pregnancy in terms of maternal obstetric complications. However, levothyroxine therapy may be considered in isolated hypothyroxinemia detected in the first trimester of pregnancy, due to its association with more favorable neuropsychological development in children. Levothyroxine therapy is not recommended in isolated cases of hypothyroxinemia detected in the second and third trimesters.

Levothyroxine therapy should be initiated in patients with TSH> 10 mU/l in the first trimester, regardless of the presence of TPOAb. Also, therapy should be initiated in pregnant women with TSH> 4 mU/L and TPOAb positive. Therapy should be considered in pregnant women with TSH of 2.5-4mU/L with positive TPOAb and in pregnant women with TSH of 2.5-10mU/L with negative TPOAb. In patients preparing for pregnancy with assisted reproductive techniques, the TSH should be <2.5 mU/L. In these patients, TSH should be determined two weeks before and two weeks after insemination and in vitro fertilization (VTO) [79].

If a decision is made to introduce substitution in pregnant women with CKD, the suggested doses of levothyroxine are: 1.20 μg / kg / day for TSH ≤ 4.2 mU / L; 1.42 μg / kg / day for TSH> 4.2–10 m IU / L and 2.33 μg / kg / day for TSH> 10 mU / L. TSH values should be checked every 4-6 weeks during the first trimester and once during the second and third trimesters.

In patients with morning sickness, late levothyroxine administration may be a legitimate option. The goal of levothyroxine treatment during pregnancy is to normalize maternal serum TSH values within trimester-specific reference values.

Most cases of SKH in pregnancy are transient and recover after pregnancy. However,

pregnant women with positive TPOAb and TSH> 5 mU/L are more likely to have persistently elevated TSH, i.e. that hypothyroidism will persist after pregnancy. After delivery, the dose of levothyroxine should be reduced to the pre-conception dose. In women diagnosed with SKH during pregnancy, whose TSH is <5 mU/L and who have negative TPOAb, as well as in women whose replacement dose was less than 50 μg of levothyroxine, discontinuation of postpartum substitution may be attempted. Thyroid status checked 6 weeks postpartum, then at 6 and 12 months. In other women diagnosed with SCC after pregnancy, thyroid status should be checked 6 months and one year after delivery and the need for substitution should be determined. Levothyroxine therapy is not recommended for euthyroid women with positive antibodies [72,12]. Evidence for screening for SKH in pregnancy is ambiguous. Although there are still no well- controlled studies to justify general screening, a large number of authors recommend screening. Also, a large number of authors advocate screening only for pregnant women who are at special risk, ie. women with a history of thyroid disease, women with a family history of thyroid disease, women with goiter, women with DM type 1, women with other autoimmune diseases, women with infertility of unknown cause, women with a history of head and neck radiotherapy, women with a history of abortion and premature birth [72,12,74,80].

SUBCLINICAL HYPOTHYROIDISM IN CHILDREN

The subject of our consideration is primarily SKH in adult population, but we will make a few remarks about this condition in children. When it comes to possible prenatal impact, the results of numerous studies on the relationship between the mother's SKH and impaired neurophysiological development of the child are not consistent, as is very clear in KH [12], and further research is needed to determine the exact impact. In newborns and early childhood, especially in the first 3 years of life, THs play an irreplaceable role in the process of maturation and brain development, and the impact on linear growth persists until the closure of the pineal gland in adolescence [81]. After birth, large changes in thyroid function occur in the newborn, and the level of TSH> 5 mU / L, can be considered elevated after 1 month of age. Therefore, it is necessary, as in the elderly population, to use age-specific reference values to interpret diagnostic biochemical findings [82]. In the general pediatric and adolescent population with SCH, hormones are normalized in over 70% of them, or persist unchanged in most of the rest, for the next 5 years after the diagnosis [12]. SKH is 10 times more common in children with Down syndrome than in the general population [83]. In obese children, a TSH level of 5-7 m IU/L is likely a consequence rather than a cause of obesity [84]. In areas with sufficient iodine intake, SKH in young children is most often idiopathic (so-called persistent "Hyperthyrotropinemia" and "Non-autoimmune" idiopathic SKH), or caused by various perinatal and genetic causes. In older children and adolescents, the most common cause is AITB [12]. To date, there is insufficient evidence to recommend levothyroxine substitution in most children with SKH and TSH <10 mU/L [85].

AMIODARON-INDUCED SUBCLINICAL HYPOTHYROIDISM

Chronic therapy with amiodarone (AMD), an iodine-rich antiarrhythmic, is associated with the appearance of predictable changes in TFT, as well as the appearance of thyroid dysfunction, which is responsible for both iodine load and cytotoxicity of the antiarrhythmic [86]. According to research by the authors of this paper, amiodarone-induced subclinical hypothyroidism (AISKH) is found in the area with sufficient iodine intake in 10% of cardiac patients treated with this antiarrhythmic, more often in women, patients with enlarged thyroid gland and patients with elevated TPOAb [87]. In most patients with AISK, the condition does not progress to KH, and in a large number there is a spontaneous normalization of thyroid status, even with continued amiodarone therapy [88]. A case of amiodarone-induced thyrotoxicosis (AIT) after AISC in a patient during continued amiodarone therapy has also been described [89]. Also, during recovery from AIT, SKH may develop, transient but also permanent [87,89]. It is recommended that thyroid status be determined before initiating amiodarone therapy and monitored regularly, usually every 6 months, during therapy with this antiarrhythmic. In patients at increased risk for thyroid dysfunction, i.e. women, patients with goiter and elevated TAT, the use of another antiarrhythmic should be considered, or thyroid

status should be monitored more frequently. We believe that it is not necessary to discontinue amiodarone therapy in AISCH, but to continue regular monitoring of thyroid status [90,91].

MICRONUTRIENTS AND SUBCLINICAL HYPOTHYROIDISM

Life habits including sleep, smoking, diet, and physical activity are significant factors influencing normal thyroid function in SKH [92]. Iodine, selenium and iron are necessary for the synthesis of thyroid hormones. Hem-bound iron is part of thyroid peroxidase (TPO), which enables the incorporation of iodine atoms into tyrosine molecules in the process of synthesis of thyroid hormones [93]. Myo-inositol, as a secondary messenger of phospholipase C, also stimulates the organization of iodine and its incorporation into thyroid hormones through the inositol phosphate / Ca 2+ / diacylglycerol signaling pathway [94]. Selenium (daily requirements are 55 μg, and in pregnancy and lactation 60-70 μg) as an integral part of the enzyme deiodinase, enables the synthesis of triiodothyronine, or inactivation of thyroxine by conversion to reverse T3. In addition, selenoproteins, glutathione peroxidase, and thioredoxin reductase affect iodine organization through their effects on the concentration of reactive oxygen species, particularly H 2 O 2., [93] .

Adequate iodine intake (about 150 μg per day), as well as adequate TSH synthesis, are the basic prerequisites for the synthesis of thyroid hormones. Iodine deficiency in the diet leads to reduced synthesis of thyroid hormones, but its excessive intake has the same effect, due to the Wolff-Chaikoff effect [94]. Due to the effect on iodine organization, iron deficiency (daily requirements are about 9 mg for men and about 15 mg for menstruating women) affects thyroid status as well as myo-inositol deficiency, which, unlike iron, selenium and iodine, can still synthesize in the body from glucose, so deficits are rare [94,95] . In the case of a combined deficiency of iodine and selenium, in order to normalize the function of the thyroid gland, it is necessary to first compensate for the deficiency of iodine, and only after that the deficiency of selenium [94,96] .

CONCLUSION

SKH is a common condition and most do not require treatment, but only follow-up. There is a consensus that levothyroxine substitution should be indicated in adult patients with SCC whose TSH is ≥ 10 m IU/L. In all other cases, the assessment is individual. Recommendations regarding SCH screening vary widely among professional associations and expert groups. Overall, screening is not recommended in the general population and should be limited to people at high risk for the condition, such as patients with autoimmune diseases, positive personal or family history of thyroid disease, and those with symptoms similar to hypothyroidism. Even in asymptomatic pregnant women, opinions about the need for universal screening are divided. Most professional associations suggest targeted screening of only certain groups of patients.

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